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ISONIAZID-RESISTANT TUBERCULOSIS IN CHILDREN

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Abstract: The epidemiological context of tuberculosis (TB) and drug resistance should be taken into account to enhance the strategies for detecting cases of drug-resistant TB (dr-TB). Surveillance data and drug resistance surveys are crucial to help determine the probability (or risk) of an individual patient or group of patients having dr-TB, which is necessary to establish effective management strategies for these cases.

Keywords: isoniazid resistance, diagnosis, treatment.

TUBERCULOSIS RESISTENTE A ISONIACIDA EN NIÑOS

Resumen. Se debe tener en cuenta el contexto epidemiológico de la tuberculosis (TB) y la resistencia a fármacos para optimizar las estrategias de detección de casos de TB resistente (TB-r). Los datos de la vigilancia y las encuestas de resistencia a medicamentos son cruciales para ayudar a determinar la probabilidad (o riesgo) de que un paciente individual o un grupo de pacientes tenga TB-r, lo cual es necesario para establecer estrategias efectivas de manejo de estos casos.

Palabras clave: resistencia a isoniacida, diagnóstico, tratamiento.

TUBERCULOSE RESISTENTE A ISONIAZIDA EM CRIANÇAS

Resumo: O contexto epidemiológico da tuberculose (TB) e da resistência a fármacos deve ser levado em consideração para otimizar as estratégias de deteção de casos de TB resistente (TB-r). Os dados de vigilância e os inquéritos de resistência a medicamentos são cruciais para ajudar a determinar a probabilidade (ou risco) de que um doente individual ou um grupo de doentes possua TB-r, o que é necessário para estabelecer estratégias de gestão eficazes destes casos.

Palavras-chave: resistência à isoniazida, diagnóstico, tratamento

ISONIAZID-RESISTANT TUBERCULOSIS IN CHILDREN

INTRODUCTION

Drug-resistant tuberculosis (dr-TB) is one of the major public health problems that hinder TB control worldwide.

According to the World Health Organization (WHO), an estimated 558,000 individuals (483,000-639,000) developed rifampicin-resistant TB (RR-TB) in 2017 worldwide, which is the most effective first-line drug, and of these individuals, 82% had multidrug-resistant TB (MDR-TB).

Data on the levels of isoniazid (H) resistance without concurrent rifampicin (R) resistance are available for 149 countries for the period 2003-2017. The global averages of H-resistant TB (Hr-TB) without concurrent R resistance were 7.1% (95% CI: 6.2-8.0%) in newly reported cases and 7.9% (95% CI 5.9-10%) in previously treated TB cases (World Health Organization, 2018).

Mycobacterium tuberculosis may become resistant to the drugs used to treat TB:

- Primary or initial resistance: by human-to-human transmission of a resistant strain
- Acquired resistance: resulting from an inadequate or incomplete treatment regime, which makes strains resistant to treatment

Transmission of dr-TB occurs in exactly the same way as the transmission of drug-sensitive TB.

H is one of the most important first-line drugs for the treatment of TB and TB infection, with an elevated bactericidal activity and a good safety profile. The emergence of Hr-TB strains threatens to reduce the effectiveness of TB treatment.

Early detection of drug resistance facilitates the use of the most appropriate treatment regimens, which has an important impact on TB control.

TYPES OF RESISTANCE

Cases resistant to anti-tuberculosis drugs are classified into categories based on the outcome of the antibiogram (World Health Organization, 2019):

1. Monoresistance: resistance to a single first-line anti-TB drug
2. Polyresistance: resistance to more than one first-line anti-TB drug, other than H + R together
3. Multidrug-resistant TB (MDR-TB): resistance to at least H + R
4. Extensively drug-resistance TB (XDR-TB): MDR-TB that is also resistant to fluoroquinolones and at least to one of the three second-line injectable drugs (capreomycin, kanamycin, and amikacin)
5. Rifampicin resistance (RR): resistance to R detected using phenotype or genotypic methods, with or without resistance to other anti-TB drugs. This includes any resistance to R, in the form of monoresistance, polyresistance, MDR-TB or XDR-TB. MDR-TB and RR-TB cases are often grouped as MDR/RR-TB.

