Infection

Radical shorter course of malaria treatment

The only widely available drug that is effective in preventing Plasmodium vivax relapses is primaquine. This is given in 14 day regimens but adherence to this regimen is poor. A randomised, double-blind, placebo-controlled compared the efficacy of the classic 14 day primaquine regimen of 0.5mg/kg/day with a radical 7 day course of primaquine given at a dosage of 1mg/kg/day. Participants included had normal glucose-6-phosphate dehydrogenase profiles and were randomised to either trial setting. The primary endpoint of the study was symptomatic malarial P. vivax parasitaemia within 12 months of follow-up. Patients given the 7 day course had similar outcomes to those randomised to the traditional 14 day course of treatment. A radical shorter course of primaquine is non-inferior to 14 days of treatment in preventing relapses of malaria and may improve adherence to treatment and therefore improve malaria outcomes.

Taylor W, Thriemer K, von Seidlein L, et al. Short-course primaquine for the radical cure of Plasmodium vivax malaria: a multicentre, randomised, placebo-controlled non-inferiority trial. The Lancet 2019. 394; p929-938

Vitamin D deficiency and tuberculosis

It is estimated that up to one-third of the world's population is burdened with tuberculosis (TB). Vitamin D is thought to be an important regulator of the immune system and laboratory studies have demonstrated interaction between vitamin D and the pathogenesis of TB. There is existing literature that identifies a relationship between vitamin D and host susceptibility to TB, but until recently little was known of the impact of low vitamin D levels on the risk of developing TB. A study conducted in Lima, Peru, measured serum vitamin D in individuals considered high risk for TB. Participants (n =6,751) were then followed up and screened for TB at 2, 6 and 12 months after enrolment. Individuals with low levels of vitamin D were found to have a higher risk of future progression to TB disease. A further meta-analysis conducted by the same team showed that the risk of TB disease is highest among HIV-positive individuals with severe vitamin D deficiency. These findings suggest that vitamin D deficiency is a risk factor for developing TB disease. The authors urge further randomised trials to determine if vitamin D supplementation acts to reduce the risk of tuberculosis.

Aibana O, Huang C-C, Aboud S, et al. (2019) Vitamin D status and risk of incident tuberculosis disease: A nested case-control study, systematic review, and individual-participant data meta-analysis. PLoS Med 16(9): e1002907.

Proton pump inhibitors and viral gastroenteritis

The use of proton pump inhibitors (PPI) to reduce gastric acid secretion is common but its long term use is associated with some significant adverse effects including osteoporotic fractures and vitamin B12 deficiency. Some data also suggests that there is an increased risk of respiratory and gastrointestinal bacterial infections associated with continuous PPI use. A study has now looked for association between continuous PPI use and viral origin gastroenteritis. The matched cohort study compared over 233,500 patients receiving continuous PPI therapy with over 626,800 patients not receiving PPI therapy, and adjusted for relative risk of occurrence of acute viral gastroenteritis. Analysis found that during periods of high circulation of enteric viruses, there was a 1.81 times higher risk of infection for those on continuous PPI therapy versus those not on PPI therapy. The authors suggest continuous PPI therapy may be associated with an increased risk of enteric viral infections, perhaps through a mechanism of reduced acid secretion affecting the immune system but this warrants further investigation.

Vilcu A, Sabatte L, Blanchon T, et al. Association Between Acute Gastroenteritis and Continuous Use of Proton Pump Inhibitors During Winter Periods of Highest Circulation of Enteric Viruses. JAMA Netw Open. 2019;2(11):e1916205.

Interventions

Robot-assisted training for post-stroke function

Following stroke, patients may experience upper limb deficits including loss of movement, coordination, sensation and dexterity, all of which can lead to difficulties in activities of daily living. As such, individuals often undergo a regimen of physiotherapy to help improve function. One study has investigated the efficacy of robot-assisted training programmes. The study specifically used the MIT-Manus robotic gym. This was compared with an enhanced upper limb therapy (EULT) programme based on repetitive functional task practice, and with usual care which was based upon local hospital policy but usually consisting of a minimum 45 minutes of therapy, for a minimum of 5 days a week during inpatient stay. The robot-assisted training and EULT programmes were given for 45 minutes, three times a week, for 12 weeks. The study found that robot-assisted training and enhanced upper limb therapy did not improve upper limb function after stroke compared to usual care for patients with moderate or severe upper limb functional limitation. The authors do not support the use of robot-assisted training programmes in this clinical setting.

