SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

FEMI

XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

OVIEDO
17-20 Noviembre 2010

Auditorio-Palacio de Congresos
"Príncipe Felipe"

II Congreso Ibérico de Medicina Interna

VII Congreso de la Sociedad Asturiana de Medicina Interna

TUBERCULOSIS 2010, el desafío continua.

XXXI Congreso Nacional de la Sociedad Española de Medicina Interna
Oviedo 17-21Noviembre 2010.

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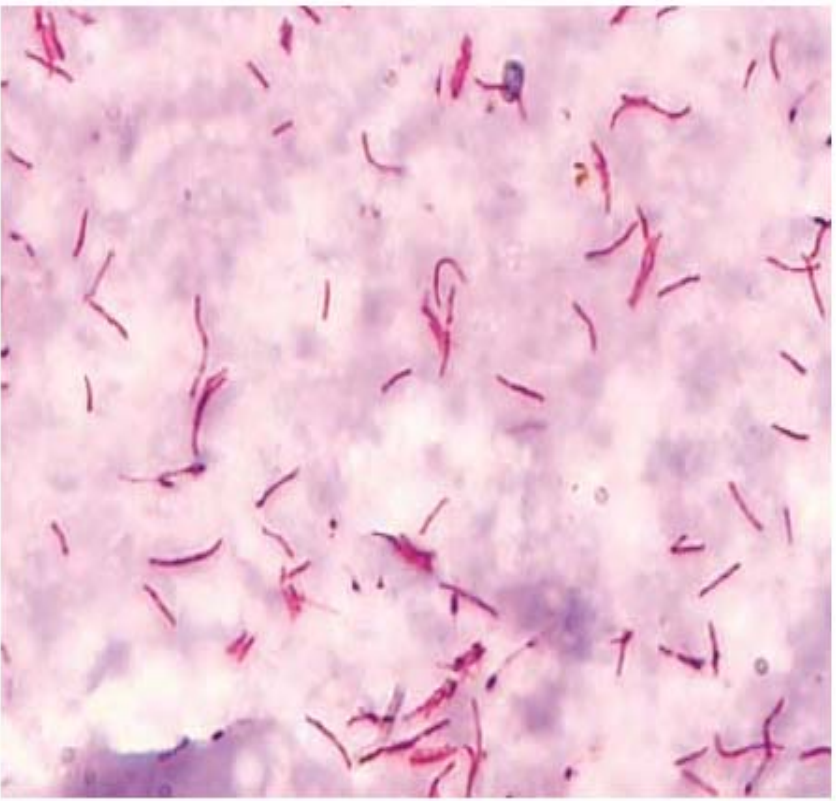


¿ Cuales son los problemas actuales en el manejo y tratamiento de los pacientes con tuberculosis ?

…… Algunos problemas

1.- Manejo de un paciente "normal" con tuberculosis a través de los estándares internacionales de cuidados.

2.- TBC extrapulmonar.

3.- TBC y VIH.

4.- TBC y toxicidad.

5.- TBC multirresistente y XDR

Bibliografía consultada

Revisión bibliográfica.

Informes de la OMS.

Guía TBC ATS 2003.

Guía TBC NICE 2007.

Guía Canadiense TBC 2007.

Guía OMS TBC-MR Emergency Update 2008.

Guías OMS: TBC 2009.

Guía SEPAR-SEIMC 2010.

La tuberculosis tiene dos mundos

* Países pobres y en desarrollo: 95% de los pacientes.

* Países ricos desarrollados: el 5% de los pacientes.

La OMS dicta normas para todos, pero fundamentalmente para los primeros.

Las sociedades científicas fundamentalmente para los segundos.

