APSR RESPIRATORY UPDATES

Volume 11 Issue 1 Newsletter Date: January 2019

APSR EDUCATION PUBLICATION

Inside this issue: Updates on Treatment in Drug Resistant Tuberculosis

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World TB Day 2018: the challenge of drug resistant tuberculosis

Gupta-Wright A, et al.
F1000Res. 2018;7:217.
https://dx.doi.org/10.12688%2Ff1000research.14088.1

Overview: Drug resistant (DR) tuberculosis (TB) persists to be a burden across the globe as the detection of DR-TB is increased although the incidence of TB is reduced. The burden lies in countries adopting weak health systems including parts of Europe, Africa and Asia. This article is reminding us that current treatments of DR-TB are demanding by term of duration, compliance of patients and drug efficacy and side effects. Meanwhile, two newest anti-TB drugs, delamanid (DMD) and bedaquiline (BDQ), have been observed to be implemented in DR -TB and newer studies found fewer drugs and shorter regimens offers good outcomes and hope in treatment compliance and completion rates improvement. One of the newest studies saw the Nix-TB regimen of pretomanid, BDQ and linezolid (LZD) (NCT02333799) offered a 6-month treatment in all form of DR-TB. Addressing socioeconomic issues that underpin TB epidemic and establishing prevention strategy among those with highest risk (children or people living with HIV) is also desperately needed to combat and to eliminate DR-TB.

Drug resistant tuberculosis: challenges and progress

Kurz SG, et al.
Infect Dis Clin North Am. 2016;30(2):509-522.
https://dx.doi.org/10.1016%2Fj.idc.2016.02.010

Overview: The 2013 World Health Organization (WHO) Global Tuberculosis Report revealed an estimated 480,000 new cases of DR-TB in the world, which are 3.5% of estimated overall 9 million TB cases. The report estimates that 210,000 of 480,000 DR-TB patients died. About 9% of DR-TB have extensively drug-resistant TB (XDR-TB) found in 100 countries and of the 1269 patients from a 2011 cohort, only 284 (22%) were treated successfully and 438 (35%) died. This article emphasized that the lack and dissemination of technology to diagnose DR-TB happens to be another challenge in countries with high DR-TB incidence. This condition would

lead to poor outcomes, causing great suffering and continued transmission: less than one-third are diagnosed, about one-fifth are treated and about 5% are completing treatment. This article reminds us that advance in molecular biology has allowed resistance detection using automated mutation-based genotypic resistance testing. The test is targeting mutations in confined gene loci related to drug resistance, for examples *rpoB* in rifampicin (RIF) resistance and *gyrA* in fluoroquinolone resistance. However, gene mutations in prodrug-activating enzymes exist and are difficult to detect: *katG* producing catalase peroxidase and *inhA* promoter in isoniazid (INH) resistance, *pncA* producing synthase inhibitor in pyrazinamide (PZA) resistance and *embCAB* cluster producing arabinosyl transferase in ethambutol (EMB). This approach would be used as the backbone in determining treatment regimen in DR-TB as indicated in the upcoming WHO treatment guideline. The article also addresses current ongoing studies in determining newest treatment regimen in DR-TB. It began from the study in Bangladesh, performed by the Damien Foundation. The study goal was to achieve well-tolerated, effective, shorter and inexpensive regimen in treating DR-TB. The "Bangladesh Regimen" consisted of an intensive phase including kanamycin (KAN), clofazimine (CLO), gatifloxacin (GAT), EMB, high dose INH, PZA, and prothionamide (PTO) given for 4 months or until culture conversion, followed by a continuation phase of CLO, GAT, EMB and PZA given for 5 months. Relapse-free cure was observed in 170 of 206 patients (82.5%) during their 2 years follow-up. The success story of Bangladesh have encouraged further study in determining shorter treatment regimen (STR) in DR-TB: STREAM-1 (ISRCTN78372190, 4 moxifloxacin [MFX]-CLO-EMB-PZA-INH-KAN-PTO/5 MFX-CLO-PZA-EMB), Trial213 (NCT01424670, 6 DMD + optimized background regimen), STAND NC-006/A5344 (NCT02342886, 6 pretomanid-MFX-PZA) and NeXT (NCT02454205, 6 – 9 linezolid [LZD]-BDQ-levofloxacin [LFX]-ethionamide [ETO]-INH-PZA based on mutational analysis); most of which are expected to be finished and reported by the end of 2018.

