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TB Clinic

Evidence Update

February 2018 (Quarterly)

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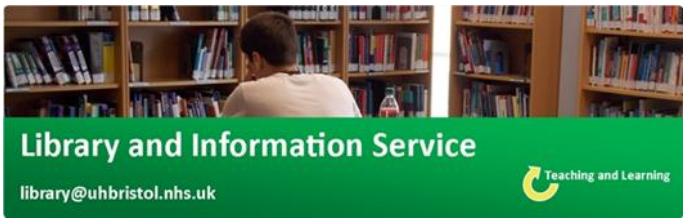

Training Calendar 2018

February (12.00-13.00)

1st (Thu)	Literature Searching
9th (Fri)	Critical Appraisal
12th (Mon)	Statistics
20th (Tue)	Literature Searching
28th (Wed)	Critical Appraisal

March (13.00-14.00)

8th (Thu)	Statistics
12th (Mon)	Literature Searching
20th (Tue)	Critical Appraisal
28th (wed)	Statistics

April (12.00-13.00)

5th (Thu)	Literature Searching
9th (Mon)	Critical Appraisal
17th (Tue)	Statistics
25th (Wed)	Literature Searching

Your Outreach Librarian: Jo Hooper

Whatever your information needs, the library is here to help. As your outreach librarian I offer **literature searching services** as well as training and guidance in **searching the evidence** and **critical appraisal** – just email me at library@uhbristol.nhs.uk

OUTREACH: Your Outreach Librarian can help facilitate evidence-based practise for all in the Orthopaedics team, as well as assisting with academic study and research. We can help with **literature searching, obtaining journal articles and books**, and setting up individual **current awareness alerts**. We also offer one-to-one or small group training in **literature searching, accessing electronic journals, and critical appraisal**. Get in touch: library@uhbristol.nhs.uk

LITERATURE SEARCHING: We provide a literature searching service for any library member. For those embarking on their own research it is advisable to book some time with one of the librarians for a one-to-one session where we can guide you through the process of creating a well-focused literature research and introduce you to the health databases access via NHS Evidence.

Contents

Updates

NICE National Institute for Health and Care Excellence

SMI B 40: Investigation of specimens for Mycobacterium species [PDF] Source: GOV UK - Source: Public Health England - 23 January 2018 - Publisher: Public Health England

WHO | Tuberculosis Source: World Health Organization - 18 January 2018

Good practices in the prevention and care of tuberculosis and drug-resistant tuberculosis in correctional facilities (2018) [PDF] Source: WHO Regional Office for Europe - WHO Europe - 24 January 2018

A cluster of multidrug-resistant Mycobacterium tuberculosis among patients arriving in Europe from the Horn of Africa: a molecular epidemiological study 08 January 2018 - Publisher: The Lancet Infectious Diseases

The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial 24 January 2018 - Publisher: The Lancet Infectious Diseases

Surveillance for control of antimicrobial resistance 22 February 2018 - Publisher: The Lancet Infectious Diseases Read Summary

Revised SPC: Olumiant (baricitinib) 2 and 4 mg Film-Coated Tablets Source: electronic Medicines Compendium - eMC - 21 February 2018 - Publisher: electronic Medicines compendium Read Summary

Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early implementation [PDF] 30 January 2018 - Publisher: World Health Organization

Antimicrobial Resistance Benchmark 2018 [PDF] 24 January 2018 - Publisher: Access to Medicine Foundation Read Summary

Revised SPC: CellCept (mycophenolate mofetil) 1g/5ml powder for oral suspension Source: electronic Medicines Compendium - eMC - 17 January 2018 - Publisher: electronic Medicines compendium Read Summary

Cochrane Library

Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis Online Publication Date: January 2018

Impact of diagnostic test Xpert MTB/RIF® on health outcomes for tuberculosis Online Publication Date: February 2018

Treatment of drug-resistant tuberculosis in patients with HIV-1 infection Online Publication Date: February 2018

MVA85A vaccine to enhance BCG for preventing tuberculosis Online Publication Date: January 2018

Symptom screening for active tuberculosis in pregnant women living with HIV Online Publication Date: January 2018

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Clinical manifestations and complications of pulmonary tuberculosis
Literature review current through: Jan 2018. | **This topic last updated:** Jan 26, 2018.

Diagnosis of pulmonary tuberculosis in adults
Literature review current through: Jan 2018. | **This topic last updated:** Jan 23, 2018.

Approach to diagnosis of latent tuberculosis infection (tuberculosis screening) in adults
Literature review current through: Jan 2018. | **This topic last updated:** Feb 13, 2018.

Tuberculosis: Natural history, microbiology, and pathogenesis
Literature review current through: Jan 2018. | **This topic last updated:** Jan 26, 2018.

Journal Tables of Contents

Click on the hyperlinked journal title or image (+Ctrl) for the most recent tables of contents. If you would like any of these papers in full text then get in touch: library@uhbristol.nhs.uk

European Respiratory Journal

February 1 2018; volume 51, issue 2

Thorax

February 2018; Volume 73, issue 2

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Recent Database Articles related to Tuberculosis Treatment

Below is a selection of articles related to tuberculosis recently added to the healthcare databases.

Drugs and Multidrug-resistance

Case report: Carbapenemase-producing enterobacteriaceae in an asylum seeker with multidrug-resistant tuberculosis

Author(s): Ravensbergen S.J.; Louka C.; Van Der Werf T.S.; Stienstra Y.; Lokate M.; Bathoorn E.

Source: American Journal of Tropical Medicine and Hygiene; 2018; vol. 98 (no. 2); p. 376-378

Publication Type(s): Article

Available at The American journal of tropical medicine and hygiene - from EBSCO (MEDLINE Complete)

Abstract:A Syrian asylum seeker with multidrug-resistant tuberculosis (TB) developed a bronchopleural fistula after pneumonectomy. Although screening tests were negative on admission, carbapenemase-producing Enterobacteriaceae were cultured after a few months ofTBtreatment. Prevalence of multidrug-resistant organisms is reported to be increased in asylum seekers compared with the general Dutch population. Arduous conditions during transit and interrupted health care delivery in our patient led to multiple-resistant microorganisms that complicated treatment. Copyright © 2018 by The American Society of Tropical Medicine and Hygiene.

Mediating effect of repeated tuberculosis exposure on the risk of transmission to household contacts of multidrug-resistant tuberculosis patients

Author(s): Lu P.; Ding X.; Liu Q.; Lu W.; Zhu L.; Yang H.; Martinez L.; Sun J.; Lu F.; Zhong C.; Jiang H.

Source: American Journal of Tropical Medicine and Hygiene; 2018; vol. 98 (no. 2); p. 364-371

Publication Type(s): Article

Available at The American journal of tropical medicine and hygiene - from EBSCO (MEDLINE Complete)

Abstract: Primary Mycobacterium tuberculosis transmission is an important driver of the global epidemic of resistance to tuberculosis drugs. A few studies have compared tuberculosis infection in contacts of index cases with different drug-resistant profiles, suggesting that contacts of multidrug-resistant (MDR) tuberculosis cases are at higher risk. Repeated tuberculosis exposure in contacts of MDR tuberculosis patients through recurrent tuberculosis may modify this relationship. We compared tuberculosis infection in household contacts of MDR and drug-susceptible (DS) tuberculosis patients from six cities in southeastern China and investigated whether repeated tuberculosis exposure was a mediating factor. Tuberculosis infection was defined as a tuberculin skin test induration 3 10 mm. In all, 111 (28.0%) of 397 household contacts of MDR tuberculosis patients and 165 (24.7%) of 667 contacts of DS tuberculosis index cases were infected with tuberculosis. In a multivariate model not including the previous tuberculosis exposure, contacts of MDR tuberculosis patients had a higher likelihood of tuberculosis infection (adjusted odds ratio [AOR] = 1.37; 95% confidence interval [CI] = 1.01-1.84; P = 0.041). In a separate multivariate model adjusted for the previous tuberculosis exposure, the odds ratio of tuberculosis infection flipped and contacts of MDR

cases were now at lower risk for tuberculosis infection (AOR = 0.55; 95% CI = 0.38-0.81; P = 0.003). These findings suggest prior tuberculosis exposure in contacts strongly mediates the relationship between tuberculosis infection and the index drug resistance profile. Prior studies showing lower risk of developing tuberculosis among contacts of MDR tuberculosis patients may be partially explained by a lower rate of tuberculosis infection at baseline. Copyright © 2018 by The American Society of Tropical Medicine and Hygiene.

An updated literature review concerning the treatment cost of multidrug-resistant tuberculosis

Author(s): Tran Q.V.; Le P.H.; Vo T.Q.; Ngo N.H.Y.; Vo N.X.

Source: Journal of Pharmacy and Pharmacognosy Research; 2018; vol. 6 (no. 2); p. 117-125

Publication Type(s): Review

Abstract: Context: According to a report by the World Health Organization (WHO), there were 1.4 million deaths worldwide in 2015 from tuberculosis (TB), with 3.9% being new cases and 21% being previously treated cases of multidrug-resistant tuberculosis (MDR-TB). Aims: To review the literature concerning the costing analysis situation of MDR-TB treatment. Methods: The study was conducted as a systematic review, with a modified checklist being used as the vital instrument. A search was performed of three databases (PubMed, Cochrane, and Scopus) using the terms (cost OR economic, socioeconomic, expenditure, burden, fee, charge, budget impact) AND (resistance OR multidrug resistance, MDR) AND (tuberculosis OR TB, Mycobacterium tuberculosis) in order to identify relevant articles published from 2006 to the present. Results: A total of 1238 abstracts were identified, and 12 papers were ultimately included in the study. The quantity of the published articles was found to increase during in the period 2008 to 2016. Almost all the studies were based on patients' and healthcare systems' perceptions. The main data sources used were medical establishments and the reports of various relevant organizations. Primary data were used twice as much as secondary data. All the costing types, including direct costs and indirect costs, were mentioned, albeit not with the same frequency. Conclusions: Africa owns one third of the articles included. Further, it was found that MDR-TB should be treated using ambulatory care rather than hospital-based models. Future research studies should focus on Asia, where drug resistance has proved to be a challenging issue. Copyright © 2018 Journal of Pharmacy & Pharmacognosy Research.

Sputum bacteriology conversion and treatment outcome of patients with multidrug-resistant tuberculosis

Author(s): Lv L.; Xu K.; Shi P.; He B.; Wang J.; Li T.; Kong W.; Sun J.

Source: Infection and Drug Resistance; 2018; vol. 11 ; p. 147-154

Publication Type(s): Article

Available at Infection and Drug Resistance - from PubMed Central

Abstract: Purpose: Multidrug-resistant tuberculosis (MDR-TB) requires long-term treatment, has a high fatality rate, and constitutes a global threat. Earlier detection of treatment failure is required to predict therapeutic efficacy. Patients and methods: We enrolled MDR-TB patients consecutively from January 2011 through December 2012 in Lianyungang, China. Sputum smear microscopy tests and sputum cultures were performed once a month for the first 6 months following initiation of antituberculosis treatment and once every 2 months thereafter until the end of therapy. The sensitivity, specificity and area under the receiver operating characteristic curve (AUC) were used with a 95% CI to estimate the role of sputum bacteriology conversion in predicting treatment outcomes. Results: Among the 92 MDR-TB patients enrolled in this study, 40.2% had poor treatment outcomes. The median initial sputum bacteriology conversion time was 1 month. Patients having 2-month sputum smear conversions (adjusted odds ratio [OR]: 7.19, 95% CI: 2.60-19.84) or culture conversions (adjusted OR: 2.88, 95% CI: 1.11-7.45) were more likely to experience good outcomes.

The sensitivity and specificity obtained when using two-month sputum smear conversions to predict treatment outcomes were 67.6% (95% CI: 50.2-82.0) and 76.4% (95% CI: 63.0-86.8), respectively. The sensitivity and specificity obtained when using 2-month culture conversions to predict treatment outcomes were 48.6% (95% CI: 32.0-65.6) and 74.5% (95% CI: 61.0-85.3), respectively. The AUC for two-month smear conversions was 0.72 (95% CI: 0.62-0.81), significantly higher than that obtained for 2-month culture conversions (0.62, 95% CI: 0.52-0.72) (chi2 = 4.18, P = 0.041). Conclusion: The prognoses of MDR-TB patients displaying persistent sputum positivity were inferior to those for whom sputum bacteriology conversion was observed. Thus, sputum smear conversion results obtained 2 months after treatment initiation may provide a potential means for predicting MDR-TB treatment outcomes. Copyright © 2018 Lv et al.

Combining bedaquiline and delamanid to treat multidrug-resistant tuberculosis

Author(s): Tadolini M.; Tiberi S.; Migliori G.B.

Source: The Lancet Infectious Diseases; 2018

Publication Date: 2018

Publication Type(s): Article In Press

Factors predicting treatment success in multi-drug resistant tuberculosis patients treated under programmatic conditions

Author(s): Janmeja A.K.; Aggarwal D.; Dhillon R.

Source: Indian Journal of Tuberculosis; 2018

Publication Type(s): Article In Press

Abstract: Background: Treatment success in multi-drug resistant tuberculosis under programmatic conditions has been far from satisfactory. Knowledge of the factors predicting treatment outcome can guide us to take appropriate corrective measures for better results. However, there is a scarcity of data on these predictors in Indian patients. The present study was sought to evaluate association of different patient and disease specific factors with treatment outcome in MDR-TB patients. Methods: It was a retrospective study that involved evaluation of data of MDR-TB patients who were started on Cat-IV treatment between January 2012 and December 2014. Medical records of 256 patients were scrutinized and necessary information on possible predicting factors like age, gender, body mass index, co-morbidities, previous TB treatment, blood investigations, treatment adherence, culture conversion time, etc. was retrieved. These factors were analyzed for their possible association with treatment outcome. Results: Of the 256 patients, 132 (51.6%) achieved successful outcome after Cat-IV anti-TB regimen. On multivariate logistic regression analysis age (adjusted OR = 0.95; 95% CI 0.91-0.98; p = 0.01), serum albumin level (adjusted OR = 3.71; 95% CI: 1.22-11.3; p = 0.02) and treatment adherence (adjusted OR = 4.52; 95% CI: 1.2-16.6; p = 0.02) were independently associated with treatment success. Co-morbidities like diabetes and alcoholism and previous anti-TB treatment didn't affect the treatment end result significantly. Conclusion: The treatment outcome in MDR-TB has not significantly improved since the inception of DOTS-Plus strategy. Interventions to improve nutrition and treatment adherence might help to improve the success rate in MDR-TB treatment. Copyright © 2018 Tuberculosis Association of India.