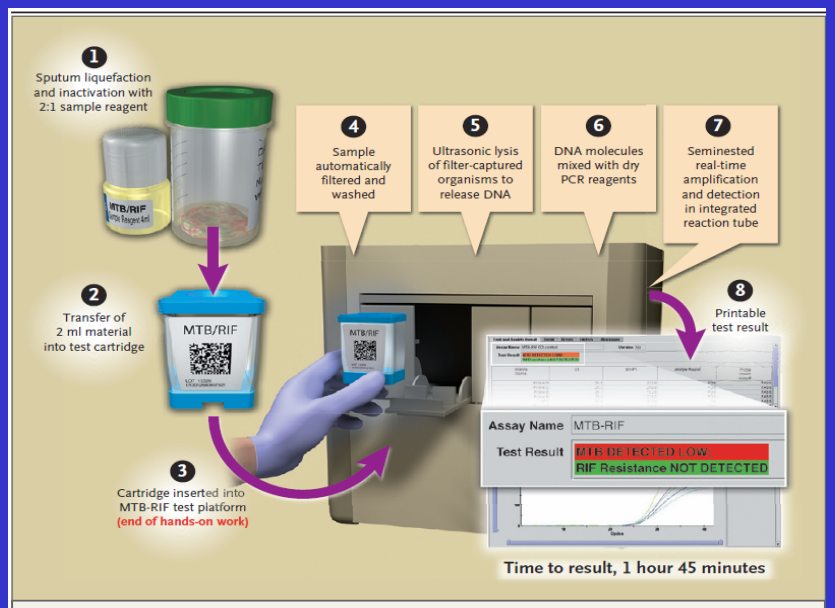


Figure 2. Assay Procedure for the MTB/RIF Test.
Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

El cuidado de un paciente con tuberculosis a través de los estándares internacionales (ISTC.OMS)

Lancet Infect Dis 2006;6:710-725.

***International Standards for Tuberculosis Care (ISTC)*, 2nd ed. The Hague, Tuberculosis Coalition for Technical Assistance, 2009.**

El propósito de los ISTC es describir un ampliamente aceptado nivel de cuidados de alta calidad que todos los médicos deberían alcanzar en los pacientes con sospecha de tuberculosis o ya diagnosticada.

Estándar: Nivel óptimo que se pretende alcanzar.

Evaluación de la calidad

*Los estándares individuales, dentro del conjunto de los ISTC, pueden ser utilizados para medir la calidad de los servicios prestados.

*Pueden ser usados como herramientas para monitorizar y evaluar la calidad identificando debilidades y por tanto áreas de mejora.

Estándares internacionales de cuidados

Los principios básicos son los mismos para todo el mundo son:

*Diagnostico rápido y preciso.

*Aplicar un tratamiento apropiado con supervisión y monitorización.

*Control salud publica.

Se resumen en….

Standards for Diagnosis

Standard 1. All persons with otherwise **unexplained productive cough lasting two-three weeks** or more should be evaluated for tuberculosis.

Standard 2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have **at least two sputum specimens** submitted for microscopic examination in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained.

Standard 3. For all patients (adults, adolescents, and children) suspected of having **extrapulmonary tuberculosis**, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, and histopathological examination.

Standard 4. All persons with **chest radiographic** findings suggestive of tuberculosis should have **sputum specimens** submitted for microbiological examination.

Standards for Diagnosis

Standard 5. The diagnosis of **sputum smear-negative pulmonary tuberculosis** should be based on the following criteria: at least two negative sputum smears (including at least one early morning specimen); chest radiographic findings consistent with tuberculosis; and lack of response to a trial of broadspectrum antimicrobial agents. (Note: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, sputum cultures should be obtained. In persons who are seriously ill or have known or suspected HIV infection, the diagnostic evaluation should be expedited and if clinical evidence strongly suggests tuberculosis, a course of antituberculosis treatment should be initiated.

Standard 6. In all **children** suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of sputum (by expectoration, gastric washings, or induced sputum) for smear microscopy and culture. In the event of negative bacteriological results, a diagnosis of tuberculosis should be based on the presence of abnormalities consistent with tuberculosis on chest radiography, a history of exposure to an infectious case, evidence of tuberculosis infection (positive tuberculin skin test or interferon-gamma release assay), and clinical findings suggestive of tuberculosis. For children suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.

Standards for Treatment

Standard 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance. To fulfill this **responsibility the practitioner** must not only prescribe an appropriate regimen, but also utilize local public health services and other agencies, when necessary, to assess the adherence of the patient and to address poor adherence when it occurs.

