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2.1 A new treatment for HIV – neutralizing antibodies?.

Studies of passive immunization with conventional anti HIV antibodies have been disappointing, because high mutation rates of HIV allowed antibody resistant strains to form. In 2011, the discovery of antibodies that neutralize most HIV strains in vitro (Nature 2011; 477:466) was greeted with excitement, because it suggested that passive immunization of HIV was possible in vivo.

A combination of "broadly neutralizing antibodies," each of which targets a different HIV antigenic epitope, was given subcutaneously once or twice weekly for a month, by an International team. Viral load dropped below detectable levels and this control of HIV viraemia continued for 60 days after treatment cessation.

Comment: These broad neutralizing antibodies were effective in the passive immunization of HIV in vivo. Unlike antiretroviral agents, these broadly neutralizing antibodies target virus directly and have a longer half life. A novel gene therapy technique has now been utilized to generate large amounts of broadly neutralizing HIV antibodies. Developing active immunization also to generate broadly neutralizing antibodies is surely to be pursued in the future.

Ref: Klein F et al Nature 2012 Oct 24;

2.2 Which is of more value for fluid resuscitation in the ICU – Hydroxy Ethyl Starch (HES) or normal saline?.

HES is a colloid and normal saline is a crystalloid. 7,000 ICU patients were randomized to receive 6% HES or normal saline for fluid resuscitation. 29% were septic and 43% were post operative.

No difference was found in 90 day mortality between HES and saline (18 vs 17%). The HES group received a lower mean total volume of fluid (1,377 vs 1,731 ml). Significantly more patients in the HES group subsequently received renal replacement therapy (7% vs 5.8%). Adverse events were also higher in the HES group (5.3% vs 2.8%) - mostly rash and pruritus.

Comment: Normal saline is preferable to HES for fluid resuscitation in the ICU.

Ref: Myburgh J.A. et al NEJ Med 2012 Nov 15; 367: 1901.

2.3 Should statins be given even for those with minimal estimated cardiovascular risk?.

Minimal cardiovascular risk is defined as a 5 year major vascular event risk of < 10%. It is known by meta analysis that statins lower incidence of major vascular events including non fatal MI, coronary death, stroke, or coronary revascularization, by about 20% for every 40mg/dl reduction in LDLC. But the net benefit of statin therapy in patients at low vascular risk has been unclear.

In a new meta analysis, 170,000 participants whose pre trial 5 year risk for major vascular events (MVEs) ranged from < 5% to > 30% were analysed. Overall statins lowered 5 year risk for

MVEs by 21% per 40mg/dl reduction in LDLC. Surprisingly, risk reductions were more pronounced in the lowest risk categories (as much as 38% /40mg/dl reduction in LDLC for participants whose 5 year vascular risk was < 5%). Similar relative risk was seen even when patients with prior vascular disease, diabetes or chronic kidney disease were excluded. Statins lowered 5 year relative risk for vascular death by atleast 12% and did not raise risk for non vascular death in patients with or without histories of vascular disease.

Comment: Among patients with a 5 year MVE risk of < 10%, statins lowered the absolute 5 year MVE risk by about 11 events per 1,000 patients for each 40mg/dl reduction in LDLC levels. This benefit substantially outweighs any known risk of statin therapy. Current guidelines generally do not recommend statin therapy for lower risk patients. The benefit of statins was seen whether the patient had prior or no prior vascular event. It was also effective in those with diabetes and chronic kidney disease. In diabetes in particular, the results confirmed the findings of the earlier CARDS study, which found statins effective in CV prevention in those with or without elevated lipids.

Ref: Cholesterol treatment trialist (CTT) Lancet 2012 May 17; e Pub. ahead of print.

2.4 A possible new treatment for osteoarthritis (OA)- Kartogenin (K) ?.

In OA, chondrocytes are deficient in either number or function. Replacing degraded joint cartilage matrix would be the ideal treatment. It has been shown that adult mesenchymal stem cells (MSCs) which are found in damaged cartilage can develop into chondrocytes, but ways to encourage the transformation have not been found. As a result, the only 2 therapies for patients with symptomatic OA are analgesics and joint surgery.

