to its poor in vitro activity against M. kansasii. Improved therapeutic regimens for this pathogen would be useful. The purpose of the present study was to evaluate the comparative in vitro activities of TR-1710, a new pyrimidoindole DNA gyraseB inhibitor, and moxifloxacin, a GyrA inhibitor, against twenty two isolates of M. kansasii. It is unlikely that cross resistance will be a problem with gyrase inhibitors targeting different enzyme subunits.

Methods & Materials: TR-1710 and moxifloxacin were obtained from Cubist Pharmaceuticals (San Diego, CA) and Bayer Pharmaceuticals (West Haven, CT) respectively. These compounds were dissolved in DMSO to a concentration of 1 mg/ml prior to freezing at -200C. They were tested in Middlebrook 7H9 broth, pH6.6 supplemented with 10% Middlebrook albumin-dextrose-catalase enrichment at 2 μg/ml – 0.002 μg/ml in polystyrene 96-well round-bottom microtiter plates. To each well, 50 μl of mycobacterial cell suspension was added to yield an initial concentration of about 1 x 105 CFU/ml (range for various isolates tested was 3.8 x103 – 1.2 x 106CFU/ml). Plates were incubated at 370C in ambient air for 7 - 10 days prior to reading.

Results: TR-1710 and moxifloxacin had similar activities against M. kansasii in vitro. The MIC50/MIC90 (μg/ml) of TR-1710 and moxifloxacin were 0.03/0.06 and 0.06/0.50 respectively.

Conclusion: Based on TR-1710's promising in vitro activity, it would be interesting to evaluate the comparative activities of TR-1710 and moxifloxacin in a murine model of M. kansasii infection, as the next step in defining the potential of gyrase inhibitors in the treatment of these infections in humans.

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Do renin-angiotensin-aldosteron system inhibitors protect kidneys during vancomycin administration?

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Background: Vancomycin is widely used for treatment of MRSA infection. For safe use of vancomycin, it is important to employ the therapeutic drug monitoring, although renal function can get worse even by maintaining the safe concentration of vancomycin. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are antihypertensives which are known to block renin-angiotensin-aldosteron system and to have renal protecting effect. However, there has been no study investigating the effect of ACEIs or ARBs on renal protection during vancomycin administration. In this study we investigated the influence of ACEIs or ARBs on renal function during the vancomycin administration.

Methods & Materials: All the hospitalized patients who receive vancomycin intravenously in the department of internal medicine in the Teikyo University hospital from September 2010 to February 2013 were enrolled. Patients who received other potential nephrotoxic agents, those who stopped receiving vancomycin due to other reason than renal dysfunction, or those who died during the treatment were excluded. All the patients were divided into three groups; ACEI/ARB groups, other antihypertensive group, and non-antihypertensive group. Clinical backgrounds, trough vancomycin concentrations, and changes of estimated glomerular filtration rates (eGFRs) were compared by reviewing medical records. Acute kidney injury (AKI) was defined as increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline.

Results: Thirty one patients were enrolled in this study. ACEI/ARB group were nine, other antihypertensive group were nine, and non-antihypertensive groups were 13. Among clinical backgrounds, only the ratio of hypertension was lower in the non-hypertensive group than in the other two groups. Mean trough vancomycin concentrations were not different between the three groups (15.3 vs 16.0 vs 14.7 μg/mL, P=0.86). Mean eGFRs at the vancomycin initiation and at the vancomycin termination were not statistically different between the three groups (59.0 vs 57.4 vs 58.8 mL/min/1.73m2, P=0.61; 60.5 vs 57.1 vs 57.2 mL/min/1.73m2, P=0.80, respectively). The ratio of AKI was not statistically different between the three groups (3/9 vs 1/9 vs 1/13, P=0.24).

Conclusion: ACEIs or ARBs did not protect renal function during vancomycin administration.

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Nitroxoline for treatment of uncomplicated UTI: IPD meta-analysis of four controlled clinical studies

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Background: Nitroxoline, a hydroxychinolin derivate, is used for many years for treatment of urinary tract infections (UTI). Four controlled clinical studies concerning treatment of uncomplicated UTI (uUTI) not published yet were meta-analysed.

Methods & Materials: The individual patient data (IPD) of 466 females with acute sporadic or acute episodes of recurrent uUTI of four prospective, controlled, single blind, randomized clinical studies with similar protocols using nitroxoline (250 mg tid) versus cotrimoxazole (960 mg bid) or norfloxacin (400 mg bid) as controls for five (three studies) or ten (one study) days were meta-analysed by the same criteria. The primary efficacy was the eradication of bacteriuria. Success was defined if pretreatment bacteriuria of $\geq 10^5$CFU/ml was reduced to < 10^4CFU/ml 7-13 days after end of therapy (test of cure). Clinical efficacy was determined by elimination of symptoms and safety by adverse events and laboratory tests.

Results: A total of 234 patients were treated orally with nitroxoline and 232 with the controls. The safety of nitroxoline was very good and comparable to the controls (total adverse events 9.4% vs 7.8%). In the modified microbiological ITT set (at least one outcome result available), in the PP set (test of cure outcome available) and in the modified PP set (missing test of cure rated failure) more than 90% of the patients showed eradication of bacteriuria with nitroxoline, which also met statistical non-inferiority compared to the controls (10% non-inferiority margin) in all three evaluation sets.