Standard 8. All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted **first-line treatment regimen** using drugs of known bioavailability. The initial phase should consist of two months of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). The continuation phase should consist of isoniazid and rifampicin given for four months. The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations (FDCs) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended.

Standard 9. To assess and foster adherence, **a patient-centered approach** to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. **Supervision and support** should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patientcentered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (**directly observed treatment or DOT**) and identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV) who is acceptable and accountable to the patient and to the health system. Appropriate incentives and enablers, including financial support, may also serve to enhance treatment adherence.

Standards for Treatment

Standard 10. Response to therapy in patients with pulmonary tuberculosis should be monitored by follow-up sputum microscopy (two specimens) at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum smears should be examined again at 3 months and, if positive, culture and drug susceptibility testing should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Standard 11. An assessment of the likelihood of **drug resistance**, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Drug susceptibility testing should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear-positive at completion of 3 months of treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely culture and testing for susceptibility/resistance to at least isoniazid and rifampicin should be performed promptly. Patient counseling and education should begin immediately to minimize the potential for transmission. **Infection control measures** appropriate to the setting should be applied.

Standard 12. Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing **second-line antituberculosis drugs**. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used and treatment should be given for at least 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Standard 13. A **written record** of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Standard 14. HIV testing and counseling should be recommended to all patients with, or suspected of having, tuberculosis. Testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure. Because of the close relationship of tuberculosis and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

Standard 15. All patients with tuberculosis and HIV infection should be evaluated to determine if **antiretroviral therapy** is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed **latent tuberculosis infection** with isoniazid for 6-9 months.

Standard 17. All providers should conduct a thorough assessment for **co-morbid conditions** that could affect tuberculosis treatment response or outcome. At the time the treatment plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualized plan of care. This plan should include assessment of and referrals for treatment of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programs, tobacco smoking cessation programs, and other psychosocial support services, or to such services as antenatal or well baby care.

Standards for Public Health

Standard 18. All providers of care for patients with tuberculosis should ensure that persons who are in **close contact** with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosisif the disease develops; and 4) is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:

- Persons with symptoms suggestive of tuberculosis
- Children aged <5 years
- Contacts with known or suspected immunocompromise, particularly HIV infection
- Contacts of patients with MDR/XDR tuberculosis

Other close contacts are a lower priority group.

Standard 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be **treated for presumed latent** tuberculosis infection with isoniazid.

Standard 20. Each healthcare facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis **infection control plan**.

Standard 21. All providers must **report** both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Algoritmo atención enfermo con Tuberculosis

Urgencias Hospitales
Planta Hospitalización
Consultas externas
Atención Primaria

Solicitud de ingreso de enfermo con TBC o sospecha*
Teléfono 915867579 / 7623

Ingreso en Unidad: Tríptico informativo*
Revisión de documentación clínica y microbiológica

Historia estandarizada* de enfermería-médica y exploración

Tratamiento y cuidados según protocolo de actuación*

Estudio de contactos según protocolo de actuación*

Determinaciones analíticas y microbiológicas

Seguimiento clínico. Indicadores proceso*

Alta hospitalaria. Declaración EDO.
Informe de alta estandarizado*

Seguimiento ambulante*

Alta definitiva. Informe y EDO final.
Indicadores resultado*

Registro

Indicadores proceso y resultado.

Ingreso

Diagnóstico:

Historia, exploración, rx tórax, BK, cultivo, antibiograma.
Serología VIH.

Tratamiento:

4 fármacos con TDO
Control clínico-analítico de efectos adversos.

Salud publica:

Estudio de contactos realizado
Solicitud de TDO extrahospitalario
Informe de alta y declaración EDO.

Indicadores proceso y resultado.