6. Resistance to H: *Mycobacterium tuberculosis* strains in which H resistance and R susceptibility have been confirmed in vitro.

Since the frequency of mono- and polyresistance to R is generally low, all TB patients infected with R-resistant strains should be treated with a full regimen of MDR-TB, including isoniazid, until sensitivity tests results are obtained and then the necessary adjustments are made. It is advisable that these cases be managed by dr-TB specialists. This bulletin will focus on Hr-TB.

MANAGEMENT OF ISONIAZID-RESISTANT TUBERCULOSIS IN CHILDREN

The diagnosis of dr-TB should be based on the patients' history and on clinical suspicion. This diagnosis is always microbiological and/or molecular (the clinical symptoms and radiological information of dr-TB are indistinguishable from those of drug-sensitive TB).

Sensitivity testing to anti-TB drugs is recommended as early as possible, as this could lead to an early introduction of an appropriate treatment, resulting in higher cure rates, lower risk of additional resistance, and less possibility of dr-TB transmission.

History and clinical suspicion

Children with dr-TB usually have initial resistance which had been transmitted from a primary case with dr-TB. This should be suspected in the following cases:

- Contact with a diagnosed case of dr-TB
- Contact with a suspected case of dr-TB, due to treatment failure, re-treatment, or death
- Children who do not respond to first-line treatment despite evidence of adherence
- Previously treated children who present with a recurrence of their disease
- Children from countries with high rates of dr-TB

Laboratory tests

The majority of young children will not be able to produce sputum samples, so sputum induction, gastric lavage, or bronchoscopy may be needed to obtain a sample.

If a sample is available, testing for sensitivity to at least H and R should be performed in all children with TB. If resistance to R and/or H is shown, testing for susceptibility to fluoroquinolones and second-line injectable drugs is recommended.

There are two types of drug sensitivity tests (Caminero et al., 2017):

- Phenotypic testing (conventional test): determines whether a strain is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug. Results take 2-3 weeks if liquid mediums are used, and up to 4-8 weeks for solid mediums.

- Genotypic testing (molecular test): detects mutations in the genome associated with a specific resistance to a drug. These tests provide results in a matter of hours, as they detect mutations in the genes that encode resistance to anti-TB drugs using gene amplification techniques. These techniques include the following:
    - Xpert MTB/RIF (Cepheid): can detect R resistance in a sputum sample within 2 hours. It may also be used as an initial diagnostic test, as it is much more sensitive than bacilloscopy.
    - GenotypeMDRplus (Hain) or Line Probe Assay: can simultaneously detect mutations in the genes encoding resistance to H (katG and inhA) and R (rpoB) in 6-24 hours.
    - GenotypeMDRsl (Hain) version 2: can detect resistance to fluoroquinolones (mutations in the gyrA and gyrB genes) and to second-line injectable drugs (mutations in the rrs genes and eis promoter regions)

Treatment

The basic principles of TB treatment are the following:

1. Drugs should be associated and administered in single dosages whenever possible to prevent resistance
2. Treatment should be extended long enough to ensure healing and prevent relapse

Most cases of TB can be cured with a proper regimen and strict monitoring of medication intake.

The treatment of children without bacteriological confirmation or an antibiogram, who have clinical evidence of TB disease and a history of contact with a case of dr-TB, should be guided by the sensitivity test results and the history of exposure of the index case to anti-TB drugs.

According to the WHO (World Health Organization, 2019), treatment with rifampicin, ethambutol, pyrazinamide, and levofloxacin for 6 months is recommended (6REZ-Lfx) for patients with confirmed resistance to H who are sensitive to R. Adding streptomycin or other injectable agents to the treatment regimen is not recommended. Sensitivity to fluoroquinolones (FQs) should be confirmed before starting treatment.