WHO Treatment Guidelines for Drug Resistant Tuberculosis: 2016 Update

Geneva: World Health Organization. 2016.
http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

Overview: The key changes in the 2016 recommendations are as follows: (1) strong recommendation for the use of rapid diagnostics for RIF resistance (RR); (2) recommendation for

STR DR-TB under specific conditions; (3) reclassification of drugs used in the conventional (longer) DR-TB treatment regimen; (4) update in optimal composition of the conventional DR-TB treatment regimen; and (5) evidence-based recommendations on the role of surgery in DR-TB. In addition, DR-TB treatment is recommended for all patients with RR-TB, regardless of confirmed INH resistance. There was no change in the duration of the conventional DR-TB regimen or in the role of new drugs (BDQ and DMD). The WHO have now compiled individual regimens in a stepwise approach which schemed in a hierarchical order from group A to group D. Medicines in groups A, B, and C were classified as "core second-line agents," while medicines in group D were classified as "add-on agents" that were not part of the core second-line agents. Group A consists of LFX, MFX and GAT; group B consists of amikacin (AMK), capreomycin (CAP), KAN and streptomycin (SPT); group C consists of ETO, D-cycloserine (DCS), LZD and CLO; group D1 consists of PZA, EMB and high dose INH; group D2 consists of BDQ and DMD; and group D3 consists of para-aminosalicylic acid (PAS), imipenem-cilastatin (IPM), meropenem (MEM) and amoxicillin/clavulanate (AMC). Overall treatment success in Asian and African patients treated with the STR (>1,100 patients) was 90.3% compared to 78.3% in patients (>5,800) treated with conventional regimens. The STR recommendation from WHO consists of a 4–6-month intensive phase with KAN, MFX, ETO, CLO, PZA, high dose INH, EMB and a 5-month continuation phase with MFX, CLO, PZA and EMB.

Eligibility for the shorter multidrug-resistant tuberculosis regimen: ambiguities in the World Health Organization recommendations

Varaine Fet al.

Am J Respir Crit Care Med. 2016;194(8):1028-9
https://doi.org/10.1164/rccm.201605-1080LE

Overview: An important criticism of eligibility of STR among multidrug (MDR) TB is described in this article. First, the eligibility criteria states "patients with rifampicin-resistant or MDR-TB in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely". However, the document later indicates that "the shorter MDR-TB regimen" should not be used in patients who "have documented or likely re-

sistance to medicines in the regimen". Problem arise due the fact that 50% of patients with MDR-TB have isolates resistant to PZA and 61% to EMB, drugs which is used in the STR. In addition, the resistance of INH is unlikely due to the direct involvement of *rpoB* mutation in RR; however, *katG* and *inhA* mutation has implication for resistance to other drugs used in STR such as high-dose INH and ETO. The recommendations suggest that representative drug-susceptibility testing (DST) surveillance data may be used to indicate populations of eligible patients. However, they fail to expand to which drugs and at what prevalence of resistance the STR can be given or should be avoided. Second, the eligibility criteria states "[patients] who have not been previously treated with second-line drugs". However, the majority of MDR-TB is due to transmission rather than acquisition (95.9%, 95% CI 68.0–99.6) by which the strain may harbor more resistance to other drugs in the regimen. Whether the strain has been exposed to second-line drugs is unknowable, so patients with this risk factor will eventually be included under the current guidance. The article suggests a rigorous application of the resistance- and exposure-based criteria would require culture-based drug-susceptibility testing. However, the diagnostic technology is not widely available and has suboptimal sensitivity for fluoroquinolones and second-line injectable drugs. Moreover, there is no validated test to rapidly identify resistance to the other drugs. The conditions exposed within the article is a strong indication of desperate need in dissemination of molecular technology to ensure drug resistance profiling in DR-TB high burden countries to avoid treatment failure during STR.