The clinical efficacy (reduction of symptoms, global assessment by patient and physician) was similar between the two treatment groups.

Conclusion: The IPD meta-analysis using objective parameters (elimination of bacteriuria) demonstrated equivalent efficacy (non-inferiority) of nitroxoline with the controls tested (cotrimoxazole, norfloxacin) in the treatment of uUTI. With a five (sporadic uUTI) or ten day (recurrent uUTI) therapy elimination of bacteriuria can be achieved in over 90% of the patients. Considering the good safety and efficacy of nitroxoline and the world wide increase of resistance of uropathogens against cotrimoxazole and fluoroquinolones, but not against nitroxoline within the last 20 years, nitroxoline should be reconsidered as one of the first line antibiotics for the treatment of uUTI.

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Repurposing avermectins as new potential TB therapies

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Background: Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. Co-infection with HIV and the emergence of drug-resistant *Mycobacterium tuberculosis* strains (MDR-and XDR-TB) has reaffirmed TB as a global public health threat. New therapies are urgently needed. An alternative approach to generate new TB treatment options in a timely and cost-effective manner is "repurposing" clinically used drugs with known pharmaceutical properties. In the course of a screening program [PMID: 21576426], we identified the *in vitro* anti-tuberculosis activity of the anthelmintic avermectins (ivermectin, selamectin, moxidectin and doramectin) [PMID: 23165468].

Methods & Materials: We performed a literature search on the pharmacological properties of the avermectins. We integrated this information with our *in vitro* data and calculated a theoretical pharmacodynamic value (AUC/MIC; a measure of drug exposure) to define potential *in vivo* efficacy. We validated our analysis by evaluating avermectins in an *in vivo* model of *M. tuberculosis* infection.

Results: An AUC/MIC ratio of 10 to 15 was calculated for bactericidal activity of the avermectins. Due to tolerability and pharmacokinetic issues the low maximal plasma concentrations of ivermectin (ng/mL range) resulted in a low calculated exposure (AUC/MIC < 1). Moxidectin had a longer half-life than ivermectin and, therefore, the calculated AUC/MIC ratios increased. However, this was still not enough to provide theoretical *in vivo* activity. In contrast, selamectin's pharmacokinetic properties suggest that it might be effective *in vivo* against *M. tuberculosis*; high plasma concentrations (μg/mL range), low toxicity (LD_{50} >1,600 mg/kg bw), and theoretical AUC/MIC ratios are consistent with potential *in vivo* activity. Interestingly, reported concentrations of selamectin in the lungs (the main site where *M. tuberculosis* resides) were ca. 2-fold higher than in plasma, suggesting even higher AUC/MIC ratios at the site of infection. We therefore tested ivermectin and selamectin for *in vivo* activity against *M. tuberculosis*. Our predictions were consistent with the *in vivo* data; while ivermectin at the highest possible safe dose did not have anti-mycobacterial activity in vivo, selamectin was active.

Conclusion: This theoretical data analysis supports the potential of selamectin for TB therapy, including MDR- and XDR-TB, and warrant further *in vivo* testing in mouse infection models.

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The life saving little tip: Intraosseous gas

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Background: Emphysematous osteomyelitis is a rare but fulminant disease. Therefore, radiologists should be aware of the implication of intraosseous gas signs for quick diagnosis.

Methods & Materials: Case: A 55-year-old woman with diabetes mellitus and hypertension was admitted to the emergency department and presented with high fever (40 °C), nausea, and pelvic pain. Physical examination revealed pelvic and pubic tenderness on deep palpation. Laboratory data included leukocytosis (12390/mm3 with 85.5% neutrophilis), high procalcitonin (33.8 ng/ml), C-reactiveprotein (211 mg/dl) levels, a high sedimentation rate (80 mm/h), also elevated blood sugar (290 mg/dl), and elevated hemoglobin A1C level (13.4%). Blood cultures were obtained prior to the initiation of antimicrobial therapy.

Abdominal ultrasonographic examination revealed cholelithiasis without gallbladder wall thickening and a small amount of isolated pelvic free fluid. A subsequent CT of her abdomen and pelvis showed multiple gas bubbles in the medullary cavity of the bilateral pubic bones, extending into the anterior acetabulum. A moderate amount of gas was seen in the soft tissues surrounding the pubis. Also, marked subcutaneous reticulation and low attenuation areas of subcutaneous gas were detected in the right gluteal region. MRI confirmed the CT findings and provided clearer images of the small abscess formations and the peripubic soft tissue component of the infection. CT-guided biopsy of prepubic soft tissue collection was performed, and *Escherichia coli* was cultured from the diagnostic specimen.

Results: Intravenosus (IV) imipenem cilastatin (4 × 500 mg) and vancomycin (2 × 1 g) was started as an empirical treatment. The patient underwent urgent surgical debridement of the soft tissue abscess. All samples (biopsy–surgical specimens and blood cultures) revealed a monomicrobial growth of E. coli. Intravenosus ciprofloxacin (2 × 400 mg) was started based on the antibiogram results. The first 3 weeks of treatment was completed as IV therapy. The patient was discharged with oral antibiotic treatment (ciprofloxacin 2 × 750 mg). The patient's treatment was completed in 6 weeks. No complications were seen and she continues to be followed up.