JOURNAL CLUB

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BIOMARKERS FOR VENTILATOR-ASSOCIATED PNEUMONIA: CHANGING PRACTICE IS THE HARDEST PART

Ventilator-associated pneumonia (VAP) is frequently misdiagnosed, leading to unnecessary antibiotic use and emerging antimicrobial resistance. A combination of low interleukin (IL)-1β and IL-8 in bronchoalveolar lavage (BAL) fluid has been validated as a biomarker for the exclusion of VAP. The VAPrapid2 trial (Hellyer, *Lancet Resp Med* 2019: doi.org/10.1016/S2213-2600(19)30367-4) aimed to evaluate if the addition of this test to clinical practice would reduce antibiotic exposure in patients with suspected VAP. In this multicentre randomised controlled trial, intensive care unit (ICU) patients with suspected VAP were randomised (1:1) to biomarker guided (n=104), or routine use of antibiotics (n=106). A diagnostic BAL was performed. For the intervention group, guidance to discontinue antibiotics was issued to clinicians if BAL biomarker results were below a previously determined threshold, with prescribing decisions remaining at the clinician's discretion. A process evaluation determined behavioural components to antibiotic prescribing. There was no significant difference in the distribution of antibiotic free days, 7 days post BAL (primary outcome), between groups, in the intention-to-treat analysis (p=0.58). In cases of biomarker-excluded VAP (n=17), the recommendation to discontinue antibiotics was only followed in four (24%) of the cases. Clinicians' concern of ongoing VAP was the most common reason to continue antibiotics, despite exclusion with a high sensitivity test, demonstrating how established prescribing practices impact on antibiotic use in an ICU setting.

EFFICACY OF OSELTAMIVIR FOR INFLUENZA-LIKE ILLNESS IN PRIMARY CARE: WHAT DIFFERENCE DOES A DAY MAKE?

Antiviral treatment for suspected (or confirmed) influenza is recommended for those with high-risk features but is not routinely used in primary care. Previous efficacy data does not represent a primary care population. Butler *et al* (*Lancet* 2019: doi.org/10.1016/S0140-6736(19)32982-4) conducted an open-label, pragmatic, randomised controlled trial, in which patients 1 year and older, presenting to primary care with an influenza-like illness, across 15 European countries, were randomised to receive usual care (n=1637), or usual care plus oseltamivir (n=1629). The primary endpoint was self-reported time to recovery, defined as return to normal activities with absence, or minor influenza-type symptoms. For all patients, recovery was faster with the addition of oseltamivir (HR 1.29, 95% Bayesian credible interval (BCrI) 1.20 to 1.39). The estimated mean benefit was 1.02 days (BCrI 0.74 to 1.31). Subgroup analysis demonstrated particular benefit in patients ≥65 years, with comorbidities, severe illness and longer illness duration prior to presentation (HR 3.20, 95% BCrI 1.00 to 5.50) with a mean benefit of 2.3 to 3.2 days. The effect appeared independent of influenza status (confirmed by nasal swab polymerase chain reaction). Treatment initiation led to faster recovery in a primary care population up to 72 hours after illness onset, but more cases of nausea and vomiting were reported. Consideration must be given to the medicalisation of a mostly self-limiting illness.

SCREENING FOR LATENT TUBERCULOSIS INFECTION: IMPROVING ACCESS FOR HIGH-RISK GROUPS

Asylum seekers from countries with a high tuberculosis (TB) burden have greater risk of TB disease following arrival in the host country. Active TB case finding with chest radiography has been used in the Netherlands, but outcomes have been suboptimal. Screening for latent TB infection (LTBI) is an alternative approach. This mixed methods study by Spruijt *et al* (*Eur Respir J* 2019; 54:1900861) aimed to establish feasibility and effectiveness. Asylum seekers from countries with a TB incidence >200 per 10 000, with no history of active/latent TB, were screened. LTBI was confirmed with an interferon-γ release assay ≥0.35 IU·ml^{-1} Patients were offered 3 months of rifampicin/isoniazid combination therapy free of charge. To enhance uptake, education was provided and delivered alongside professional interpreters. 719 people were screened (62% coverage) of which 178 (25%) were diagnosed with LTBI, 149 (84%) commenced and 129 (87%) completed treatment. Four patients had active TB, however 95 additional patients reported symptoms of active TB, but were not investigated further in breach of trial protocol. A qualitative assessment highlighted the importance of the education and language specific advocates to encourage participation and adherence. Identified barriers included relocation of asylum seekers into the community. High quality care and collaboration with supporting organisations could result in effective screening for LTBI in this vulnerable population.

A NEW ANTIBIOTIC COMBINATION THERAPY FOR TUBERCULOSIS: IMPROVING EFFICACY IN EARLY PHASE TREATMENT

The burden of standard TB treatment (6 months of isoniazid and rifampicin, alongside 2 months of pyrazinamide and ethambutol; HRZE) is prolonged by drug resistance. This multicentre phase 2b trial (*Lancet Respir Med* 2019;7:1048–58) across Southern and Eastern Africa, determined the efficacy of an 8 week novel regimen. Patients with smear positive, drug susceptible pulmonary TB were randomly assigned to pyrazinamide, pretomanid and bedaquiline (BPaZ), with two experimental bedaquiline doses: 400 mg one time per day for 14 days and 200 mg three times per week for 6 weeks (B_{load} PaZ; n=57) or 200 mg once daily (B_{200} PaZ; n=56) compared with HRZE (n=59). There was a significant difference in bactericidal activity of BPaZ compared with HRZE. B_{200}PaZ showed the highest cumulative percentage of culture negativity in liquid culture over 0 to 56 days (5.17% (95% BCrI 4.61 to 5.77)), followed by B_{load} PaZ (4.87% (95% BCrI 4.31 to 5.47)) and HRZE (4.04% (95% BCrI 3.67 to 4.42)). There was no significant difference in adverse events between groups. The regimens were well tolerated with no treatment related deaths but derangement of liver enzymes resulted in treatment cessation for 10 patients, five (8%) receiving B_{load} PaZ, three (5%) receiving B_{200}PaZ and two (3%) receiving HRZE. This novel regimen could shorten treatment duration and improve adherence; however, phase 3 trials are needed to assess treatment outcomes.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite McLenaghan D. *Thorax* 2020;**75**:436.

Thorax 2020;**75**:436.
doi:10.1136/thoraxjnl-2020-214800

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