A recent report highlights the discovery of Kartogenin, a small molecule that promotes differentiation of MSCs into chondrocytes in vitro. The team also identified the biochemical pathway by which K works. They tested intra articular K in 2 mouse models of OA and the number of chondrocytes increased, cartilage matrix was restored and serum markers of cartilage degradation dropped. A functional improvement was quite apparent and the joints were free of pain. No adverse effects were noted.

Comment: Treatment of OA with agents other than analgesics and joint surgery are of unproven value. The results of K in promoting structure and function of OA in mice will surely be explored in the future in humans, as OA is the commonest cause of arthritis for those over the age of 55.

Ref: Johnson K. et al Science 2012 May 11; 336: 717.

2.5 What is the optimal serum 25 hydroxy vitamin D level?.

Low vitamin D levels are associated with adverse bone outcomes. In a population based observational study, in 4 US communities, researchers evaluated the relation of 25 OH D levels and incidence of

1. Hip fracture.
2. Myocardial infarction.
3. Cancer.
4. Death.

The primary outcome was a composite of all these end points. 1,621 participants (mean age 74) were followed up for a median 11 years. After adjustment for multiple covariates, the 25 hydroxy D levels <20ng/ml (50 nmol/l) had higher risk for the composite outcome (HR 1.24) and death (HR 1.32). The incidence of MI, cancer and hip fracture separately were non significantly elevated.

Comment: In this observational study, researchers evaluated multiple outcomes (beyond bone health) and determined the optimal 25 OH D level to be >**20ng/ml.**

Ref: de Boer I.H. et al Ann.Intern. Med 2012 May 1; 156:627.

2.6 Treatment for seasonal allergic rhinitis (SAR).

Intra nasal steroids are the most effective pharmacologic treatment for SAR, but they can take several days to take effect. Some patients do not achieve full relief of symptoms with intra nasal steroids alone. Add on oral antihistamines or Monteleukasts do not add much benefit, when introduced after intra nasal steroids fail. What about the combination of intranasal steroids and **intranasal** antihistamines from the beginning of treatment?.

3,398 adolescent and adult patients with moderate to severe SAR were randomized to either twice daily intranasal antihistamine (Azelastine) and fluticasone nasal spray combination, either alone or placebo - for 2 weeks during the allergy season. The onset of action for the combination therapy was 30 minutes and combination therapy recipients showed significantly greater improvement in morning and evening total nasal symptoms scores vs the drugs individually. All active treatments were significantly better than placebo.

Comment: The combination of intra nasal steroids and antihistamine from the onset of treatment of SAR was superior to either drug alone. Azelastine has a bitter taste and 2 different nasal sprays increases the treatment costs.

Ref: Carr W. et al J. Allergy. Clin Immunol 2012 May; 129:1282.

2.7 Monotherapy for severe sepsis.

Higher morbidity and sepsis related mortality is seen in patients with septic shock when they receive inappropriate initial antibiotic therapy. A multicenter control trial in Germany compared Meropenem monotherapy vs Meropenem + moxifloxacin. (N = 600.) Patients infected with Methicillin resistant Staph aureus (MRSA) or Vancomycin resistant enterococcus species (VRES) were excluded (49 patients).

1/3rd of the 551 evaluable patients were positive for E.coli and Methicillin susceptible S.aureus. Pseudomonas were isolated in 2%. Meropenem monotherapy resistance was seen in 9% and 1%

in the combination group. Degree of organ failure at 14 days, or in 28 or 90 day mortality, were not significantly different in the 2 groups. Adverse events were higher in the combination group (9% vs 4%; P = 0.02). The incidence of serious adverse events were similar.

Comment: In non MRSA or VRES septicaemic patients, Meropenem monotherapy from the onset was almost as good as combination therapy of Meropenem + Moxifloxacin.

Ref: Brunkhorst F.M. et al JAMA 2012 June 13; 307: 2390.