Consulta

Tratamiento:

- **Control clínico.**
- **Control microbiologico:**
  - **BK y cultivo de esputo al 2º, 4º y 6º meses.**
- **Control analítico si procede.**
- **Cambio a fármacos de mantenimiento al 2º mes.**
- **Establecer tiempo total de tratamiento**
- **Rx tórax al finalizar el tratamiento.**

Salud publica:

- **EDO final**
- **Informe con Resultados OMS.**

Índices de diagnostico y tratamiento	**100%**
Control de efectos adversos	**100%**
Serología VIH	**98,7%**
Informe de alta hospitalaria	**99,4 %**
Seguimiento clínico	**99,4 %**
Declaración salud publica	**94,9 %**
Rx final	**94,11 %**
Informe final	**80,12 %**
Control cultivo al finalizar tratamiento	**59,70 %**
TDO extrahospitalario	**37,17 %**
Estudio de contactos	**92,90%**
Realizado	**33,33%**
Recomendado	**59,57%**

P. González-Ruano Pérez et al. XXXI Congreso Nacional de la Sociedad Española de Medicina Interna Oviedo 17-21Noviembre 2010.

27 años varón originario del Perú.

Lleva 3 años en España y vive con 4 adultos y 3 niños.

Estudio de contactos

Varios meses (antibióticos) con tos, expectoración verdosa, astenia anorexia, perdida de peso y hemoptisis.

Caquexia, anemia severa.

Rx tórax / 2BK + /test rápido R negativo

Diagnóstico y Sospecha

Aislamiento respiratorio hospital.

Declaración salud publica

Aislamiento

2HRZE

M. tuberculosis sensible

Tratamiento estándar

Alta con TDO y seguimiento clínico + 4HR

Cultivos al 2º,4º y 6º negativos.

Rx tórax final.

TDO Seguimiento y monitorización

Criterio OMS de curación.

Resultados OMS

Informe y declaración salud publica final.

Salud publica

27 años varón originario del Perú.

Lleva 3 años en España y vive con 4 adultos y 3 niños.

Estudio de contactos

Varios meses con tos, expectoración verdosa, astenia anorexia, perdida de peso y hemoptisis. (varios antibióticos)

Caquexia, anemia severa.

Rx tórax / 2BK + /test rápido R negativo

Diagnóstico y Sospecha

Aislamiento respiratorio hospital.

Declaración salud publica

2HRZE

M. tuberculosis sensible

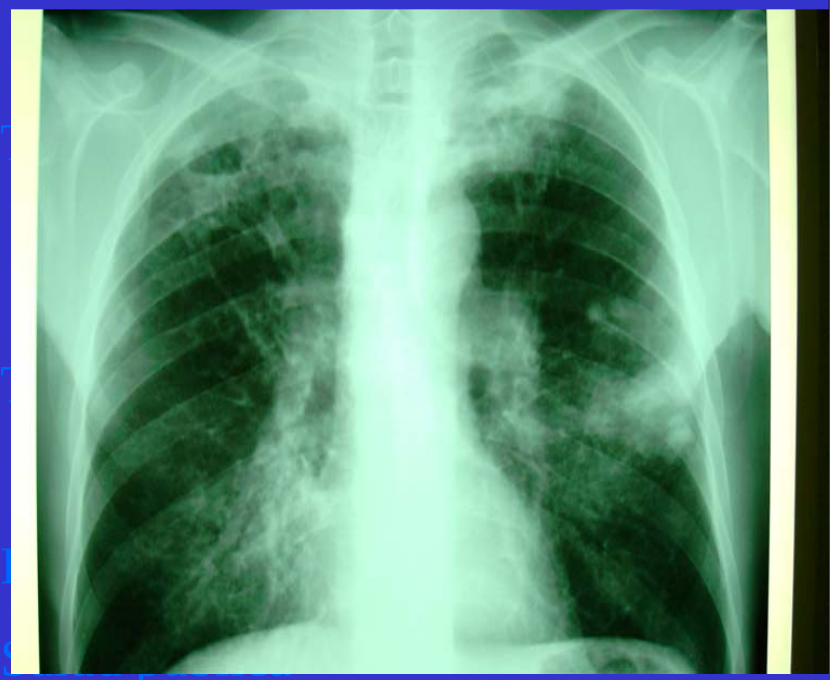
Alta con TDO y seguimiento clínico + 4HR

Cultivos al 2º,4º y 6º negativos.

Rx tórax final.

Criterio OMS de curación.

Informe y declaración salud publica final.



