JOURNAL CLUB SUMMARIES

What's hot that the other lot got

Piers Dixey

Despite clear evidence of safety of titrated oxygen therapy in critical illness, patients are frequently treated in the initial presentation with high inspired oxygen fractions (FiO_2). The Hyper2S trial, design to assess the role of hyperoxia (FiO_2 1.0 vs titrated FiO_2 for SpO_2 88–95% in first 24 hours) and hypertonic saline in the management of septic shock was stopped early due to high mortality in the hyperoxia group. Demiselle *et al* (*Ann Int Care* 2018;8:90) report a post hoc analysis of patients from the Hyper2S trial selected by the sepsis-3 criteria (septic shock requiring vasopressor support despite adequate fluid resuscitation with a lactaemia; >2 mmol/L). Three hundred and ninety-seven out of 442 patients had available lactate levels with 230 of those patients meeting the sepsis-3 definition (122 normoxia, 108 hyperoxia). As expected, patients with lactaemia were more unwell (higher Sequential OrganFailure Assessment core and Simplified Acute Physiology Score II, with more need for organ support) than those without lactaemia. There was a numerically higher mortality at 28 days in hyperoxia compared with normoxia patients (57% vs 44%), with hyperoxia demonstrating a significant impact on mortality in the multivariate analysis at both 28 (HR 1.79, 95% CI 1.21 to 2.63, p<0.003) and 90 (HR 1.57, 95% CI 1.09 to 2.28, p=0.016) days. The results further strengthen the argument against unregulated high flow oxygen in critical illness and for judicious use of targeted oxygen supplementation.

INITIAL INHALED THERAPY IN COPD: WHERE TO START?

Few data are available directly comparing different inhaled therapies at the initial treatment decision in patients with COPD. Suissa and colleagues (*Lancet Resp Med* doi:10.1016/s2213-2600(18)30368-0) used a primary care database to identify initial prescribed bronchodilator therapy in patients with COPD. Patients with a long-acting beta-agonist-inhaled corticosteroid (LABA-ICS) were matched to those prescribed a long-acting muscarinic-agonist (LAMA). The cohort was stratified by eosinophil count (<2%, 2–4% and >4%) and analysed for the rate of moderate or severe exacerbations of COPD. Twelve thousand three hundred and sixty-six patients initiated on LAMA therapy were matched to 12 366 patients on LABA-ICS. Despite matching, the cohorts differed in rates of comorbid asthma (LABA-ICS 44%; LAMA 33%) and current smoking status (LABA-ICS 86%; LAMA 93%) but were otherwise well matched for established covariates. The rates of moderate to severe exacerbations were similar in both groups at low (<2% HR 1.03, 95%CI 0.93 to 1.13) and moderate (2–4% HR 1.00, 95% CI 0.91 to 1.10) eosinophil levels. Whereas at high eosinophil levels, there was a lower rate of exacerbations in patients receiving LABA-ICS compared with LAMA (HR 0.79, 95% CI 0.70 to 0.88). However, there was an elevated risk of hospitalisation due to pneumonia in those initiated on LABA-ICS rather than LAMA (HR 1.37, 95% CI 1.17 to 1.60) albeit slightly diminished at higher eosinophil counts. The study provides further support for personalised medicine when making treatment decisions in patients with COPD.

AMOXICILLIN FOR NON-SEVERE PNEUMONIA IN CHILDREN IN MALAWI

The WHO recommendation is for treatment of non-severe fast breathing pneumonia in children with Amoxicillin. The benefits of this treatment are unclear in healthcare settings with endemic malaria when the majority of patients have a non-bacterial aetiology. Ginsburg and colleagues (*JAMA Pediatr.* 2019;173(1):21-28. doi:10.1001/jamapediatrics.2018.34.3407) present a well-conducted placebo-controlled clinical trial powered to assess the non-inferiority of placebo compared with 3 days of amoxicillin on treatment failure at day 4 in children aged 2–59 months admitted to hospital for treatment of non-severe fast breathing pneumonia in Malawi, a malaria endemic area. One thousand one hundred and twenty-six children (564 amoxicillin, 562 placebo) were randomised and were well matched for important confounders including markers of pneumonia severity. The trial was stopped early by the data monitoring committee due to the higher treatment failure rate in the placebo group. By day 4, treatment failure was 4% in the amoxicillin group and 7% in the placebo group (RR 1.78, 95% CI 1.07 to 2.97 and absolute risk difference 3.0%, 95% CI 0.4 to 5.7%) However, by day 14, there was no significant difference in treatment failure rate (RR 1.16, 95% CI 0.83 to 1.63). The proportion of patients with at least one serious adverse event by day 14 was higher in the placebo group than the amoxicillin group (9.6% vs 7.8%). While the study highlights the efficacy of amoxicillin in this group, the majority of patients recovered with placebo alone with a number needed to treat of between 18 and 250 to prevent one treatment failure at day 4 and with no definitive benefit by day 14 suggesting only a subpopulation of the trial required therapy. It would therefore be beneficial if simple tools that could be implemented in a low economic setting were available that would allow identification of children with non-severe fast breathing pneumonia most likely to benefit from treatment. This would facilitate a reduction in overall antibiotic use and thus aid attempts to tackle antibiotic resistance.

TREATMENT OF LATENT TB IN CHILDREN: SHORTER COURSE OF RIFAMPICIN IS AN EASIER PILL TO SWALLOW

The treatment of latent TB is an important step in the control of TB worldwide. However, while effective, the treatment regimens are long impacting on completion rates. Diallo *et al* (*NEJM* 2018;379:454) investigated the safety of a shortened (3 month) rifampicin regimen compared with the recommended 9-month isoniazid course in children. Trial medication was administered by parents or caregivers. Drugs were dosed according to WHO age-based recommendations. The trial was designed as an open label non-inferiority randomised trial in children with latent TB in a mix of developing and developed nations primarily examining adverse event rate. Eight hundred and forty-four children were randomised, with outcome data

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available on 422 in the rifampicin and 407 in the isoniazid group. No adverse events leading to trial drug discontinuation occurred in either group, much lower than the corresponding data for adults. The shorter rifampicin regimen was associated with significantly higher completion rates (81% vs 76%; adjusted difference 13.4%, 95% CI 7.5 to 19.3%) and a lower discontinuation rate due to patient choice (11% vs 19%; adjusted difference −12%, 95% CI −17 to −7%). There were only two cases of confirmed TB during the 16-month follow-up period both occurring in the isoniazid group. The trial confirms that both treatment regimens for latent TB are safe, but the shorter rifampicin course is associated with better completion rates and raised no safety concerns. The trial did not enrol under 5s or those with HIV co-infection and should therefore not be extrapolated to these populations.

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