2.8 Snippets.

1. What happens to the weight of smokers after smoking cessation?.
The mean weight gain was 5Kg but 50% of quitters lose weight or experience minimal gain of weight.

Ref: Aubin H.J. et al BMJ 2012 July 10; 345: e 4439.

2. What are the properties of HDLC?.

a) Promotes reverse cholesterol transport.

b) Antagonizes lipoprotein oxidation.

c) Inhibits platelet activation.

d) Participates in immunity.

e) Down regulates adhesion molecule expression.

f) Normalizes the ratio of tissue plasminogen activator to plasminogen activator inhibitor -1 (TPA/PAI -1 ratio).

g) Promotes nitric oxide production and release.

h) Modulates the pace of re endothelialization or neointimalization of coronary stents.

Ref: Seo S.M. Heart 2011; 97:1943 – 1950.

2.9 What factors affect poor adherence to drug therapy in hypertensive patients – patient's perception?.

1. Perceived stress.
2. Poor diet control.
3. Being overweight.
4. Family history of hypertension.
5. Lack of exercise.
6. Alcohol use.
7. Other factors.

Ref: Marshall .I.J. et al BMJ 2012 July 9; 345: e 3953.

2.10 What symptoms do patients associate with hypertension?.

1. Headache.
2. Dizziness.
3. Palpitations.
4. Sweating.
5. Tiredness.
6. Neck pain.
7. Nausea.
8. Chest pain.
9. Visual changes.
10. Nervousness.

Ref: Marshall .I.J. et al BMJ 2012 July 9; 345: e 3953.

2.11 Why do patients stop taking treatment for hypertension?.

1. When symptoms are absent.
2. Side effects.
3. Perception that their BP was controlled permanently.
4. Fear of dependency.
5. Preference for traditional or alternative treatments.
6. Forgetfulness.
7. Lack of time.
8. Lack of money.

Ref: Marshall .I.J. et al BMJ 2012 July 9; 345: e 3953.

2.12 Interferon assays for latent TB.

Interferon Gamma release assays (IGRAs) have many advantages over skin test (such as Mantoux) for diagnosing latent TB. They require only one medical encounter, can be repeated without boosting response and eliminate subjective interpretation of test results. However, they are not without their own problems.

486 of 7,374 newly hired employees had baseline positive IGRAs. 14 of them appeared clinically unlikely to be latent TB. These 14 had their test repeated and 10 were found to be negative. Further, 52 employees who had initial negative but who converted to positive on annual screening test, (none who had known exposure to TB) had a repeat IGRA test and 8 out of 10 such patients reverted to negative.

In contrast, a meta analysis of 28 studies, reconfirmed the usefulness of IGRAS. Overall , a positive IGRA predicted progression to active TB significantly better than skin testing. Negative predictive values exceeded 99% for both tests but were still significantly higher for IGRAs.

Comment: When IGRA is used for routine screening, positive results should be repeated routinely and marginally positive values should be interpreted with caution.

Ref: Fong K.S. et al Chest 2012 July 1st; 142: 55.
Diel R. et al IBID : 63.
Loddenkemper R. et al IBID :10.

2.13 Interactions between proton pump inhibitors (PPIs) and clopidogrel (C) – are they clinically important?.

The pro drug C is metabolized to its active form primarily by cytochrome 450 2C 19. PPIs inhibit this enzyme and lab evidence suggests that concomitant use of C and PPIs attenuates C activity. In one large randomized trial however, PPI therapy did not raise risk for adverse cardiac outcomes in C treated patients (NEJ Med 2010; 363: 1909).

A new observational study involving 24,000 patients, who were prescribed C and aspirin, 50% of whom also had taken PPIs at some point during the study, was undertaken. After adjustment for multiple factors, PPI exposure was associated with 37% higher risk for death or incident MI. Similar results were also found for other 2C 19 inhibitors such as Paroxetine and non inhibitors such as Citalopram and Ranitidine. To remove potential residual confounding between patient groups, a within subject analysis, in which the study patients served as their own controls ie investigators compared incident MI rates within patients during periods of PPI use and periods of non use. In this analysis, no association was noted between PPI exposure and incident MI. Similar results were obtained for Paroxetine, Citalopram and Ranitidine.