SOSPECHA DE ENFERMEDAD TUBERCULOSA

Antecedentes de riesgo : VIH, indigente, inmigrante, ADVP, alcohólico, psiquiátrico, historia previa tuberculosis,contactos previos, ancianos etc..

Síntomas respiratorios : **tos > 2 semanas,** expectoración, hemoptisis....) o sistémicos (fiebre, astenia, anorexia, perdida peso...) con o sin alteraciones analíticas..

Radiografía de tórax con imágenes tipo infiltrados en lóbulos superiores, cavitación, fibrosis pleural, adenopatías, nódulos, etc….

Baciloscopias no se hallan podido realizar todavía o tenga poca expectoración o de momento sea negativa en urgencias o centro de salud.

27 años varón originario del Perú.

Lleva 3 años en España y vive con 4 adultos y 3 niños. — **Estudio de contactos**

Varios meses (antibióticos) con tos, expectoración verdosa, astenia anorexia, perdida de peso y hemoptisis.

Caquexia, anemia severa.

Rx tórax / 2BK + /test rápido R negativo — **Diagnóstico y Sospecha**

Aislamiento respiratorio hospital.

Declaración salud publica — **Aislamiento y medidas de control**

2HRZE — **Tratamiento estándar**

M. tuberculosis sensible

Alta con TDO y seguimiento clínico + 4HR

Cultivos al 2º,4º y 6º negativos.

Rx tórax final. — TDO Seguimiento y monitorización

Criterio OMS de curación. — Resultados OMS

Informe y declaración salud publica final. — Salud publica

Table 3.1 **Recommended doses of first-line antituberculosis drugs for adults**

Drug	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	**Maximum** (mg)	**Dose and range** (mg/kg body weight)	**Daily maximum** (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin[a]	15 (12–18)		15 (12–18)	1000

[a] Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group (2). Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (*WHO Model Formulary 2008*, www.who.int/selection medicines/list/en/).

Treatment of tuberculosis: guidelines, 4 th ed WHO/HTM/TB/2009.420

27 años varón originario del Perú.	
Lleva 3 años en España y vive con 4 adultos y 3 niños.	Estudio de contactos
Varios meses (antibióticos) con tos, expectoración verdosa, astenia anorexia, perdida de peso y hemoptisis.	Diagnóstico y Sospecha
Caquexia, anemia severa.	
Rx tórax / 2BK + /test rápido R negativo	
Aislamiento respiratorio hospital.	Aislamiento
Declaración salud publica	
2HRZE	Tratamiento estándar
M. tuberculosis sensible	
Alta con TDO y seguimiento clínico + 4HR	TDO Seguimiento y monitorización
Cultivos al 2º,4º y 6º negativos.	
Rx tórax final.	
Criterio OMS de curación.	Resultados OMS
Informe y declaración salud publica final.	Salud publica

38 años mujer española.

Ex-adicta a drogas.

VIH +, CD4 260 y CV 5.1 e4/ml.

Abandono TARGA.

Cirrosis estadio C por VHC y alcohol.

Fiebre, MEG, sudores nocturnos mas ascitis progresiva.

***M. tuberculosis* sensible en liquido ascítico.**

Afectación extrapulmonar

HRZE

Rash, ictericia y GPT elevada: OMS IV

Suspensión y reintroducción.

E +Am + Lfx: nefrotoxicidad.

H tolerada

Rifampicina: hepatotoxicidad y rash.

Efectos adversos

Tratamiento con H +E +Lfx.

Control clínico.

VIH Targa

Afectación extrapulmonar

14% solo extrapulmonar, 20-25% con pulmonar.
Mas frecuente en pacientes VIH.
Diagnostico cultivo y biopsia.
Tratamiento 2HRZE/4HR
Control clínico.

Algunas diferencias

Afectación SNC entre 9-12 meses con esteroides iniciales.
Afectación ósea 6-9 meses.
Pericarditis: esteroides iniciales.
Cirugía en complicaciones.

38 años mujer española.

Ex-adicta a drogas.

VIH +, CD4 260 y CV 5.1 e4/ml.

Abandono TARGA.

Cirrosis estadio C por VHC y alcohol.