Limited benefit of the new shorter multidrug-resistant tuberculosis regimen in Europe

Lange C, et al.
Am J Respir Crit Care Med. 2016;194(8):1029-31
https://doi.org/10.1164/rccm.201606-1097LE

Overview: Another criticism for STR eligibility criteria was addressed in this article by projecting the MDR-TB situation in Europe population. The problem is less than 8% of patients with MDR-TB in Europe, for whom comprehensive first- and second-line DST are available, would be eligible for the STR. Eligibility for the STR would further be reduced if the following

would be excluded: patients with previous exposure to second-line drugs, intolerance to second-line drugs, pregnant women, patients with extrapulmonary TB and patients from countries where not all drugs from the short-course regimen are available. Poor reliability of the DSTs to EMB and ETO for individual patients further questions the actual possibility of using the short regimen in the European region. The article suggested comprehensive DST for first-line agents, fluoroquinolones, second line injection drugs, and preferably other core and add-on second-line agents should be available before the STR can be considered for patients with MDR-TB in Europe. Again, the article criticises the inapplicability of STR due to limited understanding of drug resistance profiling, even in region where the technology itself is possible.

Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses

Ahmad Khan F, et al.
Eur Respir J. 2017 50:1700061
https://doi.org/10.1183/13993003.00061-2017

Overview: This article revealed success rate of STR in African nations along with Bangladesh and confirmed the concern regarding the ambiguous eligibility criteria. An individual patient data (IPD) meta-analysis, was performed involving patients from Bangladesh, Cameroon, Niger, Uzbekistan and Swaziland (n=796), resulting in pooled success rate of 83.0% (95%CI 71.9 – 90.3) of MDR- and RR-TB treatment using STR. The duration of intensive phase was 4 – 8 months, continuation phase was 5 – 8 months and post-treatment follow up was 1 – 2 years. The study also shown failure/relapse was more frequent in subjects treated with MFX, showed resistance to fluoroquinolone or PZA and showed absence of culture conversion by 2 months of treatment. This part of analysis resulted in recommendation that STR may be used in MDR-TB patients not previously treated with second-line drugs, and in whom fluoroquinolone and second-line injectable resistance had been excluded or were “highly unlikely”. Due to the concerns expressed in the previous articles, however, implementing advanced molecular drug resistance profiling will provide better insight in adjusting STR in DR-TB.

Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis

Sotgiu G, Migliori GB.
Lancet Respir Med. 2017;5(3):159-61
https://doi.org/10.1016/S2213-2600(16)30432-5

Overview: This article comments a sophisticated dynamic transmission model to project the reduction in MDR-TB incidence by 2024 in southeast Asian setting by adopting the STR. In the most optimistic scenario, which the STR would double treatment access and achieve long-term efficacy, incidence of MDR-TB in 2024 would be up to 23% (95% CI 10–38%) lower compared with the continued use of longer therapy. However, in the most upsetting scenario, if 30% of patients are ineligible for the short-course regimen because of second-line drug resistance, the relative change in incidence would be −2% (95% CI −20-28%). This could be happening and could result in inapplicability of the STR in countries where second line drug resistance is problematic as it was showed in Europe population. This article shows promise of treatment success in the emerging countries in south-east Asia. Again, meticulous drug resistance profiling is required to increase the treatment success rate.

Six-month response to delamanid treatment in MDR TB patients

Hewison C, et al.
Emerg Infect Dis. 2017;23(10);1746-8
https://doi.org/10.3201/eid2310.170468

Overview: The article retrospectively observed DMD treatment in 53 difficult DR-TB cases in Armenia, Belarus, Georgia, India, Russia, South Africa and Swaziland. The article showed of subjects who were culture positive at the beginning of DMD treatment, 67.6% (25/37) culture were converted by 6 months. At 6 months, 73.6% (39/53) of patients had a favorable response. It is revealed that factors associated with unfavorable response in a univariate analysis were age >35 years (odds ratio [OR] 5.62, 95% CI 1.47–21.57; p=0.012), hepatitis C infection (OR 7.78, 95% CI 1.45–41.78; p=0.017), smear positivity at the beginning of DMD treatment (OR

5.21, 95% CI 1.35–20.06; p=0.016) and serum albumin <34 g/L (OR 7.14, 95% CI 1.6–33.3; p=0.010). In addition, 31 DMD side effects were reported in 14 patients (26.4%); most common were hepatotoxicity, electrolyte imbalance and QT prolongation. This article suggested DMD could be used to strengthen on-going DR-TB treatment regimen during difficult to treat cases.