Rodgers H, Bosomworth H, Krebs H, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. The Lancet 2019; 394: 51–62.

Internet based vestibular rehabilitation

The use of internet based vestibular rehabilitation programmes in treating adults with chronic vestibular syndrome in the general practice setting has been assessed. The clinical efficacy and safety of internet based vestibular rehabilitation (VR) either given alone or with additional physiotherapy support was compared to usual care for adults within the general practice setting with chronic vestibular syndrome in a randomised control trial. Internet VR over a 6 week course of online sessions was given either alone or with face-to-face physiotherapy support. The primary outcome assessed was vestibular symptoms after six months measured by the vertigo symptom-scale short form range. Secondary outcomes included dizziness related impairment, anxiety, and subjective improvement in symptoms after three months and six months. Both standalone and combined internet based VR were clinically effective and safe interventions for treating adults with chronic vestibular syndrome. Online vestibular rehabilitation is easy and accessible for patients and has the potential to improve care for an undertreated population.

van Vugt VA, van der Wouden JC, Essery R, et al. Internet based vestibular rehabilitation with and without physiotherapy support for adults aged 50 and older with a chronic vestibular syndrome in general practice: three-armed randomised controlled trial. BMJ 2019; 367:l5922

3-dimensional virtual reality for surgical planning

Over the last decade there has been an increasing incidence of localised renal cancers diagnosed at stage one and therefore amenable to surgery. Over recent years robotic-assisted partial nephrectomy (RAPN) has been a popular treatment method but it has traditionally relied on surgeons planning the surgery using 2-dimensional imaging modalities. The use of 3-dimensional (3-D) digital imaging planning for RAPN has been shown to improve surgeons understanding of patient anatomy and influence the surgical RAPN plan. Research has now assessed if the surgical outcomes are improved when 3-D virtual reality models are used in the planning of RAPN. The study was a single-blind randomised trial with 92 patients. The assigned surgeon viewed imaging on their smart phone in 3-D and in virtual reality using a headset. The results showed that the use of 3-D virtual reality models helped reduce operative time, estimated blood loss, clamp time, and length of hospital stay. This study demonstrated that the use of 3-D virtual reality models when planning robotic-assisted partial nephrectomies helps improve outcomes.

Shirk JD, Thiel DD, Wallen EM, et al. Effect of 3-Dimensional Virtual Reality Models for Surgical Planning of Robotic-Assisted Partial Nephrectomy on Surgical Outcomes: A Randomized Clinical Trial. JAMA Netw Open. 2019;2(9):e1911598.

Improved blood flow with electronic cigarettes

Electronic cigarette use is increasingly prevalent worldwide. A study has sought to assess the early vascular impact of switching from tobacco cigarettes (TC) to electronic cigarettes (EC) in those with smoking histories. This prospective, randomised control trial included participants who were 18 years and older and who had smoked fifteen or more cigarettes a day for two or more years and were free from established cardiovascular disease. Participants were randomised to EC containing nicotine or not-containing nicotine for one month. Those who did not quit TC were analysed in a parallel arm of the study. Vascular function was assessed by flow-mediated dilation (FMD). Within one month of switching from TC to EC there was a significant improvement in endothelial function and vascular stiffness. Females tended to benefit greater than males when switching to EC from TC. No difference in vascular effects were found between nicotine and non-nicotine containing EC within the time-frame assessed. Long term tobacco cigarette smokers gain significant improvement in vascular health within just one month of switching to electronic cigarettes.

George J, Hussain M, Vadiveloo T, et al. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. J Am Coll Cardiol 2019; doi:10.1016/j.jacc.2019.09.067

Tranexamic acid for traumatic brain injury

Intracranial bleeding following traumatic brain injury (TBI) can occur immediately or after several hours with complications including raised intracranial pressure, brain herniation, and death. We know from previous studies that extracranial bleeds post-TBI benefit from early administration of tranexamic acid which was found to reduce bleeding deaths by a third – however this existing research specifically excluded intracranial bleeds. A study has now investigated if there is any benefit from administering tranexamic acid following TBI in cases of intracranial bleeding. This randomised, placebo-controlled trial ran across 175 hospitals and 29 countries. Participants were those with TBI presenting within 3 hours of injury and a Glasgow Coma Scale score between 12 and 4. Over 9,000 participants were treated within 3 hours of TBI with either tranexamic acid or placebo. Death from head injury was reduced in patients treated with tranexamic acid versus placebo. Additionally, there was no increase in vascular occlusive events or disability in those given tranexamic acid. Both extracranial and intracranial post-traumatic bleeds may benefit from early tranexamic acid.

The CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. The Lancet 2019; 394: p1713-1723

Obs & Gyn

Ursodeoxycholic acid in obstetric cholestasis

Obstetric cholestasis presents with maternal pruritus and increased serum bile concentration and typically resolves postpartum. There are increased risks of preterm birth, meconium stained amniotic fluid, and neonatal unit admission associated with obstetric cholestasis. Additionally, those with high serum bile concentrations of 100 µmol/L and above carry an increased risk of still birth. Ursodeoxycholic acid is known to improve cholestasis in primary biliary cholangitis among other diseases and it helps with relieving pruritus. However, despite its prevalent use for treating obstetric cholestasis, the evidence base for reducing adverse outcomes is limited. A large, double-blind, multicentre, randomised placebo-controlled study that was set across 33 maternity units found that treatment of obstetric cholestasis with ursodeoxycholic acid does not reduce adverse perinatal outcomes. There was no reduction in stillbirth or spontaneous preterm birth. Additionally, there was no reduction in neonatal unit admission. Importantly, there was no clinically meaningful effect on maternal itch symptoms. The authors conclude that ursodeoxycholic acid does not have any significant clinical benefit when used routinely for women with obstetric cholestasis.

Chappell L, Bell J, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. The Lancet 2019; 394: 849–60

Laparoscopic hysterectomy for heavy menstrual bleed

Heavy menstrual bleeding can have a significant effect on a woman's life. Medical treatment is first line but has a high failure rate and subsequently many women are referred onto surgery for more definitive management. The main surgical options include endometrial ablation and hysterectomy. Previous studies have shown that conventional hysterectomy is the optimal surgical management of heavy menstrual bleeding but it is invasive and carries more risks. A trial has now assessed if less-invasive laparoscopic supracervical hysterectomy is effective versus endometrial ablation. Participants were women younger than 50 who had been referred for surgical management of heavy menstrual bleeding who were then randomly allocated to receive either laparoscopic supracervical hysterectomy or endometrial ablation. The laparoscopic approach to hysterectomy was still more effective than endometrial ablation but did not increase surgical risk. Participants receiving the laparoscopic supracervical

hysterectomy were both significantly more satisfied and had a greater quality of life following the procedure versus the endometrial ablation group. Serious adverse events were low and similar for both procedures.

Cooper K, Breeman S, Scott N, et al. Laparoscopic supracervical hysterectomy versus endometrial ablation for women with heavy menstrual bleeding (HEALTH): a parallel-group, open-label, randomised controlled trial. The Lancet 2019; 394:p1425-1436

Supine sleeping associated with low birth weight

A supine sleeping position in the third trimester is associated with reduced uterine blood flow as well as an increased risk of late stillbirth. Reduced uterine blood flow is also associated with foetal growth restriction. A study has now explored if there is any association between the sleeping position of pregnant women and infant birth weight. Participants were women at 28 weeks' gestation or more who were then separated into groups based on their sleeping position over the last 4 weeks resulting in the supine sleeping category and the non-supine sleeping category. Women were followed up until birth and birth weight of infants were recorded. The study revealed that going to sleep in the supine position in late pregnancy was significantly and independently associated with reduced birthweight and birth weight centile. The authors advocate campaigns to encourage women in the third trimester of pregnancy to sleep on their sides to help optimise birth weight.

Anderson NH, Gordon A, Li M, et al. Association of Supine Going-to-Sleep Position in Late Pregnancy With Reduced Birth Weight: A Secondary Analysis of an Individual Participant Data Meta-analysis. JAMA Netw Open. 2019;2(10):e1912614.

Induction of labour at 41 versus 42 weeks

Adverse perinatal outcomes and increased risk of stillbirth are known to increase after 40 week's gestation. A study has investigated the difference in perinatal and maternal outcomes according to date of induction. The study was set across 14 hospitals in Sweden and women with uncomplicated singleton pregnancies (n=2760) were randomly assigned induction at 41 weeks or expectant management and induction of labour at 42 week's gestation. There were no perinatal deaths in the induction group but the expectant group experienced five stillbirths and one early neonatal death (p=0.03). The study was subsequently stopped early due to a significantly higher rate of perinatal mortality within the expectant management group. Overall analysis revealed reduced perinatal mortality and no increase in adverse maternal outcomes for those randomised to 41 weeks induction versus expectant management and induction at 42 weeks. The authors argue that induction should be offered at no later than at 41 weeks to help reduce complications such as stillbirth.