Drug resistant Skeletal Tuberculosis in a tertiary care centre in South India

Author(s): Arockiaraj J.; Cherian V.M.; T.S. J.; Poonnoose P.M.; Balaji G.S.; Thomas B.P.; Michael J.S.

Source: Journal of Clinical Orthopaedics and Trauma; 2018

Publication Type(s): Article In Press

Abstract: Back ground: Drug resistant tuberculosis is alarmingly on the rise especially in developing countries. Skeletal tuberculosis accounts up to 10% of all extra pulmonary tuberculosis. World Health Organisation (WHO) has not formulated guidelines for the management of Multi-drug resistant skeletal tuberculosis. Results: A retrospective analysis of patients treated for musculoskeletal tuberculosis was done, to study drug resistance patterns. The outcome was assessed both clinically and radiologically.898 patients were treated for skeletal tuberculosis during the period of 2006-2013 (96 months). 478 (53.2%) patients were treated for tubercular spondylitis and 420 (46.8%) for extra-spinal skeletal tuberculosis. Ninety two patients (10.2%) had documented resistance to the anti-tubercular drugs. There were 42 mono resistant tuberculosis cases (4.7%), 13 poly resistant cases (1.4%), 33 multi-drug resistant cases (MDR TB) (3.7%) and 4 (0.4%) extremely drug resistant tuberculosis cases (XDR). All the patients were treated medically as per drug susceptibility patterns and protocols. Surgery was performed when indicated in 59 (66%) cases. 85% completed their course of treatment and were successfully healed as per pre-set clinical, biochemical and radiological criteria. The remaining were lost to follow up. One patient died as a result of post op respiratory infection. Conclusions: The prevalence of Multi-drug resistant tuberculosis patients in our centre was 3.7% and that of Extremely drug resistant tuberculosis cases was 0.4%. A Multi-disciplinary approach with drug susceptibility tests, sensitive drugs, and surgery if required is essential. Health education is essential to improve awareness among health care professionals about the danger of drug resistance in tuberculosis. Copyright © 2017.

Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management

Author(s): Prasad R.; Banka A.; Gupta N.

Source: Lung India; 2018; vol. 35 (no. 1); p. 78-81

Publication Type(s): Article

Available at Lung India - from PubMed Central

Abstract: Multidrug-resistant tuberculosis (MDR-TB)/rifampicin-resistant TB (RR-TB) is human-made problem and emerging due to poor management of TB and is a threat to control of TB. Early suspicion and diagnosis are important. Culture and drug susceptibility testing are gold standards, but newer molecular methods help in rapid diagnosis. Once diagnosed, prompt treatment should be started, preferably under direct observation. Treatment can be standardized or individualized. Conventional regimen takes up to 24 months but recently shorter regimen of up to 12 months was introduced in specific subset of MDR-TB/RR-TB patients. Management of MDR-TB/RR-TB is complicated, costlier, and challenging and is a concern for human health worldwide. It must be emphasized that optimal treatment of MDR-TB/RR-TB alone is not sufficient. Efforts must be made to ensure effective use of first- and second-line anti-TB drugs. Copyright © 2017 Indian Chest Society Published by Wolters Kluwer -Medknow.

Sequelae of pulmonary multidrug-resistant tuberculosis at the completion of treatment

Author(s): Singla R.; Mallick M.; Mrigpuri P.; Gupta A.; Singla N.

Source: Lung India; 2018; vol. 35 (no. 1); p. 4-8

Publication Type(s): Article

Available at Lung India - from PubMed Central

Abstract: Background: Treatment of multidrug-resistant (MDR-TB) mainly focuses on bacteriological cure. However, only limited studies have evaluated the sequelae left after the completion of treatment among MDR-TB patients. Objective: To assess the persistent symptoms, radiological sequelae, pulmonary function impairment and quality of life at the completion of treatment among MDR-TB patients. Methods: Forty six MDR-TB patients were enrolled, who completed two years of

treatment under programmatic management of Drug Resistant tuberculosis at a tertiary referral institute in Delhi, India. Detailed clinical history was taken. X-ray chest, 6 Minute Walk Test and pulmonary function tests were attempted in all patients. Quality of life was evaluated using Seattle obstructive lung disease questionnaire. Results: At the completion of MDR-TB treatment 95.7% patients had residual symptoms; 100% patients had residual bilateral chest x-ray abnormality with 82.6% patients showing far advanced disease. PFT was abnormal in 97.6% patients with mixed pattern being the commonest abnormality. Quality of Life was impaired with mean physical function of 46%. Conclusion: At the completion of MDR-TB treatment, significant numbers of patients are left with post treatment sequelae. The medical management and social support for these patients should be incorporated in the national programs. Copyright © 2017 Indian Chest Society Published by Wolters Kluwer -Medknow.

Signatures of Selection at Drug Resistance Loci in Mycobacterium tuberculosis.

Author(s): Mortimer, Tatum D; Weber, Alexandra M; Pepperell, Caitlin S

Source: mSystems; 2018; vol. 3 (no. 1)

Publication Type(s): Journal Article

Available at mSystems - from PubMed Central

Abstract: Tuberculosis (TB) is the leading cause of death by an infectious disease, and global TB control efforts are increasingly threatened by drug resistance in Mycobacterium tuberculosis. Unlike most bacteria, where lateral gene transfer is an important mechanism of resistance acquisition, resistant M. tuberculosis arises solely by de novo chromosomal mutation. Using whole-genome sequencing data from two natural populations of M. tuberculosis, we characterized the population genetics of known drug resistance loci using measures of diversity, population differentiation, and convergent evolution. We found resistant subpopulations to be less diverse than susceptible subpopulations, consistent with ongoing transmission of resistant M. tuberculosis. A subset of resistance genes ("sloppy targets") were characterized by high diversity and multiple rare variants; we posit that a large genetic target for resistance and relaxation of purifying selection contribute to high diversity at these loci. For "tight targets" of selection, the path to resistance appeared narrower, evidenced by single favored mutations that arose numerous times in the phylogeny and segregated at markedly different frequencies in resistant and susceptible subpopulations. These results suggest that diverse genetic architectures underlie drug resistance in M. tuberculosis and that combined approaches are needed to identify causal mutations. Extrapolating from patterns observed for well-characterized genes, we identified novel candidate variants involved in resistance. The approach outlined here can be extended to identify resistance variants for new drugs, to investigate the genetic architecture of resistance, and when phenotypic data are available, to find candidate genetic loci underlying other positively selected traits in clonal bacteria. IMPORTANCEMycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a significant burden on global health. Antibiotic treatment imposes strong selective pressure on M. tuberculosis populations. Identifying the mutations that cause drug resistance in M. tuberculosis is important for guiding TB treatment and halting the spread of drug resistance. Whole-genome sequencing (WGS) of M. tuberculosis isolates can be used to identify novel mutations mediating drug resistance and to predict resistance patterns faster than traditional methods of drug susceptibility testing. We have used WGS from natural populations of drug-resistant M. tuberculosis to characterize effects of selection for advantageous mutations on patterns of diversity at genes involved in drug resistance. The methods developed here can be used to identify novel advantageous mutations, including new resistance loci, in M. tuberculosis and other clonal pathogens.

Chest X-Ray Findings Comparison between Multi-drug-resistant Tuberculosis and Drug-sensitive Tuberculosis.

Author(s): Icksan, Aziza Ghanie; Napitupulu, Martin Raja Sonang; Nawas, Mohamad Arifin; Nurwidya, Fariz

Source: Journal of natural science, biology, and medicine; 2018; vol. 9 (no. 1); p. 42-46

Publication Type(s): Journal Article

Available at Journal of Natural Science, Biology and Medicine - from Europe PubMed Central - Open Access

Abstract: BackgroundImaging has a big role in tuberculosis (TB) diagnosis and chest X-ray is preferable because it is available in primary health care and can point out the location, area, and morphology of lesions, such as cavity, consolidation, pleural effusions, and fibrosis. We aimed to compare the chest X-ray findings in multi-drug resistant TB (MDR-TB) and in drug-sensitive TB (DS-TB) cases.MethodsThis is a retrospective cross-sectional study which compares chest X-ray findings of two groups of patients, involving 183 DS-TB patients and 183 MDR-TB patients. Radiologic findings that we analyzed were infiltrate, consolidation, cavity, ground glass opacity, fibrosis, bronchiectasis, calcification, node, atelectasis, bullae, emphysema, and other nonlung parenchymal findings.ResultsMDR-TB group have 177 (96%) patients with large lesions, 6 (4%) with medium lesions, and no small lesions. DS-TB group have 55 (30%) patients with small lesions, 78 (43%) with medium lesions, and 50 (27%) with large lesions. Active TB lesions in the forms of infiltrate and ground-glass opacity were more dominant in DS-TB group, whereas consolidation, cavity, fibrosis, bronchiectasis, calcification, node, atelectasis, bullae, emphysema, and other nonlung parenchymal findings, were more dominant in MDR-TB.ConclusionsThere were significant differences in chest X-ray findings between MDR-TB and DS-TB in terms of lesion size and morphology. Recognition of chest X-ray findings could help the physician to differentiate patient with suspected MDR-TB.

Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children

Author(s): Schaaf H.S.; Garcia-Prats A.J.; Seddon J.A.; McKenna L.

Source: Expert Review of Clinical Pharmacology; Mar 2018; vol. 11 (no. 3); p. 233-244

Publication Type(s): Review

Abstract: Introduction: New and repurposed antituberculosis drugs are urgently needed to more safely and effectively treat multidrug-resistant (MDR) tuberculosis (TB) in children. Multiple challenges limit timely access to new MDR-TB treatments in children. Areas covered: Diagnosis of MDR-TB in children remains a barrier, with few children with MDR-TB diagnosed and treated. Other barriers to timely access to new and repurposed drugs are discussed, and include delayed initiation of paediatric trials, limited funding for paediatric drug development, fragmented regulatory systems and operational challenges. The status of access to current repurposed and novel drugs is presented. Expert commentary: More timely initiation of paediatric trials is needed and paediatric work should happen and be funded in parallel with each phase of adult trials. Better quality data, increased regulator resources and expertise, harmonization of regulatory requirements across borders/organisations and registration fee waivers would improve registration timelines. Improved diagnosis, recording and reporting will establish better demand. Improved systems for procurement and supply chain management would reduce in-country operational barriers to getting medications to children. The challenges must be addressed to ensure timely and equitable access to new drugs and regimens that are urgently needed for effective, safe and shorter treatment of children with MDR-TB. Copyright © 2017 Informa UK Limited, trading as Taylor & Francis Group.

Automated real-time detection of drug-resistant Mycobacterium tuberculosis on a lab-on-a-disc by Recombinase Polymerase Amplification

Author(s): Law I.L.G.; Kong S.K.; Loo J.F.C.; Kwok H.C.; Wu S.Y.; Ho H.P.; Yeung H.Y.; Kwan Y.W.

Source: Analytical Biochemistry; Mar 2018; vol. 544 ; p. 98-107

Publication Type(s): Article

Abstract: With the emergence of multi- and extensive-drug (MDR/XDR) resistant Mycobacterium tuberculosis (M. tb), tuberculosis (TB) persists as one of the world's leading causes of death. Recently, isothermal DNA amplification methods received much attention due to their ease of translation onto portable point-of-care (POC) devices for TB diagnosis. In this study, we aimed to devise a simple yet robust detection method for M. tb. Amongst the numerous up-and-coming isothermal techniques, Recombinase Polymerase Amplification (RPA) was chosen for a real-time detection of TB with or without MDR. In our platform, real-time RPA (RT-RPA) was integrated on a lab-on-a-disc (LOAD) with on-board power to maintain temperature for DNA amplification. Sputa collected from healthy volunteers were spiked with respective target M. tb samples for testing. A limit of detection of 102 colony-forming unit per millilitre in 15 min was achieved, making early detection and differentiation of M. tb strains highly feasible in extreme POC settings. Our RT-RPA LOAD platform has also been successfully applied in the differentiation of MDR-TB from H37Ra, an attenuated TB strain. In summary, a quantitative RT-RPA on LOAD assay with a high level of sensitivity was developed as a foundation for further developments in medical bedside and POC diagnostics. Copyright © 2018 Elsevier Inc.

Identification and characterization of potential druggable targets among hypothetical proteins of extensively drug resistant Mycobacterium tuberculosis (XDR KZN 605) through subtractive genomics approach

Author(s): Uddin R.; Siddiqui Q.N.; Azam S.S.; Saima B.; Wadood A.