Combined use of delamanid and bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis: a systematic review

Migliori GB, et al.
Int J Mol Sci. 2017;18(2):341
https://dx.doi.org/10.3390%2Fijms18020341

Overview: The article highlighted studies (n=3) reporting two cases of difficult DR-TB in Congo and Tibet and its course during combined use of DMD and BDQ. The analysis suggested when the number of drugs are not enough to reach the recommended number of at least four to design an effective regimen, some clinicians have considered using DMD and BDQ in combination. Due to its side effect, a baseline electrocardiogram and electrolytes prior to starting the combination treatment and regularly examination during treatment should be performed. The article also showed possibility of DMD and BDQ combination during conventional DR-TB regimen treatment failure.

Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-Resistant Tuberculosis (MDR/RR-TB)

Geneva: World Health Organization. 2018.
https://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf

Overview: A draft on an updated WHO treatment guideline for DR-TB was released by the end of 2018 in regards emergence of newest evidence. The update included the results from STREAM-1 stage 1 randomised controlled trial (RCT), Otsuka phase III RCT (Trial213) of DMD, updated IPD database involving over 12,000 patients from 50 studies of longer DR-TB regimens and new data analysis from 26 African and Asian countries following the use of STR and

the worldwide use of BDQ. Key medicine change in longer treatment regimen in this update emphasized a revised grouping in TB medicines. The new groups were ranked according to its balance of effectiveness to safety and were consist of group A (prioritised and use all of three unless inapplicable: LFX/MFX, BDQ and DMD), group B (addition and use both unless inapplicable: CLO and DCS/terizidone) and group C (to complete regimen and/or when A or B is inapplicable: ETO, DMD, PZA, IPM, MEM, AMK [STE], ETO and PAS). Medicines no longer considered were KAN and CAP. The regimen choice was determined by a preference for oral over injectable agents, DST results and its reliability, population drug resistance levels, history of previous use of the medicine, drug tolerability and potential drug-drug interactions. The final decision upon the duration of intensive phase and continuation phase from this update will be finalised and published shortly. Another key change was in the STR, by which the following must be excluded prior to starting the regimen: (1) resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except INH resistance); (2) exposure to one or more second line medicines in the regimen for >1 month (unless susceptibility these second line medicines is confirmed); (3) intolerance to any medicine in the STR or risk of toxicity; (4) pregnancy; and (5) disseminated, meningeal or central nervous system TB; or any extrapulmonary disease in HIV patients. It should be noted, however, STR were associated with higher risk of treatment failure and relapse compared to longer regimens, especially when resistance to key medicines in the shorter regimen was present or when longer regimens included one or more of the group A medicines. In addition, programs and stakeholders needed to prepare towards implementation of the upcoming WHO guidelines which required adequate capacity for monitoring drug safety. This would yield the caregivers to adjust treatment in individual patients, notably the injectables (e.g. replace KAN with AMK in shorter regimen immediately); to inform patients on treatment about the relative benefits and harms of continuing their current regimen, notably KAN and ETO; and intensify clinical, safety and microbiological monitoring in order to rapidly switch patients to new DR-TB regimens upon first signs of non-response, ototoxicity or drug intolerance. Meanwhile, the reclassification of TB drugs that have changed numerous times and the inevitable introduction of new TB drugs would have a consequence that needs to be globally addressed: how should we now define a DR-TB case as an MDR, a pre-XDR, an XDR and a totally drug resistant (TDR)?

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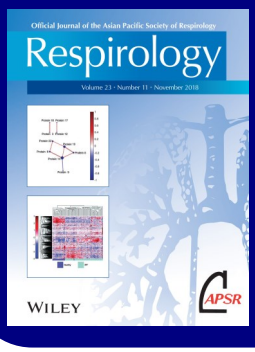

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