Wennerholm UB, Saltvedt S, Wessberg A, et al. Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Post-term Induction Study, SWEPIS): multicentre, open label, randomised, superiority trial. BMJ 2019; 367 :l6131

Pregnancy duration and endometrial cancer

Endometrial cancer is the commonest gynaecological cancer in developed countries. Pregnancy is said to be protective against endometrial cancer likely due to the effect of suppressing menstrual cycle exposure for a period of time. Little is known about the effect of duration of pregnancy on endometrial cancer risk and so a study has set out to explore this association. The study measured relative risk of endometrial cancer by pregnancy type, number and duration using data from over 2.3 million Danish women, including nearly 4 million total pregnancies. Analysis found that the risk of endometrial cancer was reduced regardless of whether a pregnancy ended shortly after conception, such as through miscarriage or termination, or whether it was continued to 40 weeks of gestation. The authors discuss whether this effect is due to biological processes occurring within the first week or so following conception. There is a protective association between pregnancy and endometrial cancer regardless of duration and outcome of pregnancy.

Husby A, Wohlfahrt J, Melbye M. Pregnancy duration and endometrial cancer risk: nationwide cohort study. BMJ 2019; 366 :l4693

Paedriatrics

Rotavirus vaccine not linked to intussusception

Intussusception is a life threatening condition in children and neonates. The rotavirus vaccine is credited with significantly reducing the occurrence and severity of rotavirus-related gastroenteritis and mortality in children. However, the evidence base for this is somewhat controversial. This is because efficacy of the vaccine has been placed between 36% and 96%. Additionally, there is some research that suggests the rotavirus vaccine may increase risk of intussusception. Again, this existing research is controversial. A systematic review and meta-analysis has now analysed randomised clinical trials of neonates and infants and compared outcomes of intussusception rates after the vaccine or after placebo. The study included results from over 200,000 participants across 33 countries. The various forms of rotavirus vaccine were not associated with an increased risk in intussusception when compared to placebo at 2 years post-vaccination in neonates or infants. The authors argue that the potential benefits of the rotavirus vaccine outweigh any risk of intussusception.

Lu H, Ding Y, Goyal H, Xu H. Association Between Rotavirus Vaccination and Risk of Intussusception Among Neonates and Infants: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(10):e1912458.

Biomarker for necrotising enterocolitis

Necrotising enterocolitis (NEC) is a common neonatal gastrointestinal emergency with a high mortality rate and long-term complications. Current diagnostic use of abdominal x-ray and blood cultures causes diagnostic overlap of NEC with sepsis which can be troublesome as both are managed differently. The search for a robust biomarker for NEC has found that intestinal alkaline phosphatase (IAP) may be of interest. The goal of this study was to assess if IAP could be used as a biomarker specific for NEC and not associated with sepsis. The trial enrolled 136 premature infants across 3 hospitals and stool samples were collected between 24 and 40 or more weeks post-conceptual age. Stool samples were assessed for enzyme activity and abundance of IAP. This diagnostic study found that both high amounts of IAP protein in stool and low IAP enzyme activity were associated with a diagnosis of NEC. Importantly, there was no association of non-gastrointestinal tract infections with this biochemical pattern which allows NEC to be distinguished from sepsis.

Heath M, Buckley R, Gerber Z, et al. Association of Intestinal Alkaline Phosphatase With Necrotizing Enterocolitis Among Premature Infants. JAMA Netw Open. 2019;2(11):e1914996.

Chorioamnionitis and respiratory outcomes in preterm infants

Bronchopulmonary dysplasia is a chronic lung disease that remains one of the commonest complications of very preterm birth. A systematic review, meta-analysis and meta-regression study has now highlighted a very important link between bronchopulmonary dysplasia (BPD) with chorioamnionitis in preterm infants. BPD was defined as supplemental oxygen requirement at 28 days postnatal (BP28) or at postmenstrual age of 36 weeks (BPD36). Analysis revealed a significant association between both BPD28 and BPD36 with chorioamnionitis exposure. Additionally, there were significant differences found between infants exposed to chorioamnionitis and those not exposed with regards to gestational age, birth weight, small for gestational age, exposure to antenatal corticosteroids, and both early- and late- onset sepsis. Interestingly, chorioamnionitis was not significantly associated with respiratory distress syndrome. Preterm infants exposed to chorioamnionitis have a higher risk of developing bronchopulmonary dysplasia.