Comment: PPIs are useful to lower the risk for GIT bleeds in patients who receive dual antiplatelet blockade with a combination of C + aspirin. Reassuringly, these results suggest that interactions between PPIs and C do not undermine the cardioprotection afforded by dual antiplatelet therapy.

Ref: Douglas I.J. et al BMJ 2012 July 10; 345: e 4388.

2.14 Does multivitamin supplementation prevent CVD in men?.

Observational studies of multivitamins for prevention of CVD have yielded inconsistent and mostly negative results. RCTs of individual vitamins and minerals viz Beta carotene, selenium, Vit B,C and E have also shown negative results.

15,000 male Physicians (mean age 64) were randomized in a controlled trial to a commercial multivitamin preparation or placebo and followed up for a median 11 years.

No difference was found between the two groups for any major adverse CVD events, including MI, stroke or cardiac related mortality. It was not effective for both primary and secondary prevention.

Comment: Vitamin supplementation has no beneficial effect in preventing CVD in men. Its value in preventing cancer, eye disease and cognitive decline are forthcoming.

Ref: Sesso H.D. et al JAMA 2012 Nov 7; 308: 1751.

2.15 Does fish consumption or fish oil supplementation decrease cerebrovascular risk?.

Fish consumption and long chain omega 3 fatty acid intake are associated with lower coronary heart disease(CHD) risk. Does this extend to cerebrovascular disease (CeVD)?.

21 prospective cohort studies involving 675,000 participants were assessed for fish consumption and CeVD risk. Compared with <1 servings of fish, 2-4 servings and >5 servings per week was associated with 6% and 12% lower risk resp. In contrast , in 14 prospective studies involving 305,000 participants, there was no association between intake of long chain omega 3 fatty acids and CeVD risk. Typically, oil capsules 1.8gm/day for 3 years was not associated with CeVD risk.

Comment: In this large analysis, larger the **fish** consumption, better the decrease in CeVD risk. This is not true however for **fish oil** consumption.

Ref: Chowdhury R. et al BMJ 2012 Oct 30; 345: e 6698.

2.16 Can explanted implantable cardioverter defibrillators (ICDs) be used in others after the death of the first users?.

Commonly, ICDs are removed from patients because of infection, upgrades or death. These explanted ICDs are discarded, even though they often retain substantial battery life. Researchers report on 81 patients in India with class 1 indications for ICDs who had no resources to buy them and who consented to receive explanted ICDs. The ICDs were explanted in the US, cleaned, transported by researchers or their family in their personal baggage to India and sterilized prior to reimplantation. A total of 106 ICDs were reimplanted in 81 patients. 22 patients received second devices and 3 received 3 devices after the battery life was exhausted. Follow up data were available for 93% of participants with a mean duration of follow up of 28 months. No infectious complications occurred. Overall mortality was 11%. Mean time from 1st implantation to death was 26 months.

Comment: These researchers found that explanted ICDs can be reused safely to help people who otherwise would not be able to afford them.

Ref: Pavri B.B. et al Ann. Intern. Med 2012Oct 16; 157: 542.
Farmer B and Bukhman B IBID : 591.

2.17 Asymptomatic bacteriuria (ASB) – should it be treated?.

Many Physicians treat patients who have ASB, but many studies have confirmed that ASB treatment provides no benefit in many groups, including older people, diabetic patients and those with spinal cord injuries. ASB is defined as a positive urine culture in the absence of urinary symptoms. What about ASB in young women with recurrent UTIs?.

700 premenopausal women with ASB were randomized to receive unblinded treatment or to be followed up without treatment. All participants had experienced at least 1 UTI in the previous year. Those who received oral antibiotics were given the drugs according to the drug sensitivity of the cultural isolates. Most of the bacterial isolates were either E coli (39%) or Enterococcus faecalis (33%).