Source: European Journal of Pharmaceutical Sciences; Mar 2018; vol. 114 ; p. 13-23

Publication Type(s): Article

Abstract: Among the resistant isolates of tuberculosis (TB), the multidrug resistance tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) are the areas of growing concern for which the front-line antibiotics are no more effective. As a result, the search of new therapeutic targets against TB is an imperative need of time. On the other hand, the target identification is an a priori step in drug discovery based research. Furthermore, the availability of the complete proteomic data of extensively drug resistant Mycobacterium tuberculosis (XDR-MTB) made it possible to carry out in silico analysis for the discovery of new drug targets. In the current study, we aimed to prioritize the potential drug targets among the hypothetical proteins of XDR-TB via subtractive genomics approach. In the subtractive genomics, we stepwise reduced the complete proteome of XDR-MTB to only two hypothetical proteins and evidently proposed them as new therapeutic targets. The 3D structure of one of the two target proteins was predicted via homology modeling and later on, validated by various analysis tools. Our study suggested that the domains identified and the motif hits found in the sequences of the shortlisted drug targets are crucial for the survival of the XDR-MTB. To the best of our knowledge, the current study is the first attempt in which the complete proteomic data of XDR-MTB was subjected to the computational subtractive genomics approach and therefore, would provide an opportunity to identify the unique therapeutic targets against deadly XDR-MTB. Copyright © 2017 Elsevier B.V.

Molecular tests expedite the diagnosis of multidrug-resistant tuberculosis in childhood.

Author(s): Namiiro, S; Wobudeya, E; Colebunders, R; Worodria, W

Source: The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease; Mar 2018; vol. 22 (no. 3); p. 349-350

Publication Type(s): Journal Article

Available at The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease - from IngentaConnect - Open Access

Genotyping Multidrug-Resistant Mycobacterium tuberculosis from Primary Sputum and Decontaminated Sediment with an Integrated Microfluidic Amplification Microarray Test.

Author(s): Linger, Yvonne; Knickerbocker, Christopher; Sipes, David; Golova, Julia; Franke, Molly

Source: Journal of clinical microbiology; Mar 2018; vol. 56 (no. 3)

Publication Type(s): Journal Article

Abstract: There is a growing awareness that molecular diagnostics for detect-to-treat applications will soon need a highly multiplexed mutation detection and identification capability. In this study, we converted an open-amplicon microarray hybridization test for multidrug-resistant (MDR) Mycobacterium tuberculosis into an entirely closed-amplicon consumable (an amplification microarray) and evaluated its performance with matched sputum and sediment extracts. Reproducible genotyping (the limit of detection) was achieved with ~25 M. tuberculosis genomes (100 fg of M. tuberculosis DNA) per reaction; the estimated shelf life of the test was at least 18 months when it was stored at 4°C. The test detected M. tuberculosis in 99.1% of sputum extracts and 100% of sediment extracts and showed 100% concordance with the results of real-time PCR. The levels of concordance between M. tuberculosis and resistance-associated gene detection were 99.1% and 98.4% for sputum and sediment extracts, respectively. Genotyping results were 100% concordant between sputum and sediment extracts. Relative to the results of culture-based drug susceptibility testing, the test was 97.1% specific and 75.0% sensitive for the detection of rifampin resistance in both sputum and sediment extracts. The specificity for the detection of isoniazid (INH) resistance was 98.4% and 96.8% for sputum and sediment extracts, respectively, and the sensitivity for the detection of INH resistance was 63.6%. The amplification microarray reported the correct genotype for all discordant phenotype/genotype results. On the basis of these data, primary sputum may be considered a preferred specimen for the test. The amplification microarray design, shelf life, and analytical performance metrics are well aligned with consensus product profiles for next-generation drug-resistant M. tuberculosis diagnostics and represent a significant ease-of-use advantage over other hybridization-based tests for diagnosing MDR tuberculosis.

Bilateral cavitary multidrug- or extensively drug-resistant tuberculosis: role of surgery.

Author(s): Marfina, Galina Yu; Vladimirov, Kirill B; Avetisian, Armen O; Starshinova, Anna A

Source: European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery; Mar 2018; vol. 53 (no. 3); p. 618-624

Publication Type(s): Journal Article

Abstract:OBJECTIVESCavitary disease and bilateral lesions are among the risk factors for poor outcome of pulmonary tuberculosis (TB). Our aim was to explore the value and limits of surgery in patients with advanced TB.METHODSA retrospective study of 57 consecutive patients who underwent thoracic surgery for culture-positive bilateral cavitary pulmonary TB was performed. Forty-four (77.2%) patients were men and 13 (22.8%) patients were women; their ages were in the range of 18-61 years. Twenty-two (38.6%) patients had multidrug-resistant (MDR) TB and 35 (61.4%) patients had extensively drug-resistant (XDR) TB confirmed with cultures. On admission, 49 (86.0%) patients had sputum smear microscopy positive for acid-fast bacilli. The main indication for surgery was treatment failure manifested as contagious persisting cavities despite best available therapy. The surgical procedures included combinations of pulmonary resections of different levels, selective thoracoplasties and/or endobronchial valve treatment. The operations were performed consecutively, starting with the most affected side. TB therapy preceded the operation for a minimum of 6 months and was continued after the operation on the basis of the patient's

susceptibility to drugs for Mycobacterium tuberculosis.RESULTSWe performed 121 operations: 42 in 22 patients with MDR TB (1.9 operations per patient) and 79 procedures in 35 patients with XDR TB (2.3 operations per patient). No deaths occurred in the 1st year. Two late deaths followed, 1 unrelated to and 1 due to TB progression. Ten major complications (1 complication per patient) developed: main bronchus stump fistula (n = 4), prolonged air leak (n = 3), respiratory failure (n = 2) and wound seroma (n = 1). At the 1-month follow-up visit, sputum smear conversion was observed in 11 (68.8%) patients with MDR and in 15 (45.5%) patients with XDR TB. At the late (20-36 months) follow-up visit, culture negativity was achieved in 21 (95.5%) patients with MDR TB and in 23 (65.7%) patients with XDR TB (P = 0.015).CONCLUSIONSThoracic surgery may significantly improve patients' outcomes and even result in a cure in a good portion of patients with bilateral cavitary MDR and XDR TB and should be considered as the essential element of multimodality treatment for MDR and XDR TB, even in patients with bilateral cavitary disease and borderline respiratory reserves.

Secretome profile analysis of multidrug-resistant, monodrug-resistant and drug-susceptible Mycobacterium tuberculosis.

Author(s): Putim, Chanyanuch; Phaonakrop, Narumon; Jaresitthikunchai, Janthima;

Source: Archives of microbiology; Mar 2018; vol. 200 (no. 2); p. 299-309

Publication Type(s): Journal Article

Abstract: The emergence of drug-resistant tuberculosis has generated great concern in the control of tuberculosis and HIV/TB patients have established severe complications that are difficult to treat. Although, the gold standard of drug-susceptibility testing is highly accurate and efficient, it is time-consuming. Diagnostic biomarkers are, therefore, necessary in discriminating between infection from drug-resistant and drug-susceptible strains. One strategy that aids to effectively control tuberculosis is understanding the function of secreting proteins that mycobacteria use to manipulate the host cellular defenses. In this study, culture filtrate proteins from Mycobacterium tuberculosis H37Rv, isoniazid-resistant, rifampicin-resistant and multidrug-resistant strains were gathered and profiled by shotgun-proteomics technique. Mass spectrometric analysis of the secreted proteome identified several proteins, of which 837, 892, 838 and 850 were found in M. tuberculosis H37Rv, isoniazid-resistant, rifampicin-resistant and multidrug-resistant strains, respectively. These proteins have been implicated in various cellular processes, including biological adhesion, biological regulation, developmental process, immune system process localization, cellular process, cellular component organization or biogenesis, metabolic process, and response to stimulus. Analysis based on STITCH database predicted the interaction of DNA topoisomerase I, 3-oxoacyl-(acyl-carrier protein) reductase, ESAT-6-like protein, putative prophage phiRv2 integrase, and 3-phosphoshikimate 1-carboxyvinyltransferase with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, suggesting putative roles in controlling the anti-tuberculosis ability. However, several proteins with no interaction with all first-line anti-tuberculosis drugs might be used as markers for mycobacterial identification.

Molecular epidemiology of tuberculosis in Tasmania and genomic characterisation of its first known multi-drug resistant case

Author(s): Gautam S.S.; O'Toole R.F.; Aogain M.M.; Cooley L.A.; Haug G.; Fyfe J.A.; Globan M.

Source: PLoS ONE; Feb 2018; vol. 13 (no. 2)

Publication Type(s): Article

Available at PloS one - from EBSCO (MEDLINE Complete)

Abstract: Background The origin and spread of tuberculosis (TB) in Tasmania and the types of strains of Mycobacterium tuberculosis complex (MTBC) present in the population are largely unknown. Objective The aim of this study was to perform the first genomic analysis of MTBC isolates from

Tasmania to better understand the epidemiology of TB in the state. Methods Whole-genome sequencing was performed on cultured isolates of MTBC collected from 2014-2016. Single-locus variant analysis was applied to determine the phylogeny of the isolates and the presence of drug-resistance mutations. The genomic data were then cross-referenced against public health surveillance records on each of the cases. Results We determined that 83.3% of TB cases in Tasmania from 2014-2016 occurred in non-Australian born individuals. Two possible TB clusters were identified based on single locus variant analysis, one from November-December 2014 (n = 2), with the second from May-August 2015 (n = 4). We report here the first known isolate of multi-drug resistant (MDR) M. tuberculosis in Tasmania from 2016 for which we established its drug resistance mutations and potential overseas origin. In addition, we characterised a case of M. bovis TB in a Tasmanian-born person who presented in 2014, approximately 40 years after the last confirmed case in the state's bovids. Conclusions TB in Tasmania is predominantly of overseas origin with genotypically-unique drug-susceptible isolates of M. tuberculosis. However, the state also exhibits features of TB that are observed in other jurisdictions, namely, the clustering of cases, and drug resistance. Early detection of TB and contact tracing, particularly of overseas-born cases, coordinated with rapid laboratory drug-susceptibility testing and molecular typing, will be essential for Tasmania to reach the World Health Organisation's TB eradication goals for low-incidence settings. Copyright © 2018 Gautam et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Drug-Resistant Miliary Tuberculosis in a Child

Author(s): Bao Y.; Zheng Y.

Source: The New England journal of medicine; Feb 2018; vol. 378 (no. 7)

Publication Type(s): Article

Available at The New England journal of medicine - from Ovid (Journals @ Ovid)

MTBDRplus for the rapid diagnosis of ocular tuberculosis and screening of drug resistance

Author(s): Sharma K.; Sharma M.; Thakur A.; Gupta A.; Singh R.; Aggarwal K.; Bansal R.; Prakash S.

Source: Eye (Basingstoke); Feb 2018; vol. 32 (no. 2); p. 451-456

Publication Type(s): Article

Abstract: PurposeTimely diagnosis of intraocular tuberculosis (IOTB) along with detection of drug resistance can save many eyes from visual impairment. With the growing incidence of IOTB and rising drug resistance, a reliable diagnostic platform for simultaneous detection of the agent and mutated gene is urgently needed. The MTBDRplus assay was evaluated directly on vitreous fluid samples for the same.Patients and methodsIn a prospective study, The MTBDRplus assay was performed on 127 vitreous fluid samples (77 'study group' comprising cases of presumed ocular tuberculosis and 50 'control group' cases of disease controls (n=25) and non-uveitic controls (n=25)). All samples positive by MTBDRplus assay were subjected to gene sequencing to confirm the mutations for rifampicin and isoniazid resistance.ResultsThe MTBDRplus assay produced a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 36.36%, 100%, 100%, and 50.50%, respectively, for the detection of IOTB. Among the 28 cases from study group that were positive by MTBDRplus assay, rifampicin resistance was reported in six and isoniazid resistance in two cases. On sequencing of rpoB and katG gene, one case of false rifampicin-resistant by MTBDRplus was found. The other resistant isolates showed concordant mutations between MTBDRplus assay and sequencing.ConclusionThe MTBDRplus assay is an effective tool for the rapid diagnosis of IOTB along with detection of drug resistance, thereby improving the outcome in IOTB.

Genome-wide analysis of multi- and extensively drug-resistant Mycobacterium tuberculosis

Author(s): Coll F.; Phelan J.; Mallard K.; Portelli S.; Oppong Y.; Campino S.; Furnham N.; Hibberd M.L

Source: Nature Genetics; Feb 2018; vol. 50 (no. 2); p. 307-316

Publication Type(s): Article

Abstract: To characterize the genetic determinants of resistance to antituberculosis drugs, we performed a genome-wide association study (GWAS) of 6,465 Mycobacterium tuberculosis clinical isolates from more than 30 countries. A GWAS approach within a mixed-regression framework was followed by a phylogenetics-based test for independent mutations. In addition to mutations in established and recently described resistance-associated genes, novel mutations were discovered for resistance to cycloserine, ethionamide and para-aminosalicylic acid. The capacity to detect mutations associated with resistance to ethionamide, pyrazinamide, capreomycin, cycloserine and para-aminosalicylic acid was enhanced by inclusion of insertions and deletions. Odds ratios for mutations within candidate genes were found to reflect levels of resistance. New epistatic relationships between candidate drug-resistance-associated genes were identified. Findings also suggest the involvement of efflux pumps (drrA and Rv2688c) in the emergence of resistance. This study will inform the design of new diagnostic tests and expedite the investigation of resistance and compensatory epistatic mechanisms. Copyright © 2017 The Author(s).

Limited effect of later-generation fluoroquinolones in the treatment of ofloxacin-resistant and moxifloxacin-susceptible multidrug-resistant tuberculosis

Author(s): Lee H.; Jeon K.; Kwon O.J.; Koh W.-J.; Ahn S.; Hwang N.Y.; Huh H.J.; Lee N.Y.; Kim C.-K.