Dr. Caminero (Caminero et al., 2017) proposes alternative treatment guidelines for cases with Hr-TB (mono or polyresistant), with sensitivity to R:

- 9HRZE (isoniazid + rifampicin + pyrazinamide + ethambutol for 9 months). If this scheme is chosen, high dosages of H should be administered.
- 2FQ-REZ / 7FQ-RE (2 months with fluoroquinolone + rifampicin + pyrazinamide + ethambutol and 7 months with fluoroquinolone + rifampicin + ethambutol).
- 2RZE/10RE (2 months with rifampicin + pyrazinamide + ethambutol and 10 months with rifampicin + ethambutol)

FQs (Lfx or moxifloxacin) should only be introduced into the regimen if it is administered from the beginning with the rest of the drugs. It should not be added if the result of H resistance is

received after 3-4 weeks of treatment because of the possible risk of performing a covert monotherapy. In that case, the use of 9HRZE is recommended.

Although FQs have been shown to retard cartilage development in beagle puppies, similar effects have not been shown in humans. The benefit of FQs in treating dr-TB in children has been shown to outweigh any risks (World Health Organization, 2014).

Close clinical monitoring is essential for all patients receiving this regimen, particularly for liver function tests, given the hepatotoxic potential of prolonged use of Z. All patients should be tested monthly for transaminases, if possible. In addition, to prevent and control the possible toxic effects of E in children (e.g. retrobulbar neuritis), it is necessary to administer the correct dosages recommended for children. Early signs of E toxicity can be assessed in older children using red-green colour discrimination tests.

In general, anti-TB drugs should be dosed according to body weight (Table 1. Recommended dosages of anti-TB drugs used in children with Hr-TB and their main adverse effects). Consequently, monthly recording of weight is especially important in paediatric cases, and dosages should be adjusted as children gain weight.

The expert opinion is that all drugs, including FQs, should be dosed at the upper end of the recommended ranges whenever possible, except E, which should be dosed at 15 mg/kg, rather than 25 mg/kg, as sometimes used in adults with dr-TB, as it is more difficult to manage optic neuritis in children.

Adherence to treatment is one of the main challenges, especially during the continuation phase. This is why it is important to advise children and their families on the importance of completing the full TB treatment cycle and to administer said treatment under direct supervision.

In children, microbiological monitoring of their responses to treatment is often difficult (for the same reasons that a microbiological diagnosis is difficult to obtain). This makes the diagnosis of treatment failure difficult. Persistent abnormalities on chest X-rays do not necessarily mean a lack of improvement. Weight loss or, more commonly, the inability to gain weight adequately with an adequate food intake is often one of the first (or only) signs of treatment failure. This is another fundamental reason for careful weight control in children.

When additional resistance is suspected or confirmed, treatment regimens should be designed individually, and referral to a specialised dr-TB treatment unit is advised.

Table 1. Recommended dosages of anti-TB drugs used in children with Hr-TB and their main adverse effects

Drug	Dosage/kg/day	Maximum daily dosage	Toxicity
Rifampicin (R)	10-20 mg	600 mg	Gastrointestinal intolerance, arthralgia, flu-like syndrome, 1% hepatitis, interstitial nephritis, orange-coloured secretions
Ethambutol (E)	15-25 mg	2.5 g	Optic neuritis, altered colour perception
Pyrazinamide (Z)	30–40 mg	2 g	Hyperuricaemia, hepatitis, gastrointestinal intolerance, arthralgia, photosensitivity
Levofloxacin (Lfx)	15-20 mg	1.5 g	Gastrointestinal discomfort, paraesthesia, insomnia, tendon rupture, QT prolongation
Moxifloxacin (Mfx)[1]	10-15 mg	400 mg	Gastrointestinal discomfort, paraesthesia, insomnia, tendon rupture, QT prolongation
Isoniazid (H)[2]	15-20 mg	300 mg	Hepatotoxicity, peripheral neuropathy

[1] 10 mg/kg during <6 months [2] large doses

Source: (World Health Organization, 2019). WHO consolidated guidelines on drug-resistant tuberculosis treatment; (Mellado Peña et al., 2018). Actualización del tratamiento de la tuberculosis en niños.

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RINSAD

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