Villamor-Martinez E, Álvarez-Fuente M, Ghazi AMT, et al. Association of Chorioamnionitis With Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review, Meta-analysis, and Metaregression. JAMA Netw Open. 2019;2(11):e1914611.

Metformin versus insulin exposure and growth

Gestational diabetes mellitus (GDM) is a common pregnancy complication known to have adverse outcomes for both the mother and infant. Both insulin and metformin may be used as agents to reduce blood sugar levels in expectant mother. A systematic review of 28 studies compared outcomes on weight and growth of infants born from women treated for GDM with either metformin or insulin. Infants born from mothers taking metformin weighed just over 100g less at birth than those born from mothers treated with insulin during pregnancy and had a lower risk of being born large for gestation (>90th centile) at delivery. However, metformin-exposed infants were 0.44 kg heavier by 24 months than insulin-exposed infants and by mid-childhood (5-9 years) metformin-exposed children had a higher body mass index than those exposed to insulin. It is known that infants who are born small and then experience catch-up growth are at increased risk of cardiovascular disease in later life and now the authors urge further understanding if this risk applies to infants exposed to metformin.

Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis. PLoS Med 2019;16(8): e1002848.

Misc

Physician depression and medical errors

Medical errors are a major source of morbidity and financial loss and account for a large amount of preventable patient deaths annually. A new study has looked at the association between depressive symptoms in doctors and risk of medical errors. The research consisted of a systematic review and meta-analysis of 11 studies involving over 21,500 doctors. The overall relative risk (RR) for medical errors among doctors with a positive screening for depression was 1.95. The study also found that an event of medical error increases RR for physician depressive symptoms subsequent to the event (RR 1.67). These results suggest there is a bidirectional association between depressive symptoms in doctors and medical errors, with a stronger associated seen for depressive symptoms with increase in subsequent medical error. The authors urge for further research to evaluate if interventions aimed at reducing physician depressive symptoms might mitigate this risk, improve physician well-being, and patient outcomes.

Pereira-Lima K, Mata DA, Loureiro SR, et al. Association Between Physician Depressive Symptoms and Medical Errors: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(11):e1916097.

Citation of retracted research

There is some discussion around how retracted scientific research is cited in ongoing literature, and with whom the responsibility lies with to ensure future works citing the retracted research also inform readers of its retraction. Using the controversial and now retracted article by Wakefield et al as an example, a study has examined the characteristics of citations from new literature to investigate whether authors accurately cite retracted references. This particular research was infamous for falsely linking the measles, mumps and rubella (MMR) vaccine to an increased risk of autism spectrum disorder and was subsequently linked with a drop in vaccination uptake rates. A cross-sectional bibliographic analysis took place assessing over 1,150 works citing the paper in question since its retraction in 2010. The study found that a significant number of articles citing the work did not indicate that the article had been retracted. These findings suggest improvements are needed from publishers, databases, and citation management software to ensure that retracted articles are somehow accurately documented.

Suelzer EM, Deal J, Hanus KL, et al. Assessment of Citations of the Retracted Article by Wakefield et al With Fraudulent Claims of an Association Between Vaccination and Autism. JAMA Netw Open. 2019;2(11):e1915552.

Social contact and risk of dementia

The population is ageing and as such we are seeing rising numbers of people with dementia. Identifying risk factors of developing dementia is becoming more important so that prevention efforts can be properly implemented. Retrospective analysis form participants of the Whitehall II longitudinal prospective cohort study has looked at the effect of social contact on dementia risk. Participants completed cognitive tests at five points between 1997 and 2016 and were asked about social contact at six points between 1985 and 2013. Those with a greater frequency of social contact at 60 years of age had an associated lower risk of developing dementia. Interestingly, this link was seen with social contact directed through friends rather than relatives. Frequent social contact during early and midlife may build cognitive reserve, which is maintained and delays or prevents the expression of dementia. The authors also offer an alternative explanation for this association, whereby early cognitive differences may affect individual's subsequent ability to establish and maintain social relationships and may increase susceptibility to dementia.

Sommerlad A, Sabia S, Singh-Manoux A, et al. Association of social contact with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. PLoS Med 2019;16(8): e1002862.