Source: Antimicrobial Agents and Chemotherapy; Feb 2018; vol. 62 (no. 2)

Publication Type(s): Article

Abstract: Recent data conflict on the clinical efficacy of later-generation fluoroquinolones, such as moxifloxacin or levofloxacin, for the treatment of multidrug-resistant tuberculosis (MDR-TB) that is resistant to ofloxacin but susceptible to moxifloxacin. The purpose of the present study was to evaluate whether later-generation fluoroquinolones can improve treatment outcomes in patients with ofloxacin-resistant, moxifloxacin-susceptible MDR-TB. A retrospective cohort study was performed on 208 patients with moxifloxacin-susceptible MDR-TB who were treated between 2006 and 2011. Later-generation fluoroquinolones were used for all patients. Overall, 171 patients (82%) had ofloxacin-susceptible, moxifloxacin-susceptible MDR-TB (ofloxacin-susceptible group), and 37 (18%) had ofloxacin-resistant, moxifloxacin-susceptible MDR-TB (ofloxacin-resistant group). Compared to the ofloxacin-susceptible group, the ofloxacin-resistant group was more likely to have a history of MDR-TB treatment (P <0.001) and cavitary lesions on chest radiography (P <0.001). In addition, the ofloxacin-resistant group was more likely than the ofloxacin-susceptible group to have resistance to the drugs pyrazinamide (P =0.003), streptomycin (P =0.015), prothionamide (P <0.001), and para-aminosalicylic acid (P <0.001). Favorable outcomes were more frequently achieved for the ofloxacin-susceptible group than for the ofloxacin-resistant group (91% [156/171] versus 57% [21/37], respectively [P <0.001]). In multivariable regression logistic analysis, the ofloxacin-susceptible group was about 5.36 (95% confidence interval, 1.55 to 18.53) times more likely than the ofloxacin-resistant group (P <0.001) to have favorable outcomes. Despite in vitro moxifloxacin susceptibility, the frequency of favorable treatment outcomes for ofloxacin-resistant MDR-TB was significantly lower than that for ofloxacin-susceptible MDR-TB, even when later-generation fluoroquinolones were used, indicating that more-aggressive therapies may be needed for ofloxacin-resistant MDR-TB. Copyright © 2018 American Society for Microbiology. All Rights Reserved.

Levofloxacin population pharmacokinetics in south african children treated for multidrug-resistant tuberculosis

Author(s): Denti P.; Wiesner L.; McIlleron H.M.; Garcia-Prats A.J.; Draper H.R.; Winckler J

Source: Antimicrobial Agents and Chemotherapy; Feb 2018; vol. 62 (no. 2)

Publication Type(s): Article

Abstract: Levofloxacin is increasingly used in the treatment of multidrug-resistant tuberculosis (MDR-TB). There are limited pediatric pharmacokinetic data to inform dose selection for children. Children routinely receiving levofloxacin (250-mg adult tablets) for MDR-TB prophylaxis or disease in Cape Town, South Africa, underwent pharmacokinetic sampling following receipt of a dose of 15 or 20 mg/kg of body weight given as a whole or crushed tablet(s) orally or via a nasogastric tube. Pharmacokinetic parameters were estimated using nonlinear mixed-effects modeling. Model-based simulations were performed to estimate the doses across weight bands that would achieve adult exposures with 750-mg once-daily dosing. One hundred nine children were included. The median age was 2.1 years (range, 0.3 to 8.7 years), and the median weight was 12 kg (range, 6 to 22 kg). Levofloxacin followed 2-compartment kinetics with first-order elimination and absorption with a lag time. After inclusion of allometric scaling, the model characterized the age-driven maturation of clearance (CL), with the effect reaching 50% of that at maturity at about 2 months after birth and 100% of that at maturity by 2 years of age. CL in a typical child (weight, 12 kg; age, 2 years) was 4.7 liters/h. HIV infection reduced CL by 16%. By use of the adult 250-mg formulation, levofloxacin exposures were substantially lower than those reported in adults receiving a similar dose on a milligram-per-kilogram basis. To achieve adult-equivalent exposures at a 750-mg daily dose, higher levofloxacin pediatric doses of from 18 mg/kg/day for younger children with weights of 3 to 4 kg (due to immature clearance) to 40 mg/kg/day for older children may be required. The doses of levofloxacin currently recommended for the treatment of MDR-TB in children result in exposures considerably lower than those in adults. The effects of different formulations and formulation manipulation require further investigation. We recommend age- and weight-banded doses of 250-mg tablets of the adult formulation most likely to achieve target concentrations for prospective evaluation. Copyright © 2018 American Society for Microbiology. All Rights Reserved.

What is resistance? Impact of phenotypic versus molecular drug resistance testing on therapy for multi-and extensively drug-resistant tuberculosis

Author(s): Heyckendorf J.; Olaru I.D.; Lange C.; Beckert P.; Kohl T.A.; Niemann S.; Andres S.

Source: Antimicrobial Agents and Chemotherapy; Feb 2018; vol. 62 (no. 2)

Publication Type(s): Article

Available at Antimicrobial Agents and Chemotherapy - from PubMed Central

Abstract: Rapid and accurate drug susceptibility testing (DST) is essential for the treatment of multi- and extensively drug-resistant tuberculosis (M/XDR-TB). We compared the utility of genotypic DST assays with phenotypic DST (pDST) using Bactec 960 MGIT or Lowenstein-Jensen to construct M/XDR-TB treatment regimens for a cohort of 25 consecutive M/XDR-TB patients and 15 possible anti-TB drugs. Genotypic DST results from Cepheid GeneXpert MTB/RIF (Xpert) and line probe assays (LPAs; Hain GenoType MTBDRplus 2.0 and MTBDRsl 2.0) and whole-genome sequencing (WGS) were translated into individual algorithm-derived treatment regimens for each patient. We further analyzed if discrepancies between the various methods were due to flaws in the genotypic or phenotypic test using MIC results. Compared with pDST, the average agreement in the number of drugs prescribed in genotypic regimens ranged from just 49% (95% confidence interval [CI], 39 to 59%) for Xpert and 63% (95% CI, 56 to 70%) for LPAs to 93% (95% CI, 88 to 98%) for WGS. Only the WGS regimens did not contain any drugs to which pDST showed resistance. Importantly, MIC testing revealed that pDST likely underestimated the true rate of resistance for key drugs (rifampin, levofloxacin, moxifloxacin, and kanamycin) because critical concentrations (CCs) were too high. WGS can be used to rule in resistance even in M/XDR strains with complex resistance patterns, but pDST

for some drugs is still needed to confirm susceptibility and construct the final regimens. Some CCs for pDST need to be reexamined to avoid systematic false-susceptible results in low-level resistant isolates. Copyright © 2018 Heyckendorf et al.

Alarming levels of multidrug-resistant tuberculosis in Ukraine: Results from the first national survey

Author(s): Pavlenko E.; Barbova A.; Hovhannesyan A.; Tsenilova Z.; Slavuckij A.; Shcherbak-Verlan B

Source: International Journal of Tuberculosis and Lung Disease; Feb 2018; vol. 22 (no. 2); p. 197-205

Publication Type(s): Review

Available at International Journal of Tuberculosis and Lung Disease - from IngentaConnect - Open Access

Abstract:SETTING: The true prevalence of multidrug-resistant tuberculosis (MDR-TB) in Ukraine is not known. Available data are a decade old and limited to only one province. OBJECTIVE : To determine the prevalence of MDR-TB among new and previously treated TB cases in Ukraine and explore the risk factors associated with drug resistance. METHODS : A total of 1550 sputum smear-positive pulmonary TB patients were recruited from 40 clusters throughout Ukraine. Sputum specimens were examined using culture, drug susceptibility testing and pncA gene sequencing. RESULT S : The proportion of MDR-TB among new and previously treated TB cases was respectively 24.1% (95%CI 20.7-27.6) and 58.1% (95%CI 52.1-64.1). More than one third (38.0%) of MDR-TB or rifampicin (RMP) resistant cases showed resistance to either a fluoroquinolone (FQ) or a second-line injectable agent or both. Resistance to pyrazinamide and FQs was low in patients with RMP-susceptible TB. Among new TB cases, the odds of MDR-TB were higher among patients who were younger, female and living in south-eastern provinces, as well as among human immunodeficiency virus-positive patients who belonged to a low socioeconomic group. CONCLUS IONS : Our study showed that the burden of MDR-TB in Ukraine was much greater than previously assumed. Urgent actions are needed to prevent further spread of drug-resistant TB in Ukraine. Copyright © 2018 The Union.

Investigation of a cluster of multi-drug resistant tuberculosis in a high-rise apartment block in Singapore

Author(s): Ho Z.J.M.; Koh H.F.; Lee V.J.M.; Chee C.B.E.; Wang Y.T.; Hsu L.Y.; Ong R.T.-H.; Cook A.R.;

Source: International Journal of Infectious Diseases; Feb 2018; vol. 67 ; p. 46-51

Publication Type(s): Article

Available at International Journal of Infectious Diseases - from ScienceDirect

Abstract: Objective Between February 2012 and May 2016, six residents of an 11-storey apartment block were diagnosed with MDR-TB. Based on initial tests, all isolates had similar genotypic profiles, although there were no identifiable epidemiological transmission patterns between three cases. We present findings from the cluster investigation and results of a mass screening exercise. Design Free voluntary TB screening was offered to past and current residents of the apartment block, comprising an interview, Chest X-Ray, and Interferon Gamma Release Assay or Tuberculin skin test. Expected latent TB proportions were calculated using a reference population, and whole genome sequencing (WGS) was performed. Results The index case was involved in a separate gaming centre outbreak involving five patrons. 241 current (67.9% of 355 residents) and 18 past residents were screened. The latent TB proportion was 19.9%, which was at the higher end of the expected range. WGS confirmed relatedness of cases' MDR-TB isolates- eight of 10 isolates were genetically identical, while the remaining two were one Single Nucleotide Polymorphism apart. Conclusion With WGS, TB clusters not apparent through regular activity-based contact tracing may be detected. Mass

screening may help inform the extent of transmission, but is limited by participation and difficulties in interpretation. Copyright © 2017 The Author(s)

Molecular drug resistance profiles of Mycobacterium tuberculosis from sputum specimens using ion semiconductor sequencing

Author(s): Park J.; Jang W.; Kim M.; Kim Y.; Shin S.; Shin S.Y.; Park K.; Kim M.S.

Source: Journal of Microbiological Methods; Feb 2018; vol. 145 ; p. 1-6

Publication Type(s): Article

Abstract: The increasing burden of multidrug resistant (MDR)-TB, defined by resistance to rifampin (RFP) and isoniazid (INH), and extensively drug resistant-TB, defined by MDR-TB with additional resistance to fluoroquinolones (FQs) and more than one second-line injectable drug, is a serious impediment to global TB control. We evaluated the feasibility of full-length gene analysis including inhA, katG, rpoB, pncA, rpsL embB, eis, and gyrA using a semiconductor NGS with the Ion AmpliSeq TB panel to directly analyse 34 sputum specimens confirmed by phenotypic DST: INH, RFP, ethambutol (EMB), pyrazinamide (PZA), amikacin, kanamycin, streptomycin (SM), FQs including ofloxacin, moxifloxacin, and levofloxacin. The molecular drug resistance profiles showed "very good" and "substantial" strength of agreement for the phenotypic DST results of RFP and EMB, PZA, SM, FQs resistance with specificities of 96%, and 88%, 97%, 100% and sensitivities of 100%, and 88%, 60%, 67%, respectively. The strength of agreement for the detection of resistance to INH was "substantial" compared between katG mutation and phenotypic INH only. Ion semiconductor NGS could make possible detection of several uncommon or novel amino acid changes in the full coding regions of these eight genes. However, molecular drug resistant profile should be complemented and validated by subsequent phenotypic DST studies at the same time. Copyright © 2017

Multi and extensively drug-resistant pulmonary tuberculosis: advances in diagnosis and management.

Author(s): Pontali, Emanuele; Visca, Dina; Centis, Rosella; D'Ambrosio, Lia; Spanevello, Antonio

Source: Current opinion in pulmonary medicine; Feb 2018

Publication Type(s): Journal Article

Abstract:PURPOSE OF REVIEWMultidrug-resistant (MDR) tuberculosis (TB) and extensively drug-resistant (XDR)-TB epidemics are key obstacles towards TB control and elimination.RECENT FINDINGSDiagnosis of MDR/XDR-TB is difficult and requires several weeks. New diagnostic tools are being tested and proposed allowing for shorter time to diagnosis and reduced delays in starting an adequate treatment regimen. MDR/XDR-TB treatment strategies are currently on an evolving stage. New shortened treatments based on the recommended 'Bangladesh regimen' or on the newer anti-TB drugs, delamanid and bedaquiline may represent part of the future scenario. In addition, more information on safety and efficacy of delamanid and bedaquiline has been published, allowing to better position these drugs. Recent information on treatment regimens for the paediatric age, with or without delamanid or bedaquiline, has become available. This is of great help in designing safer and more efficacious regimens for the treatment of MDR/XDR-TB in children and adolescents.SUMMARYThe accessibility, sustainability and scale-up of new diagnostic technologies are lagging behind and more efforts are needed. In addition, we need high-quality information on safety and efficacy of various combinations of drugs to obtain the best possible regimens to treat the largest possible proportion of patients.

Structure-activity relationships for analogs of the tuberculosis drug bedaquiline with the naphthalene unit replaced by bicyclic heterocycles.

Author(s): Sutherland, Hamish S; Tong, Amy S T; Choi, Peter J; Conole, Daniel; Blaser, Adrian

Source: Bioorganic & medicinal chemistry; Feb 2018

Publication Type(s): Journal Article

Abstract: Replacing the naphthalene C-unit of the anti-tuberculosis drug bedaquiline with a range of bicyclic heterocycles of widely differing lipophilicity gave analogs with a 4.5-fold range in clogP values. The biological results for these compounds indicate on average a lower clogP limit of about 5.0 in this series for retention of potent inhibitory activity (MIC90s) against M.tb in culture. Some of the compounds also showed a significant reduction in inhibition of hERG channel potassium current compared with bedaquiline, but there was no common structural feature that distinguished these.

Elevated Plasma Moxifloxacin Concentrations and SLCO1B1 g.-11187G>A Polymorphism in Adults with Pulmonary Tuberculosis.

