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DEPARTMENT OF HEALTH

CLINICAL EXPERIENCE OF TREATING XDR-TB AT JOSE PEARSON TB HOSPITAL

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JOSE PEARSON TB HOSPITAL

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Overview of JOSE PEARSON TB HOSPITAL

- Situated in the out skirts of Nelson Mandela Bay Metro Municipality. It is a 227 bedded hospital with 2 MDR TB ward and 2 XDR TB wards
- It also has a fully functional Out Patients Department. The Xray , Pharmacy, Audiology departments are located in the same building.
- Head count in a quarter is around 1400 patients
- The establishment is staffed by 3 medical officers inclusive of the Clinical Medical Manager and very few nursing staff.
- It is regarded as a Centre of Excellence in the Province as it admits Pre XDR and XDR TB patients and complicated MDR TB patients

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- It supports Nelson Mandela Bay Metro Municipality, and Sarah Baartman predominantly but also the rest of the province especially with XDR paediatrics
- It also supports the PHC in the area and more so SUB DISTRICT B due to proximity with their MDR TB patients
- It also supports Correctional Services in the region with St Albans being the gate way through which Correctional Services refers the inmates.

XDR TB

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- Eastern cape region especially Nelson Mandela Bay Metro has a unique strain of Drug Resistant TB called the atypical Beijing Strain. This strain has shown increasing levels of mutations and resistance to the 2nd line drugs. This has resulted in an increase in XDR TB more so the primary XDR TB.
- NICD has uncovered that there seems also to be an increase in the spread of the same strain among patients in the Metro which was mapped out to patients who seem to be gravitating to common areas in the region. This information indicated to us the likelihood of patients who perhaps move in the same social circles (e.g taverns etc)

Diagnostics

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- Since the introduction and roll out of Gene Xpert in the Province, the time from diagnosis of a DR TB patient has become shorter and this has assisted in linking more patients to care, as well as putting them on the appropriate treatment. Better Gene Xpert called GXP Ultra is to be introduced which will enable us to do tests on samples other than sputum for Extra Pulmonary TB.
- With the introduction of Line Probe Assay 1 were able to refine the dynamics and streamline our patient population more.
- In resent times, with the introduction of Line probe Assay 2(Drug Resistance TB reflex testing), the time has been reduced further to around 28 days on average sometimes earlier. This is indeed has been a break through in XDR TB Management
- Phenotypic DST remains the gold standard of diagnosing XDR TB in patients who have been previously exposed to 2nd line TB drugs.

Diagnostics cont.

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- With XDR TB there are varying forms of XDR TB depending on the extend of resistance as shown through further testing using Extended Drug sensitivity(ESDST) methods which employs testing for newer drugs in addition to the normal Drugs used for XDR TB.
- This has assisted the country and the province through NICD to revisit cases which were earlier classified as Totally Resistant TB (TDR TB). More and more patients have been shown to have sensitivity to some drugs which they were exposed to and has offered them a chance with the introduction of Newer drugs Bedaquiline, Delaminid, Pretonamid,etc. in combination with the repurposed drugs like Clofazimine, Rifabutin and some antibiotics which have shown good results in DR TB management eg. Linezolid, Carbapenems.

Treatment-BEDAQUILINE

- XDR TB Treatment has come a long way from the old regimen with Capreomycin to the current standard use of Bedaquiline, Linezolid,Clofazimine .
- Premise for WHO-recommended regimen: (which South Africa has adopted and introduction came through BCAP.
  - Z + at least 4 drugs considered to be effective
  - Test for *in vitro* resistance (NB: shortcomings of conventional DST)
- Bedaquiline may be indicated if regimen is not feasible due to:
  - additional resistance to fluoroquinolones or injectable
  - known adverse drug reactions, poor tolerance, or contraindication
- Potential role in XDR-TB (Group 5 drugs) group D2
- Dose and duration to be strictly observed – 400mg daily for the first two weeks, followed by 200mg three times per week for 22 weeks (6 months total duration)
- *Not to be added alone to a failing regimen !*

Cont: Eligibility Criteria

- Patients 18 years and above
- Laboratory confirmed RR-TB by culture DST or LPA or PCR from all sites pulmonary or extra-pulmonary sites
- No history of QT prolongation or family history and a baseline QTcF >450msec
- Any one of the following:

-Drug Resistance in addition to RR TB(XDR TB or Pre XDR Or both KatG and inhA mutations

-Documented intolerance to 2nd line TB drugs at baseline e.g hearing loss, renal dysfunction

-History of or surgical candidate for pneumonectomy or lobectomy

This is irrespective of site of TB infection.

Bedaquiline is for 6months, beyond this presentation to the clinical advisory committee should be made.