After 3 months – 3.5% of untreated women and 8.8% of treated women experienced new symptomatic UTIs. The curves continue to diverge and by 1 year, UTI recurrent rates were dramatically higher in the treated group being 24% in the untreated group and 83% in the treated group.

Comment: This study, adds sexually active young women to the list in whome ASB should not be treated. In fact treatment was harmful**. Treatment of ASB is endorsed only during pregnancy and before urinary instrumentation.**

Ref: Cai T. et al Clin Infect. Dis 2012 Sept 15; 55: 771.
Wagenlehner F.M.E. and Naber K.G. IBID :778.

2.18 Is thalidomide(T) of use in idiopathic pulmonary fibrosis (IPF)?.

IPF patients have a disabling not productive cough. 24 patients underwent a double blind crossover trial with T vs placebo for a 12 week period each in random order. During the T phase, patients showed a significant mean improvement in the Cough Quality of Life Questionnaire and in the severity of the cough. Constipation was the commonest side effect.

Comment: T has immunomodulatory and anti- inflammatory properties. It is already being used in the treatment of multiple myeloma. No other effective treatment for the cough of IPF is available. T joins Pirfenidone and N - Acetyl Cysteine as new therapies for IPF. Whether T can slow the progression of IPF is unknown.

Ref: Horton M.R. et al Ann. Intern. Med 2012 Sept 18; 157: 398.

2.19 A new medical treatment for chronic mitral regurgitation (MR) – Beta blockers.

No medical therapy is beneficial in patients with asymptomatic MR before symptoms or evidence of LV dysfunction prompt surgical repair. In a randomized double blind study, investigators assigned 38 patients (average age 55) with moderate to severe MR to receive placebo or metoprolol to a maximum dose of 100mg/d for 2 years. All patients had thickening and prolapse of leaflets, ejection fraction (EF) >55% and NYHA class 1 or 2 symptoms. Cardiac MRI to assess LV geometry was performed at 6 month intervals.

At 2 years, LVEF was unchanged in the metoprolol group but decreased in the placebo group by a mean 5% ($p = 0.006$). LV volume and LV mass remained unchanged in both groups. LV diastolic function declined in the placebo group but improved in the metoprolol group significantly.

Comment: In this pilot study, metoprolol – a Beta 1 adrenergic receptor blocker improved LV function at 2 years in patients with asymptomatic severe MR. Whether it can delay onset of heart failure or need for surgical intervention, may need a longer follow up or a bigger study.

Ref: Ahmed M.I. et al J. Am. Coll. Cardiol. 2012 Aug 28; 60: 833.
Carabello B.A. IBID: 839.

2.20 Are use of PPIs detrimental in decompensated cirrhosis?.

Acid suppressive therapy predisposes users to bacterial overgrowth and bacterial translocation. A previous small study showed that PPIs were associated with higher rates of spontaneous bacterial peritonitis in patients with cirrhosis (Clin. Gastroenterol Hepatol 2012; 10: 422).

In a retrospective cohort study of 4,181 patients in the US Veteran's Health Administration (VHA) database, investigators compared rates of serious infection in 1,905 PPI users vs 248 H2 receptor agonist users in decompensated cirrhosis and compared them with 2,028 non users with decompensated cirrhosis. Serious infection was defined as any infection requiring hospitalization or acid suppression related pneumonia, bacteraemia, C difficile infection and spontaneous bacterial peritonitis.

Compared with non users, PPI users had a higher incidence of serious infections (hazard ratio 1.66) as well as acid suppression related infections (HR 1.75). However, infection rates among H2 receptor antagonists and non users did not differ significantly.

Comment: PPI use but not H2 receptor antagonist use – is associated with risk for serious infections in patients with decompensated cirrhosis. Switching from a PPI to an H2 receptor antagonist in patients who need acid suppression but have decompensated cirrhosis appears to be a reasonable approach.

Ref: Bajaj J.S. et al Aliment. Pharmacol. Ther. 2012 Sept 11.

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