Author(s): Weiner, Marc; Gelfond, Jon; Johnson-Pais, Teresa L; Engle, Melissa; Peloquin, Charles A

Source: Antimicrobial agents and chemotherapy; Feb 2018

Publication Type(s): Journal Article

Abstract: Moxifloxacin exhibits concentration-dependent prolongation of human QTc intervals and bactericidal activity against Mycobacterium tuberculosis However, moxifloxacin plasma concentrations are variable between patients. We evaluated whether human gene polymorphisms affect moxifloxacin plasma concentrations in tuberculosis patients from two geographic regions. We enrolled a convenience sample of 49 adults with drug-sensitive pulmonary tuberculosis from Africa and the United State s enrolled in two treatment trials of moxifloxacin as part of multidrug therapy. Pharmacokinetic parameters were evaluated by noncompartmental techniques. Human single-nucleotide polymorphisms of transporter genes were evaluated with analysis of covariance on moxifloxacin exposure and peak concentration (Cmax). Moxifloxacin area under the concentration-time curve from 0 to 24 h (AUC0-24) and Cmax were significantly increased by drug mg/kg dosage and genotype of variant g.-11187G>A in the SLCO1B1 gene (rs4149015), but not by geographic region. Median moxifloxacin AUC0-24 was 46% higher and Cmax 30% higher in 4 (8% of) participants who had the SLCO1B1 g.-11187 AG genotype compared with 45 participants who had the wild type GG genotype (median from model, AUC0-24 34.4 vs. 23.6 µg*h/mL, P =.005; Cmax 3.5 vs. 2.7 µg/mL, P =.009, ANCOVA). Because moxifloxacin exhibits concentration-dependent prolongation of human QTc intervals, and prolonged QTc intervals are associated with cardiac arrhythmia, further study is needed to evaluate risk associated with the SLCO1B1 g.-11187G>A variant.

Widespread use of incorrect PCR ramp rate negatively impacts multidrug-resistant tuberculosis diagnosis (MTBDRplus).

Author(s): Derendinger, B; de Vos, M; Nathavitharana, R R; Dolby, T; Simpson, J A; van Helden, P D

Source: Scientific reports; Feb 2018; vol. 8 (no. 1); p. 3206

Publication Type(s): Journal Article

Available at Scientific Reports - from PubMed Central

Abstract: The scale-up of rapid drug resistance testing for TB is a global priority. MTBDRplus is a WHO-endorsed multidrug-resistant (MDR)-TB PCR assay with suboptimal sensitivities and high indeterminate rates on smear-negative specimens. We hypothesised that widespread use of incorrect thermocycler ramp rate (speed of temperature change between cycles) impacts performance. A global sample of 72 laboratories was surveyed. We tested 107 sputa from Xpert MTB/RIF-positive patients and, separately, dilution series of bacilli, both at the manufacturer-recommended ramp rate (2.2 °C/s) and the most frequently reported incorrect ramp rate (4.0 °C/s). Mycobacterium tuberculosis-complex DNA (TUB-band)-detection, indeterminate results, accuracy,

and inter-reader variability (dilution series only) were compared. 32 respondents did a median (IQR) of 41 (20-150) assays monthly. 78% used an incorrect ramp rate. On smear-negative sputa, 2.2 °C/s vs. 4.0 °C/s improved TUB-band positivity (42/55 vs. 32/55; p = 0.042) and indeterminate rates (1/42 vs. 5/32; p = 0.039). The actionable results (not TUB-negative or indeterminate; 41/55 vs. 28/55) hence improved by 21% (95% CI: 9-35%). Widespread use of incorrect ramp rate contributes to suboptimal MTBDRplus performance on smear-negative specimens and hence limits clinical utility. The number of diagnoses (and thus the number of smear-negative patients in whom DST is possible) will improve substantially after ramp rate correction.

Prevalence and risk factors of drug-resistant extrapulmonary tuberculosis.

Author(s): Boonsarngsuk, Viboon; Mangkang, Khattiya; Santinirand, Pitak

Source: The clinical respiratory journal; Feb 2018

Publication Type(s): Journal Article

Abstract:BACKGROUNDPhysicians are usually aware of the occurrence of drug-resistant (DR) pulmonary tuberculosis (PTB), but lack concern about DR-extrapulmonary TB (EPTB). Data regarding the prevalence and risk factors of DR-EPTB remain limited.OBJECTIVESTo determine the prevalence and risk factors of DR-EPTB.METHODSA retrospective study was performed in patients who had culture-proven Mycobacterium tuberculosis (MTB) from various specimens between January 2013 and December 2015. Patients were classified into three groups: PTB, EPTB, and concomitant PTB and EPTB (PTB+EPTB). Clinical data, chest radiographic extent of disease, and patterns of DR were collected.RESULTSThere were 1,014 culture-proven MTB specimens (716 pulmonary specimens and 298 extrapulmonary specimens) from 986 patients (648 PTB, 218 EPTB, and 120 PTB+EPTB). The prevalences of isoniazid-, rifampicin-, and multidrug-resistant EPTB were 7.8%, 0.5% and 0.5%, respectively, which were lower than those of PTB. When PTB and EPTB coexisted, a higher rate of DR-TB was observed than for PTB alone. Of 338 EPTB patients, the extent of radiographic disease was associated with isoniazid-, rifampicin-, and multidrug-resistant TB. Previous history of TB and use of steroids/immunosuppressive drugs were also associated with rifampicin- and multidrug-resistant TB in multivariate analysis.CONCLUSIONSThe prevalence of DR-EPTB was high in patients who had concomitant PTB. Although the prevalences of rifampicin- and multidrug-resistant TB were low in isolated EPTB, the prevalence of isoniazid-resistant TB remained high. Therefore, drug susceptibility testing should be performed in EPTB patients, especially those who carry the aforementioned risk factors. This article is protected by copyright. All rights reserved.

Regulatory T Cells Subvert Mycobacterial Containment in Patients Failing Extensively Drug-resistant TB Treatment.

Author(s): Davids, Malika; Pooran, Anil S; Pietersen, Elize; Wainwright, Helen C; Binder, Anke

Source: American journal of respiratory and critical care medicine; Feb 2018

Publication Type(s): Journal Article

Available at American journal of respiratory and critical care medicine - from EBSCO (MEDLINE Complete)

Abstract:RATIONALEThe advent of extensively (XDR-TB) and totally drug-resistant TB, with limited or no treatment options, has facilitated renewed interest in host directed immunotherapy, particularly for therapeutically destitute patients. However, the selection and utility of such approaches depend upon understanding the host immune response in XDR-TB, which hitherto remains unexplored.OBJECTIVESTo determine the host immunological profile in patients with XDR-TB, compared to drug-sensitive TB, using peripheral blood and explanted lung tissue.METHODSBlood and explanted lung tissue were obtained from patients with XDR-TB (n=31), drug-sensitive TB (DS-TB, n=20) and presumed latent-TB infection (LTBI, n=20). T-cell phenotype (Th1/Th2/Th17/Tregs)

was evaluated in all patient groups, and Treg function assessed in XDR-TB non-responders by co-culturing PPD pre-primed effector T-cells with H37Rv-infected monocyte-derived macrophages, with or without autologous Tregs. Mycobacterial containment was evaluated by counting colony-forming units.MAIN RESULTSPatients failing XDR-TB treatment had an altered immuno-phenotype characterized by a substantial increase in the frequency (median; IQR) of CD4+CD25+FoxP3+ regulatory T-cells (11.5; 5.9-15.2) compared to DS-TB (3.4 %; 1.6-5.73; $p < 0.001$) and presumed LTBI (1.8 % 1.2-2.3; $p < 0.001$), which was unrelated to disease duration. Tregs isolated from XDR-TB patients suppressed T-cell proliferation (up to 90%) and subverted containment of H37Rv-infected monocyte-derived macrophages (by 30%; $p= 0.03$) by impairing effector T-cell function through a mechanism independent of direct cell-to-cell contact, IL-10, TGF-beta and CTLA-4.CONCLUSIONSCollectively, these data suggest that Tregs may be contributing to immune dysfunction, and bacterial persistence, in patients with XDR-TB. The relevant cellular pathways may serve as potential targets for immunotherapeutic intervention.

Palliative care for drug-resistant tuberculosis: when new drugs are not enough.

Author(s): Hughes, Jennifer; Snyman, Leigh

Source: The Lancet. Respiratory medicine; Feb 2018

Publication Type(s): Journal Article

Moxifloxacin target site concentrations in patients with pulmonary TB utilizing microdialysis: a clinical pharmacokinetic study.

Author(s): Heinrichs, M Tobias; Vashakidze, Sergo; Nikolaishvili, Ketino; Sabulua, Irina;

Source: The Journal of antimicrobial chemotherapy; Feb 2018; vol. 73 (no. 2); p. 477-483

Publication Type(s): Journal Article

Abstract: BackgroundMoxifloxacin is a second-line anti-TB drug that is useful in the treatment of drug-resistant TB. However, little is known about its target site pharmacokinetics. Lower drug concentrations at the infection site (i.e. in severe lung lesions including cavitary lesions) may lead to development and amplification of drug resistance. Improved knowledge regarding tissue penetration of anti-TB drugs will help guide drug development and optimize drug dosing.MethodsPatients with culture-confirmed drug-resistant pulmonary TB scheduled to undergo adjunctive surgical lung resection were enrolled in Tbilisi, Georgia. Five serum samples per patient were collected at different timepoints including at the time of surgical resection (approximately at Tmax). Microdialysis was performed in the ex vivo tissue immediately after resection. Non-compartmental analysis was performed and a tissue/serum concentration ratio was calculated.ResultsAmong the seven patients enrolled, the median moxifloxacin dose given was 7.7 mg/kg, the median age was 25.2 years, 57% were male and the median creatinine clearance was 95.4 mL/min. Most patients (71%) had suboptimal steady-state serum Cmax (total drug) concentrations. The median free moxifloxacin serum concentration at time of surgical resection was 1.23 μg/mL (range = 0.12-1.80) and the median free lung tissue concentration was 3.37 μg/mL (range = 0.81-5.76). The median free-tissue/free-serum concentration ratio was 3.20 (range = 0.66-28.08).ConclusionsMoxifloxacin showed excellent penetration into diseased lung tissue (including cavitary lesions) among patients with pulmonary TB. Moxifloxacin lung tissue concentrations were higher than those seen in serum. Our findings highlight the importance of moxifloxacin in the treatment of MDR-TB and potentially any patient with pulmonary TB and severe lung lesions.

Associations between Mycobacterium tuberculosis Beijing genotype and drug resistance to four first-line drugs: a survey in China.

Author(s): Liu, Haican; Zhang, Yuanyuan; Liu, Zhiguang; Liu, Jinghua; Hauck, Yolande; Liu, Jiao

Source: Frontiers of medicine; Feb 2018; vol. 12 (no. 1); p. 92-97

Publication Type(s): Journal Article

Abstract: Investigations on the genetic diversity of Mycobacterium tuberculosis in China have shown that Beijing genotype strains play a dominant role. To study the association between the M. tuberculosis Beijing genotype and the drug-resistance phenotype, 1286 M. tuberculosis clinical isolates together with epidemiological and clinical information of patients were collected from the center for tuberculosis (TB) prevention and control or TB hospitals in Beijing municipality and nine provinces or autonomous regions in China. Drug resistance testing was conducted on all the isolates to the four first-line anti-TB drugs (isoniazid, rifampicin, streptomycin, and ethambutol). A total of 585 strains were found to be resistant to at least one of the four anti-TB drugs. The Beijing family strains consisted of 499 (53.20%) drug-sensitive strains and 439 (46.80%) drug-resistant strains, whereas the non-Beijing family strains comprised 202 (58.05%) drug-sensitive strains and 146 (41.95%) drug-resistant strains. No significant difference was observed in prevalence ($\chi 2 = 2.41$, $P > 0.05$) between the drug-resistant and drugsensitive strains among the Beijing family strains. Analysis of monoresistance, multidrug-resistant TB, and geographic distribution of drug resistance did not find any relationships between the M. tuberculosis Beijing genotype and drug-resistance phenotype in China. Results confirmed that the Beijing genotype, the predominant M. tuberculosis genotype in China, was not associated with drug resistance.

Treatment Outcomes and Cohort Studies

Human cytomegalovirus epidemiology and relationship to tuberculosis and cardiovascular disease risk factors in a rural Ugandan cohort.

Author(s): Stockdale, Lisa; Nash, Stephen; Nalwoga, Angela; Painter, Hannah; Asiki, Gershim;

Source: PloS one; 2018; vol. 13 (no. 2); p. e0192086

Publication Type(s): Journal Article

Available at PloS one - from EBSCO (MEDLINE Complete)

Abstract: Human cytomegalovirus (HCMV) infection has been associated with increased mortality, specifically cardiovascular disease (CVD), in high-income countries (HICs). There is a paucity of data in low- and middle-income countries (LMICs) where HCMV seropositivity is higher. Serum samples from 2,174 Ugandan individuals were investigated for HCMV antibodies and data linked to demographic information, co-infections and a variety of CVD measurements. HCMV seropositivity was 83% by one year of age, increasing to 95% by five years. Female sex, HIV positivity and active pulmonary tuberculosis (TB) were associated with an increase in HCMV IgG levels in adjusted analyses. There was no evidence of any associations with risk factors for CVD after adjusting for age and sex. HCMV infection is ubiquitous in this rural Ugandan cohort from a young age. The association between TB disease and high HCMV IgG levels merits further research. Known CVD risk factors do not appear to be associated with higher HCMV antibody levels in this Ugandan cohort.

Infection and Microbiome: Impact of Tuberculosis on Human Gut Microbiome of Indian Cohort.