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- ABSOLUTE:
  - Patient refuses consent,
  - High risk of cardiac complications
  - history of severe allergic reaction to Bedaquiline
  - Note all the drug interactions to TCA(amytryptaline), Neuroleptics(haloperidol)

  RELATIVE:

  Avoid Moxifloxacin as it may prolong QTc interval rather use Levofloxacin. If there is proven resistance to Levofloxacin , use Moxifloxacin with weekly QTc monitoring for the 1st month on BDQ

Regimen

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- Bedaquiline 400mg daily for 2 weeks
- Bedaquiline 200mg 3 X weekly 22 weeks
- Levofloxacin 1000mg daily
- Linezolid 600mg daily
- Clofazimne 100mg daily
- PAS 8g daily
- Terizidone 750mg
- Then+/- High dose INH 600mg
- Ethambutol 1200mg daily
- PZA 1750mg daily

Treatment cont.(Active Pharmacovigilance)

- Special measures are in place to ensure early detection and proper management of adverse drug reactions
- PLHIV who will be receiving bedaquiline as part of MDR-TB treatment should have ART regimens designed in close consultation with HIV specialists
- Mandatory monitoring is required:
  - Cardiac dysrhythmia, QT prolongation
  - Liver dysfunction, renal impairment, other
  - Caution: potential additive effects of drugs causing QT prolongation (eg. moxifloxacin, clofazimine)

Treatment-DELAMANID

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- Delamanid may be indicated if such a regimen is not feasible because of:
  - additional resistance to fluoroquinolones or injectable second-line drugs
  - Higher risk for poor outcomes (eg drug intolerance or contra-indication, extensive or advanced disease)
  - Delaminid is also following a National protocol through DCAP
- While experience in the use of delamanid in the management of XDR-TB is very limited, there may be a benefit given the limitations in designing an effective regimen. No recommendation on the joint administration of bedaquiline and delamanid (no data available) . However there had been agreements on a per patient basis to use them in combination through Compassionate Use Program
- Delamanid should not be added alone to a failing regimen.
- All possible measures should be taken to protect the efficacy of the drug.
- The recommended dose of delamanid in adults is 100 mg twice a day, irrespective of body-weight, for a period of 6 months.

Treatment cont.

- Sound treatment and management protocols, clear patient eligibility criteria, defined roles and responsibilities of all professionals involved
- prospective data capture for effectiveness and safety
- preferably, approval by national ethics body
- preferably, independent oversight and monitoring (e.g. national MDR-TB advisory group)
- all measures to enable patient's adherence must be in place before starting treatment to avoid emergence of resistance

Treatment cont.(Active pharmacovigilance)

- Special measures are in place to ensure early detection and proper management of adverse drug reactions and DDIs
- Limited data available on DDI with ARVs – PLHIV who will be receiving delamanid as part of MDR-TB treatment should have ART regimens designed in close consultation with HIV specialists
- Caution on potential interaction other QT prolonging drugs (fluoroquinolones, clofazimine) that may potentially increase the risk of cardiotoxicity.
- Active pharmacovigilance techniques will be needed to improve the early detection of adverse drug reactions.

Patient Readiness-Informed consent, adherence counselling and social support.

- Due process for informed consent of the patient according to national policies is followed. Patients are informed on novel nature of the product, benefits and potential harms, reasons for inclusion
- Applies to all situations where bedaquiline and delamanid is used, including compassionate use.
- Patients are referred to a Social Worker and counsellors for adherence counselling, home assessments and social circumstances are assessed, as well as social support through assistance with Grant applications with SASSA, facilitation of ID applications with Home Affairs. These form the core when we consider patients willingness to start treatment.

Outcomes and Decentralization

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- XDR TB success rate has improved greatly from 18% before 2015 to >60 % in the 2015 cohort. Evaluated now in 2017.
- ALOES has become shorter from 6months to about 3months average
- Sputum conversion rate both smear and culture has improved. More patients convert in a month or two.
- Death rate has generally improved
- More patients are then followed up at the decentralized sites in the Metro and Sarah Baartman. Referral pathways have been developed which have made it easy and more defined for UP and Down referrals
- 22 patients were treated on Compassionate Use Delaminid program and are doing well after 6 months on treatment

Challenges

- Lost to follow up remains a challenge
- Increased incidences of patients refusing hospital treatment (RHT) which has actually led us to institute Out patient Bedaquiline management, however more so in MDR TB patients than XDR TB patients
- Infrastructure in terms of Infection control standards is lacking. The New Ext Building of single cubicles has become more of infection control nightmare, rain comes through and dust as PE is a highly windy city. The rest of the wards are old and of dormitory style and difficult to isolate patients. This has also affected the rapidity with which Compassionate Use program takes off.
- Staffing shortages, especially clinical and nursing and the absence of disciplines like Dietetics, physiotherapy and psychologist.

New Developments

- DCAP and the Compassionate Use Program for Delaminid
- Analysis of the 1st cohort of 9 month regimen
- Research and Development of research space
- Paediatric intensified case finding scale up assisted by URC-SA

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- Partnerships with NGOs in the Metro URC-SA,JPSA, etc.
- SAMRC

References

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- **Current WHO policy recommendations on the use of new drugs (Bedaquiline and Delamanid) presentation by Ernesto Jaramillo**
- **Introduction of New Drugs and Drug regimens for the Management of Drug Resistant Tuberculosis in South Africa:Policy framework v1.1:June 2015**

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Thank You.