Author(s): Sood, Utkarsh; Bajaj, Abhay; Kumar, Roshan; Khurana, Sachin; Kalia, Vipin Chandra

Source: Indian journal of microbiology; Mar 2018; vol. 58 (no. 1); p. 123-125

Publication Type(s): News

Evaluation of a Urine-Based Rapid Molecular Diagnostic Test with Potential to Be Used at Point-of-Care for Pulmonary Tuberculosis: Cape Town Cohort.

Author(s): Patel, Krutarth; Nagel, Matilde; Wesolowski, Maria; Dees, Stefan; Rivera-Milla, Eric; Geldmacher, Christof; Dheda, Keertan; Hoelscher, Michael; Labugger, Ines

Source: The Journal of molecular diagnostics : JMD; Mar 2018; vol. 20 (no. 2); p. 215-224

Publication Type(s): Journal Article

PubMedID: 29269279

Abstract: Tuberculosis (TB) diagnosis among sputum-scarce patients is time consuming. Thus, a nonsputum diagnostic alternative is urgently needed. The Mycobacterium tuberculosis-specific transrenal (Tr) DNA from urine is a potential target for TB diagnostics. In this study, a new urine-based Tr-DNA molecular assay was evaluated for diagnosis of pulmonary tuberculosis among 428 adults suspected of having pulmonary TB (164 HIV positive, 263 HIV negative) from Cape Town, South Africa. Tr-DNA was isolated from 4 mL of EDTA urine, and a rapid, double-stranded, primer-based PCR method was performed targeting the Mycobacterium tuberculosis-specific direct repeat region. Each Tr-DNA eluate was tested in triplicate using an automated molecular analyzer with controls included in each test. With liquid culture used as the gold standard, the Tr-DNA assay showed sensitivity of 42.9% (n = 75/175; 95% CI, 35.4%-50.5%) and specificity of 88.6% (n = 210/237; 95% CI, 83.9%-92.4%). Among HIV-infected patients with TB, sensitivity and specificity were 45.2% and 89.0%, respectively. The combination of smear microscopy and Tr-DNA increased the sensitivity to 83.8% (smear microscopy alone, 75.1%), with 96.6% specificity. This study indicates that Tr-DNA has a moderate specificity with low sensitivity for diagnosis of pulmonary TB. Despite low sensitivity, this diagnostic test may have potential in combination with smear microscopy to support TB diagnosis in HIV-endemic regions, where sputum-scarce patients are common.

False-Positive Xpert MTB/RIF Results in Retested Patients with Previous Tuberculosis: Frequency, Profile, and Prospective Clinical Outcomes.

Author(s): Theron, Grant; Venter, Rouxjeane; Smith, Liezel; Esmail, Aliasgar; Randall, Philippa; Sood, Vishesh; Oelfese, Suzette; Calligaro, Greg; Warren, Robin; Dheda, Keertan

Source: Journal of clinical microbiology; Mar 2018; vol. 56 (no. 3)

Publication Date: Mar 2018

Publication Type(s): Journal Article

PubMedID: 29305538

Abstract: Globally, Xpert MTB/RIF (Xpert) is the most widely used PCR test for the diagnosis of tuberculosis (TB). Positive results in previously treated patients, which are due to old DNA or active disease, are a diagnostic dilemma. We prospectively retested sputum from 238 patients, irrespective of current symptoms, who were previously diagnosed to be Xpert positive and treated successfully. Patients who retested as Xpert positive and culture negative were exhaustively investigated (repeat culture, chest radiography, bronchoscopy with bronchoalveolar lavage, long-term clinical follow-up). We evaluated whether the duration since previous treatment completion, mycobacterial burden (the Xpert cycle threshold [CT] value), and reclassification of Xpert-positive results with a very low semiquantitation level to Xpert-negative results reduced the rate of false positivity. A total of 229/238 (96%) of patients were culture negative. Sixteen of 229 (7%) were Xpert positive a median of 11 months (interquartile range, 5 to 19 months) after treatment completion. The specificity was 93% (95% confidence interval [CI], 89 to 96%). Nine of 15 (40%) Xpert-positive, culture-negative patients reverted to Xpert negative after 2 to 3 months (1 patient declined further participation). Patients with false-positive Xpert results had a lower mycobacterial burden than patients with true-positive Xpert results (CT , 28.7 [95% CI, 27.2 to 30.4] versus 17.6 [95% CI, 16.9 to 18.2]; P < 0.001), an increased likelihood of a chest radiograph not compatible with active TB (5/15 patients versus 0/5 patients; P = 0.026), and less-viscous sputum (15/16 patients versus 2/5 patients whose sputum was graded as mucoid or less; P = 0.038). All patients who initially retested as Xpert positive and culture negative ("Xpert false positive") were clinically well without treatment after follow-up. The duration

since the previous treatment poorly predicted false-positive results (a duration of ≤2 years identified only 66% of patients with false-positive results). Reclassifying Xpert-positive results with a very low semiquantitation level to Xpert negative improved the specificity (+3% [95% CI, +2 to +5%]) but reduced the sensitivity (-10% [95% CI, -4 to -15%]). Patients with previous TB retested with Xpert can have false-positive results and thus not require treatment. These data inform clinical practice by highlighting the challenges in interpreting Xpert-positive results, underscore the need for culture, and have implications for next-generation ultrasensitive tests.

Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea.

Author(s): Mok, Jeongha; Kang, Hyungseok; Hwang, Soo Hee; Park, Jin Su; Kang, Bohyoung;

Source: The Journal of antimicrobial chemotherapy; Feb 2018; vol. 73 (no. 2); p. 503-508

Publication Type(s): Journal Article

Abstract: ObjectivesDelamanid is a new anti-TB drug, but few data exist on its use outside clinical trials. The purpose of this study was to evaluate the efficacy as well as the safety and tolerability of a delamanid-containing regimen for 24 weeks in the treatment of MDR- and XDR-TB.MethodsWe performed a retrospective cohort study among patients with MDR/XDR-TB who were treated with a delamanid-containing regimen in seven hospitals in South Korea.ResultsA total of 32 patients with MDR-TB, of which 6 (18.8%) were XDR-TB, were included and all completed 24 weeks of delamanid treatment. Of 19 patients (59.4%) who had positive culture sputum at the initiation of delamanid treatment, the proportion of culture conversion at 8 weeks was 72.2% (13 of 18) in solid medium and 50.0% (7 of 14) in liquid medium. The proportion of culture conversion at 24 weeks was 94.4% (17 of 18) in solid medium and 92.9% (13 of 14) in liquid medium. The median time to culture conversion was 33 days (range = 5-81) using solid medium and 57 days (range = 8-96) using liquid medium. Of the 32 patients, there was no serious adverse event or death. Three patients developed a transient QTcF of > 500 ms.ConclusionsThe use of delamanid combined with optimized background regimens has the potential to achieve high culture conversion rates at 24 weeks with an acceptable safety and tolerability profile in patients with MDR/XDR-TB.

Tuberculin skin test versus interferon-gamma release assay in refugee children: A retrospective cohort study.

Author(s): Elliot, Chris; Marais, Ben; Williams, Phoebe; Joshua, Paul; Towle, Sherri; Hart, Graham

Source: Journal of paediatrics and child health; Feb 2018

Publication Type(s): Journal Article

Abstract:AIMThe aim of this study was to assist clinicians evaluating refugee children for latent tuberculosis infection (LTBI) by comparing paired tuberculin skin test (TST) and Quantiferon Gold In-Tube (QGIT) test results with clinical management decisions and follow-up data in a large cohort of newly arrived refugee children.METHODSThis was a retrospective analysis of all refugee children (<15 years of age) evaluated for LTBI with both TST and interferon-γ release assay between 2007 and 2010 in the Illawarra-Shoalhaven region of New South Wales, Australia. Demographics, country of origin, bacille Calmette-Guerin (BCG) vaccination status, chest X-ray results, TST and QGIT test results, clinical management and outcome on long-term follow-up were assessed.RESULTSOf 272 children evaluated, complete results were available for 212 (78%). The vast majority (207; 98%) were from Africa or Southeast Asia. Overall, 33 (16%) children were treated for LTBI; 13 (39%) had concordant TST and QGIT results and 20 (61%) discordant results. Of 63 (30%) TST-positive (≥10 mm) children, 46 (73%) were QGIT assay-negative, 44 (70%) had a BCG scar, 3 (5%) were younger than 2 years and 6 (10%) were treated for LTBI. Of 32 QGIT assay-positive children, 15 (47%) were TST negative, 31 (97%) had a BCG scar, all were older than 2 years and 14 (44%) were treated for LTBI.CONCLUSIONSDiscordant TST and QGIT results were found in a high percentage of refugee

children. QGIT is convenient and more specific than TST to diagnose LTBI in BCG-vaccinated children, although a careful tuberculosis exposure history and clinical assessment to rule out active disease remain important.

Acute biliary events during anti-tuberculosis treatment: hospital case series and a nationwide cohort study.

Author(s): Chang, Lih-Yu; Lee, Chih-Hsin; Chang, Chia-Hao; Lee, Ming-Chia; Lee, Meng-Rui;

Source: BMC infectious diseases; Feb 2018; vol. 18 (no. 1); p. 64

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available at BMC Infectious Diseases - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUNDTuberculosis (TB) remains one of the major infectious diseases worldwide. Adverse reactions are common during TB treatment. Few reports, however, are available on treatment-related acute biliary events (ABEs), such as cholelithiasis, biliary obstruction, acute cholecystitis, and cholangitis.METHODSWe first report four pulmonary TB patients who developed ABEs during anti-TB treatment. Abdominal sonography revealed multiple gall stones with dilated intrahepatic ducts in three patients and cholecystitis in one patient. To investigate the incidence of and risk factors for ABEs during anti-TB treatment, we subsequently conducted a nationwide cohort study using the National Health Insurance Research Database of Taiwan.RESULTSA total of 159,566 pulmonary TB patients were identified from the database between 1996 and 2010, and among them, 195 (0.12%) developed ABEs within 180 days after beginning anti-TB treatment. Logistic regression analysis revealed that the risk factors associated with ABEs are older age (relative risk [RR]: 1.32 [1.21-1.44] per 10-year increment) and diabetes mellitus (RR: 1.59 [1.19-2.13]).CONCLUSIONSAlthough infrequently encountered, ABEs should be considered among patients with TB who experience abdominal discomfort with hyperbilirubinemia, especially patients who have older age or diabetes.

Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study.

Author(s): Ferlazzo, Gabriella; Mohr, Erika; Laxmeshwar, Chinmay; Hewison, Catherine

Source: The Lancet. Infectious diseases; Feb 2018

Publication Type(s): Journal Article

Abstract:BACKGROUNDBedaquiline and delamanid have been approved for treatment of multidrug-resistant (MDR) tuberculosis in the past 5 years. Because of theoretical safety concerns, patients have been unable to access the two drugs in combination. Médecins Sans Frontières has supported the use of combination bedaquiline and delamanid for people with few treatment options since 2016. We describe early safety and efficacy of regimens containing the bedaquiline and delamanid combination in patients with drug-resistant tuberculosis in Yerevan, Armenia; Mumbai, India; and Khayelitsha, South Africa.METHODSWe retrospectively analysed a cohort of all patients who received 6-12 months of oral bedaquiline and delamanid in combination (400 mg bedaquiline once per day for 2 weeks, then 200 mg bedaquiline three times per week and 100 mg delamanid twice per day) in MSF-supported projects. We report serious adverse events, QTc corrected using the Fridericia formula (QTcF) interval data, and culture conversion data during the first 6 months of treatment.FINDINGSBetween Jan 1, 2016, and Aug 31, 2016, 28 patients (median age 32·5 years [IQR 28·5-40·5], 17 men) were included in the analysis. 11 (39%) of 28 patients were HIV-positive. 24 patients (86%) had isolates resistant to fluoroquinolones; 14 patients (50%) had extensively drug-resistant tuberculosis. No patient had an increase of more than 500 ms in their QTcF interval. Four patients (14%) had six instances of QTcF increase of more than 60 ms from baseline but none

permanently discontinued the drugs. 16 serious adverse events were reported in seven patients. Of 23 individuals with positive baseline cultures, 17 (74%) converted to negative by month 6 of treatment.INTERPRETATIONUse of the bedaquiline and delamanid combination appears to reveal no additive or synergistic QTcF-prolonging effects. Access to bedaquiline and delamanid in combination should be expanded for people with few treatment options while awaiting the results of formal clinical trials.FUNDINGMédecins Sans Frontières (MSF).

Time to Multidrug-Resistant Tuberculosis Treatment Initiation in Association with Treatment Outcomes in Shanghai, China.

Author(s): Chen, Yong; Yuan, Zhengan; Shen, Xin; Wu, Jie; Wu, Zheyuan; Xu, Biao

Source: Antimicrobial agents and chemotherapy; Feb 2018

Publication Type(s): Journal Article

Abstract: In high TB-burden countries like China, the diagnosis of multidrug-resistant tuberculosis (MDR-TB) using conventional drug susceptibility testing (DST) takes months, making treatment delay inevitable. Poor outcomes of MDR-TB might be associated with delayed, even inappropriate treatment. The purpose of this study was to investigate the time to MDR-TB treatment initiation, and to assess the association between early treatment and treatment outcomes. Between April 2011 and December 2014, this population-based, retrospective cohort study collected the demographic and clinical characteristics, and the drug susceptibility profiles of all registered MDR-TB patients in Shanghai, China. Dates of TB and MDR-TB diagnoses, DST performing and treatment initiation were extracted to calculate the time to treatment. In total, 284 of 346 MDR-TB patients were eligible for analysis, and 68.3% (194/284) had favored outcomes. The median time to treatment initiation from TB diagnosis was 172 days among those with favored outcomes and 190 days among those with poor outcomes. Treatment initiated within 60 days after DST performing (OR 2.56, 95% CI 1.22-5.36) and empiric treatment (OR 2.09, 95% CI 1.01-4.32) were positively associated with favored outcomes. Substantial delays to MDR-TB treatment were observed when conventional DST was used. Early treatment predicted favored outcomes. Rapid diagnostic methods should be scaled up and, improvements should be made in patient management and information linkage to reduce treatment delay.

Clinical outcome of multidrug-resistant tuberculosis patients receiving standardized second-line treatment regimen in China.

Author(s): Xu, Caihong; Pang, Yu; Li, Renzhong; Ruan, Yunzhou; Wang, Lixia; Chen, Mingting; Zhang, Hui

Source: The Journal of infection; Feb 2018

Publication Type(s): Journal Article

Abstract:OBJECTIVESThe aim of this study was to retrospectively analyze the clinical outcome and the risk factors associated with poor outcome of MDR-TB patients receiving standardized second-line treatment regimen in China.METHODSBetween January 2008 and December 2010, a total of 12,100 clinical diagnosed TB cases at high risk of drug-resistant TB (DR-TB) were enrolled in this study. Routine follow-up tests were conducted every month during the 6-month intensive phase, and every two months during the 18-month continuation phase.RESULTSOn the basis of phenotypical drug susceptibility test (DST) results, 2322 MDR-TB patients were confirmed, of which 1542 further received standardized second-line anti-TB regimen. The treatment success rate was 47.6% (734/1542): 688 patients (44.6%) were cured and 46 (3.0%) completed treatment. The percentage of cases with favorable outcome in previously untreated patients (57.6%) was significantly higher than that in treatment-experienced patients (46.1%, OR: 1.58, 95% CI: 1.17-2.14). In addition, a significant lower percentage of male MDR-TB cases with favorable outcome (45.8%)

was observed using female MDR-TB cases as a reference (52.0%, OR: 1.31, 95% CI: 1.03-1.60). The proportion of MDR-TB cases with favorable outcome was significantly decreased in older age groups.CONCLUSIONSIn conclusion, our data demonstrate that less than half of these patients receiving standardized second-line treatment regimen meet the definition of successful treatment during a 3-year period in China. More attention should be paid to the MDR-TB population at high-risk of poor clinical outcome, including male, elderly age, and those who have received prior treatment.

Effects of fluconazole on the clinical outcome and immune response in fungal co-infected tuberculosis patients.

Author(s): Ren, Xiaojuan; Liu, Wei; Liu, Yi

Source: Microbial pathogenesis; Feb 2018; vol. 117 ; p. 148-152

Publication Type(s): Journal Article

Abstract: With overuse of the broad-spectrum antibiotics, the pulmonary fungal infection increasingly becomes the most common complication associated with senile pulmonary tuberculosis (TB) and attracts intensive attentions from clinicians. Here we presented the retrospective analysis of impact of fluconazole treatment on the clinical outcome and immune response in fungal co-infected tuberculosis patients. A randomized, double-blind, placebo-controlled trial of fluconazole (100 mg per day for consecutive weeks) in fungal-positive senile tuberculosis patients was conducted in our hospital. Peripheral eosinophil counts were computed by the automatic hematology analyzer. The secretory inflammatory cytokines interferon (IFN)-γ, tumor necrosis factor (TNF)-α and chemokines chemokine C-X-C motif ligand (CXCL)9, CXCL10, CXCL11 were determined with enzyme-linked immunosorbent assay kits. The peripheral T helper 1 cells (Th1) and regulatory T cells (Treg) population were analyzed by flow cytometry. None of significant difference in respect to baseline TB score was observed between placebo and fluconazole groups. Administration of fluconazole significantly stimulated eosinophils population and secretion of inflammatory cytokines IFN-γ and TNF-α. Simultaneously, the peripheral Th1% and chemokines including CXCL9, CSCL10, CXCL11 were markedly induced in response to fluconazole treatment. Fungal infection significantly affected host immunity during tuberculosis which was effectively reversed by fluconazole treatment.

A comparative study of single-stage transpedicular debridement, fusion, and posterior long-segment versus short-segment fixation for the treatment of thoracolumbar spinal tuberculosis in adults: minimum five year follow-up outcomes.

Author(s): Liu, Zheng; Zhang, Penghui; Zeng, Hao; Xu, Zhengquan; Wang, Xiyang

Source: International orthopaedics; Feb 2018

Publication Type(s): Journal Article

Abstract:DESIGNThis a retrospective study in single centre.OBJECTIVEThe objective of this retrospective clinical study is to compare the long-term clinical efficacy of posterior long-segment and short-segment fixation with single-stage transpedicular debridement and fusion for the treatment of thoracolumbar spinal tuberculosis in adults.METHODSSixty-six cases of thoracolumbar tuberculosis were treated by single-stage transpedicular debridement, bone graft fusion, and pedicle screw fixation. Thirty-five cases were under long-segment fixation (group A) and 31 cases were under short-segment fixation (group B). These patients were followed up for a minimum of five years. The clinical and radiographic results for these patients were analyzed and compared.RESULTSAll 66 patients were completely cured during the follow-up. All patients had significant improvement of neurological condition and visual analogue scale pain scores at the final follow-up. The average operation duration and blood loss in group A were more than that in group B. Kyphosis Cobb angle of both groups was significantly corrected after surgical management. The

correction rate of Cobb angle in group A was significantly higher than that in group B at the time of immediate post-operative period or the last follow-up (P < 0.05). The correction loss of group A was significantly less than that in group B (P < 0.05).CONCLUSIONBoth posterior long-segment and short-segment pedicle screw fixations for the treatment of thoracolumbar spinal tuberculosis have significant effects in the correction of kyphosis and the improvement of neurological function. Although the blood loss and operation time of long-segment fixation were more than that of short-segment fixation, long-segment fixation was superior to the short-segment fixation in the correction of kyphosis and the maintenance of spinal stability, especially in the prevention of long-term correction loss.

Predicting treatment outcome of drug-susceptible tuberculosis patients using machine-learning models.

Author(s): Hussain, Owais A; Junejo, Khurum N

Source: Informatics for health & social care; Feb 2018 ; p. 1-17

Publication Type(s): Journal Article

Abstract: Tuberculosis (TB) is a deadly contagious disease and a serious global health problem. It is curable but due to its lengthy treatment process, a patient is likely to leave the treatment incomplete, leading to a more lethal, drug resistant form of disease. The World Health Organization (WHO) propagates Directly Observed Therapy Short-course (DOTS) as an effective way to stop the spread of TB in communities with a high burden. But DOTS also adds a significant burden on the financial feasibility of the program. We aim to facilitate TB programs by predicting the outcome of the treatment of a particular patient at the start of treatment so that their health workers can be utilized in a targeted and cost-effective way. The problem was modeled as a classification problem, and the outcome of treatment was predicted using state-of-art implementations of 3 machine learning algorithms. 4213 patients were evaluated, out of which 64.37% completed their treatment. Results were evaluated using 4 performance measures; accuracy, precision, sensitivity, and specificity. The models offer an improvement of more than 12% accuracy over the baseline prediction. Empirical results also revealed some insights to improve TB programs. Overall, our proposed methodology will may help teams running TB programs manage their human resources more effectively, thus saving more lives.

Correlates of poor treatment outcomes in patients with multi-drug resistant tuberculosis in a tertiary centre in Rivers State.

Author(s): Iwunze, Ezinne C; Okeafor, Ibitein N

Source: Infectious diseases (London, England); Feb 2018; vol. 50 (no. 2); p. 150-151

Publication Type(s): Journal Article

Controlled Trials and Systematic Reviews

Evaluation of interferon-gamma release assays in extrasanguinous body fluids for diagnosing tuberculosis: A systematic review and meta-analysis

Author(s): Wen A.; Qu X.-H.; Zhang K.-N.; Wu X.-M.; Ren Y.; Leng E.-L.

Source: Life Sciences; Mar 2018; vol. 197 ; p. 140-146

Publication Type(s): Article

Abstract: Aims: In this study, we conducted a meta-analysis to systematically compare the diagnostic accuracy of IGRAs performed for extrasanguinous body fluids with that performed for blood in the diagnosis of TB. Main methods: Multiple English and Chinese databases were searched up to

November 2017. Studies that complied with the guidelines for the Quality Assessment of Diagnostic Accuracy Studies and used QuantiFERON-TB Gold In-Tube and/or T-SPOT.TB (ELISPOT) assays on both blood and extrasanguinous body fluids were included. Statistical analysis was performed using Stata 12.0 software. Since publication bias is a concern in the meta-analysis of diagnostic studies, we tested for this using Begg's funnel plots. Key finding: Among the 1332 articles searched from the databases, 24 articles met the inclusion criteria, which included 1040 samples in the patient group and 1044 samples in the control group. For extrasanguinous body fluids, the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) area under the curve (AUC) were 87% (95% CI: 0.81-0.91), 89% (95% CI: 0.84-0.93), 8.22 (95% CI 5.38-12.56), 0.15 (95% CI: 0.10-0.21), 44.92 (95% CI: 25.61-78.81), and 0.94 (95% CI: 0.92-0.96), respectively. For peripheral blood, these values were 83% (95% CI: 0.79-0.87), 74% (95% CI: 0.68-0.79), 3.17 (95% CI 2.63-3.84), 0.23 (95% CI: 0.19-0.29), 12.99 (95% CI: 10.19-16.57), and 0.86 (95% CI: 0.82-0.89), respectively. Significance: IGRAs performed on extrasanguinous body fluids exhibited a better diagnostic accuracy compared with IGRAs performed on peripheral blood for diagnosing TB. Copyright © 2018 Elsevier Inc.

Age-Specific Global Prevalence of Hepatitis B, Hepatitis C, HIV, and Tuberculosis Among Incarcerated People: A Systematic Review

Author(s): Kinner S.A.; Snow K.; Wirtz A.L.; Beyrer C.; Altice F.L.; Dolan K.

Source: Journal of Adolescent Health; Mar 2018; vol. 62 (no. 3)

Publication Type(s): Review

Abstract: Purpose: This study aims to compare the global prevalence of hepatitis B, hepatitis C, HIV, and tuberculosis in incarcerated adolescents and young adults (AYAs) and older prisoners. Methods: This study is a systematic review and meta-analysis of studies reporting the age-specific prevalence of each infection in prisoners. We grouped age-specific prevalence estimates into three overlapping age categories: AYA prisoners (<25 years), older prisoners (>=25 years), and mixed category (spanning age 25 years). We used random effects meta-analysis to estimate the relative risk (RR) of each infection in AYAs versus older prisoners. Results: Among 72 studies, there was marked heterogeneity in prevalence estimates among AYA prisoners for all infections: hepatitis B (.4%-25.2%), hepatitis C (.0%-70.6%), HIV (.0%-15.8%), and active tuberculosis (.0%-3.7%). The pooled prevalence of HIV (RR =.39, 95% confidence interval.29-.53, I2 = 79.2%) and hepatitis C (RR =.51, 95% confidence interval.33-.78, I2 = 97.8%) was lower in AYAs than in older prisoners. Conclusions: The prevalence of HIV and hepatitis C is lower in AYA prisoners than in older prisoners. Despite lower prevalence, acquisition begins early among incarcerated populations. There is an urgent need for targeted, age-appropriate prevention, treatment, and harm reduction measures in and beyond custodial settings to reduce the incidence of infection in these extremely vulnerable young people. Copyright © 2017 The Society for Adolescent Health and Medicine

Impact of quality improvement in tuberculosis laboratories in low- and lower-middle-income countries: a systematic review.

Author(s): Olaru, I D; Albert, H; Zallet, J; Werner, U-E; Ahmed, N; Rieder, H L; Salfinger, M; Kranzer, K

Source: The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease; Mar 2018; vol. 22 (no. 3); p. 309-320

Publication Type(s): Journal Article

Available at The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease - from IngentaConnect - Open Access

Abstract:BACKGROUNDThe effect of quality improvement measures on the performance of diagnostic tuberculosis (TB) laboratories in low- and lower-middle-income countries is not known,

and is the subject of this review.METHODSThree databases were searched for quality improvement studies presenting data on performance parameters before and after the implementation of quality improvement interventions.RESULTSTwenty-one studies were included in this review. Quality improvement measures were most frequently implemented by an external organization; settings targeted ranged from microscopy centers, hospitals, districts, regional and national reference laboratories. Quality improvement interventions and outcome measurements were highly heterogeneous. Most studies investigated interventions aimed at improving smear microscopy (n = 17). Two studies evaluated comprehensive quality improvement measures (n = 2) and another three studies focused on mycobacterial culture and drug susceptibility testing. Most studies showed an improvement in outcomes measured on before-after or time trend analysis.CONCLUSIONQuality improvement measures implemented in TB laboratories showed a positive impact on various outcomes. Due to the high heterogeneity of outcome reporting and interventions and the low quality of the studies, the effect size was not clear. Identification of standardized quality indicators and their link to the quality of patient care would improve knowledge in this field.

Potential of polymeric particles as future vaccine delivery systems/adjuvants for parenteral and non-parenteral immunization against tuberculosis: A systematic review

Author(s): Khademi F.; Derakhshan M.; Yousefi-Avarvand A.; Tafaghodi M.

Source: Iranian Journal of Basic Medical Sciences; Feb 2018; vol. 21 (no. 2); p. 116-123

Publication Type(s): Review

Available at Iranian Journal of Basic Medical Sciences - from Europe PubMed Central - Open Access

Abstract: Objective(s): Production of effective tuberculosis (TB) vaccine is necessity. However, the development of new subunit vaccines is faced with concerns about their weak immunogenicity. To overcome such problems, polymers-based vaccine delivery systems have been proposed to be used via various routes. The purpose of this study was to determine the potential of polymeric particles as future vaccine delivery systems/adjuvants for parenteral and non-parenteral immunization against TB. Materials and Methods: PubMed, Scopus, Science-Direct, and the ISI web of knowledge databases were searched for related keywords. A total of 420 articles, written up to June 25, 2016, were collected on the potential of polymeric particles as TB vaccine delivery systems after parenteral and non-parenteral immunization. Thirty-one relevant articles were selected by applying inclusion and exclusion criteria. Results: It was shown that the immunogenicity of TB vaccines had been improved by using biodegradable and non-biodegradable synthetic polymers as well as natural polymers and they are better able to enhance the humoral and cellular immune responses, compared to TB vaccines alone. The present study revealed that various polymeric particles, after M. tuberculosis challenge in animal models, provide long-lasting protection against TB. PLGA (poly (lactide-co-glycolide)) and chitosan polymers were widely used as TB vaccine delivery systems/adjuvants. Conclusion: It seems that PLGA and chitosan polymers are well-suited particles for the parenteral and non-parenteral administration of TB vaccines, respectively. Non-biodegradable synthetic polymers in comparison with biodegradable synthetic and natural polymers have been used less frequently. Therefore, further study on this category of polymers is required.
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The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis

Author(s): Chang T.-E.; Huang Y.-S.; Perng C.-L.; Huang Y.-H.; Hou M.-C.; Chang C.-H.

Source: Journal of the Chinese Medical Association; Feb 2018; vol. 81 (no. 2); p. 111-118

Publication Type(s): Article

Available at Journal of the Chinese Medical Association : JCMA - from ScienceDirect

Abstract: Background: Anti-tuberculosis drug-induced liver injury (ATDILI) is a major safety concern in the treatment of tuberculosis (TB). The impact of chronic hepatitis C (CHC) infection on the risk of ATDILI is still controversial. We aimed to assess the influence of CHC infection on ATDILI through a systematic review and meta-analysis. Methods: We systemically reviewed all English-language literature in the major medical databases with the subject search terms "anti-tuberculosis drug-induced liver injury" and "anti-tuberculosis drug-induced hepatotoxicity". We then performed a systematic review and meta-analysis of the papers relevant to hepatitis C in qualified publications. Results: A total of 14 studies were eligible for analysis, which included 516 cases with ATDILI and 4301 controls without ATDILI. The pooled odds ratio (OR) of all studies for CHC infection to ATDILI was 3.21 (95% confidence interval (CI): 2.30-4.49). Subgroup analysis revealed that the CHC carriers had a higher risk of ATDILI than those without CHC both in Asians (OR = 2.96, 95% CI: 1.79-4.90) and Caucasians (OR = 4.07, 95% CI: 2.70-6.14), in those receiving standard four combination anti-TB therapy (OR = 2.94, 95% CI: 1.95-4.41) and isoniazid monotherapy (OR = 4.18, 95% CI: 2.36-7.40), in those with a strict definition of DILI (serum alanine aminotransferase [ALT] > 5 upper limit of normal value [ULN], OR = 2.59, 95% CI: 1.58-4.25) and a loose definition of DILI (ALT > 2 or 3 ULN, OR = 4.34, 95% CI: 2.96-6.37), and in prospective studies (OR = 4.16, 95% CI: 2.93-5.90) and case-control studies (OR = 2.43, 95% CI: 1.29-4.58). Conclusion: This meta-analysis suggests that CHC infection may increase the risk of ATDILI. Regular liver tests are mandatory for CHC carriers under anti-TB therapy. Copyright © 2017

The effect of text messaging on latent tuberculosis treatment adherence: a randomised controlled trial.

Author(s): Johnston, James C; van der Kop, Mia L; Smillie, Kirsten; Ogilvie, Gina; Marra, Fawziah

Source: The European respiratory journal; Feb 2018; vol. 51 (no. 2)

Publication Type(s): Journal Article

Abstract: There is limited high-quality evidence available to inform the use of text messaging to improve latent tuberculosis infection (LTBI) treatment adherence.We performed a parallel, randomised controlled trial at two sites to assess the effect of a two-way short message service on LTBI adherence. We enrolled adults initiating LTBI therapy from June 2012 to September 2015 in British Columbia, Canada. Participants were randomised in a 1:1 ratio to standard LTBI treatment (control) or standard LTBI treatment plus two-way weekly text messaging (intervention). The primary outcome was treatment completion, defined as taking ≥80% prescribed doses within 12 months (isoniazid) or 6 months (rifampin) of enrolment. The trial was unblinded except for the data analyst.A total of 358 participants were assigned to the intervention (n=170) and control (n=188) arms. In intention-to-treat analysis, the proportion of participants completing LTBI therapy in the intervention and control arms was 79.4% and 81.9%, respectively (RR 0.97, 95% CI 0.88-1.07; p=0.550). Results were similar for pre-specified secondary end-points, including time-to-completion of LTBI therapy, completion of >90% of prescribed LTBI doses and health-related quality of life.Weekly two-way text messaging did not improve LTBI completion rates compared to standard LTBI care; however, completion rates were high in both treatment arms.

Sequelae of multidrug-resistant tuberculosis: protocol for a systematic review and meta-analysis.

Author(s): Alene, Kefyalew Addis; Clements, Archie C A; McBryde, Emma S; Jaramillo, Ernesto

Source: BMJ open; Feb 2018; vol. 8 (no. 2); p. e019593

Publication Type(s): Journal Article

Available at BMJ open - from HighWire - Free Full Text

Abstract:INTRODUCTIONThe sequelae of multidrug-resistant tuberculosis (MDR-TB) are poorly understood and inconsistently reported. We will aim to assess the existing evidence for the clinical,

psychological, social and economic sequelae of MDR-TB and to assess the health-related quality of life in patients with MDR-TB.METHODS AND ANALYSISWe will perform a systematic review and meta-analysis of published studies reporting sequelae of MDR-TB. We will search PubMed, SCOPUS, ProQuest, Web of Science and PsychINFO databases up to 5 September 2017. MDR-TB sequelae will include any clinical, psychological, social and economic effects as well as health-related quality of life that occur after MDR-TB treatment or illness. Two researchers will screen the titles and abstracts of all citations identified in our search, extract data, and assess the scientific quality using standardised formats. Providing there is appropriate comparability in the studies, we will use a random-effects meta-analysis model to produce pooled estimates of MDR-TB sequelae from the included studies. We will stratify the analyses based on treatment regimen, comorbidities (such as HIV status and diabetes mellitus), previous TB treatment history and study setting.ETHICS AND DISSEMINATIONAs this study will be based on published data, ethical approval is not required. The final report will be disseminated through publication in a peer-reviewed scientific journal and will also be presented at relevant conferences.PROSPERO REGISTRATION NUMBERCRD42017073182.

Multidrug-resistant tuberculosis treatment adherence in migrants: a systematic review and meta-analysis

Author(s): Nellums, Laura B; Rustage, Kieran; Hargreaves, Sally; Friedland, Jon S

Source: BMC medicine; Feb 2018; vol. 16 (no. 1); p. 27

Publication Type(s): Journal Article

Available at BMC Medicine - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUNDMultidrug-resistant tuberculosis (MDR-TB) is a growing concern in meeting global targets for TB control. In high-income low-TB-incidence countries, a disproportionate number of MDR-TB cases occur in migrant (foreign-born) populations, with concerns about low adherence rates in these patients compared to the host non-migrant population. Tackling MDR-TB in this context may, therefore, require unique approaches. We conducted a systematic review and meta-analysis to identify and synthesise data on MDR-TB treatment adherence in migrant patients to inform evidence-based strategies to improve care pathways and health outcomes in this group.METHODSThis systematic review and meta-analysis was conducted in line with PRISMA guidelines (PROSPERO 42017070756). The databases Embase, MEDLINE, Global Health and PubMed were searched to 24 May 2017 for primary research reporting MDR-TB treatment adherence and outcomes in migrant populations, with no restrictions on dates or language. A meta-analysis was conducted using random-effects models.RESULTSFrom 413 papers identified in the database search, 15 studies reporting on MDR-TB treatment outcomes for 258 migrants and 174 non-migrants were included in the systematic review and meta-analysis. The estimated rate of adherence to MDR-TB treatment across migrant patients was 71% [95% confidence interval (CI) = 58-84%], with non-adherence reported among 20% (95% CI = 4-37%) of migrant patients. A key finding was that there were no differences in estimated rates of adherence [risk ratio (RR) = 1.05; 95% CI = 0.82-1.34] or non-adherence (RR = 0.97; 95% CI = 0.79-1.36) between migrants and non-migrants.CONCLUSIONSMDR-TB treatment adherence rates among migrants in high-income low-TB-incidence countries are approaching global targets for treatment success (75%), and are comparable to rates in non-migrants. The findings highlight that only just over 70% of migrant and non-migrant patients adhere to MDR-TB treatment. The results point to the importance of increasing adherence in all patient groups, including migrants, with an emphasis on tailoring care based on social risk factors for poor adherence. We believe that MDR-TB treatment targets are not ambitious enough.

Quality of reporting of outcomes in phase III studies of pulmonary tuberculosis: a systematic review.

Author(s): Bonnett, Laura Jayne; Ken-Dror, Gie; Davies, Geraint Rhys

Source: Trials; Feb 2018; vol. 19 (no. 1); p. 134

Publication Type(s): Journal Article Review

Available at Trials - from PubMed Central

Abstract:BACKGROUNDDespite more than 60 years of clinical trials, tuberculosis (TB) still causes a high global burden of mortality and morbidity. Treatment currently requires multiple drugs in combination, taken over a prolonged period. New drugs are needed to shorten treatment duration, prevent resistance and reduce adverse events. However, to improve on current methodology in drug development, a more complete understanding of the existing clinical evidence base is required.METHODSA systematic review was undertaken to summarise outcomes reported in phase III trials of patients with newly diagnosed pulmonary TB. A systematic search of databases (PubMed, MEDLINE, EMBASE, CENTRAL and LILACs) was conducted on 30 November 2017 to retrieve relevant peer-reviewed articles. Reference lists of included studies were also searched. This systematic review considered all reported outcomes.RESULTSOf 248 included studies, 229 considered "on-treatment" outcomes whilst 148 reported "off-treatment" outcomes. There was wide variation and ambiguity in the definition of reported outcomes, including their relationship to treatment and in the time points evaluated. Additional challenges were observed regarding the analysis approach taken (per protocol versus intention to treat) and the varying durations of "intensive" and "continuation" phases of treatment. Bacteriological outcomes were most frequently reported but radiological and clinical data were often included as an implicit or explicit component of the overall definition of outcome.CONCLUSIONSTerminology used to define long-term outcomes in phase III trials is inconsistent, reflecting evolving differences in protocols and practices. For successful future cumulative meta-analysis, the findings of this review suggest that greater availability of individual patient data and the development of a core outcome set would be desirable. In the meantime, we propose a simple and logical approach which should facilitate combination of key evidence and inform improvements in the methodology of TB drug development and clinical trials.

Effects of social protection on tuberculosis treatment outcomes in low or middle-income and in high-burden countries: systematic review and meta-analysis.

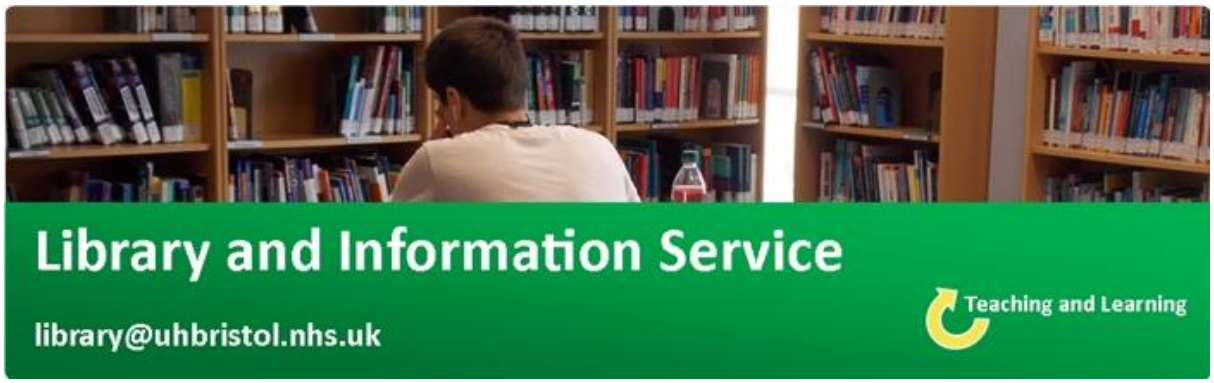
Author(s): Andrade, Kaio Vinicius Freitas de; Nery, Joilda Silva; Souza, Ramon Andrade de;

Source: Cadernos de saude publica; Feb 2018; vol. 34 (no. 1); p. e00153116

Publication Type(s): Journal Article

Available at Cadernos de Saúde Pública - from scielosp.org

Abstract: Tuberculosis (TB) is a poverty infectious disease that affects millions of people worldwide. Evidences suggest that social protection strategies (SPS) can improve TB treatment outcomes. This study aimed to synthesize such evidences through systematic literature review and meta-analysis. We searched for studies conducted in low- or middle-income and in high TB-burden countries, published during 1995-2016. The review was performed by searching PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and LILACS. We included only studies that investigated the effects of SPS on TB treatment outcomes. We retained 25 studies for qualitative synthesis. Meta-analyses were performed with 9 randomized controlled trials, including a total of 1,687 participants. Pooled results showed that SPS was associated with TB treatment success (RR = 1.09; 95%CI: 1.03-1.14), cure of TB patients (RR = 1.11; 95%CI: 1.01-1.22) and with reduction in risk of TB treatment default (RR = 0.63; 95%CI: 0.45-0.89). We did not detect effects of SPS on the outcomes treatment failure and death. These findings revealed that SPS might improve TB treatment outcomes in lower-middle-income economies or countries with high burden of this disease. However, the overall quality of evidences regarding these effect estimates is low and further well-conducted randomized studies are needed.



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