Fiebre, MEG, sudores nocturnos mas ascitis progresiva.

M. tuberculosis sensible en liquido ascítico.

HRZE

Rash, ictericia, GPT > 10 veces : OMS IV

Suspensión y reintroducción.

E +Am + Lfx: nefrotoxicidad.

H tolerada

Rifampicina: hepatotoxicidad y rash.

Tratamiento con H +E +Lfx.

Control clínico.

Afectación extrapulmonar

Efectos adversos

VIH Targa

MANEJO DE EFECTOS ADVERSOS

Hepatotoxicidad OMS:

Grado 1: ALT 51 a 125 U/L, o 1.25 to 2.5 veces basal.

Grado 2 :ALT 126 a 250 U/L, o 2.6 to 5.0 veces basal.

Grado 3: ALT 251 a 500 U/L, o 5.1 to 10.0 veces basal.

Grado 4: ALT mayor de 500 U/L, o >10 veces basal, o si mayor de 250 U/L acompañado de sintomas.

(WHO ART Adverse Drug Reaction Terminology. Geneva: WHO Collabo-rating Center for Drug International Monitoring; 1979.)

38 años mujer española.

Ex-adicta a drogas.

VIH +, CD4 260 y CV 5.1 e4/ml.

Abandono TARGA.

Cirrosis estadio C por VHC y alcohol.

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Rash, ictericia y GPT elevada: OMS IV

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H tolerada

Rifampicina: hepatotoxicidad y rash.

Tratamiento con H +E +Lfx.

Control clínico.

Afectación extrapulmonar

Efectos adversos

VIH Targa

Table 4.2 **Symptom-based approach to managing side-effects of anti-TB drugs**

Side-effects	Drug(s) probably responsible	Management
Minor		*Continue anti-TB drugs, check drug doses*
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily (*3*)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (*3*)

Treatment of tuberculosis: guidelines, 4 th ed WHO/HTM/TB/2009.420

Table 4.2 **Symptom-based approach to managing side-effects of anti-TB drugs**

Side-effects	Drug(s) probably responsible	Management
Major		*Stop responsible drug(s) and refer to clinician urgently*
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin

Treatment of tuberculosis: guidelines, 4 th ed WHO/HTM/TB/2009.420

MANEJO DE EFECTOS ADVERSOS

Tipo	Síntomas y signos	Causa habitual	Valoración
Hepatitis	Anorexia, nauseas, Vómitos, ictericia	H, R, Z, raro E	Otros fármacos Gastritis Virus

Solución

Retirar fármacos si transaminasas >3-5, bilirrubina elevada con/sin síntomas.
Si paciente grave poner drogas no hepatotóxicas (S,E,Lfx)
Repetir a la semana. Dependiendo gravedad ingreso (preferible) o consulta.

Reintroducción: (Si colostasis más probable R, si citolisis H, R, Z). Opciones: HRZ, ZHR o ZRH con una semana de intervalo o solo HR.

American Thoracic Society, CDC, Infectious Diseases Society of America. Treatment of tuberculosis. *Morbidity and Mortality Weekly Report: Recommendations and Reports*, 2003,52(RR-11):1–77.

Saukkonen JJ et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *American Journal of Respiratory and Critical Care Medicine*, 2006, 174:935–952.

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Ex-adicta a drogas.

VIH +, CD4 260 y CV 5.1 e4/ml.

Abandono TARGA.

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Afectación extrapulmonar

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Rash, ictericia y GPT elevada: OMS IV

Suspensión y reintroducción.

E +Am + Lfx: nefrotoxicidad.

H tolerada

Rifampicina: hepatotoxicidad y rash.

Efectos adversos

Tratamiento con H +E +Lfx.

Control clínico, TDO y declaración.

VIH Targa

Infección VIH: se trata de manera similar pero con el problema de la introducción de los antirretrovirales y el síndrome de reconstitución inmune.

Tratamiento TBC Y TARGA

Inicio de terapia TBC Y TARGA: ¿Cuándo?

Ventajas retrasar inicio:

Menos frecuente IRIS.

Menos interacciones farmacológicas.

Menos efectos adversos.

Desventajas de retrasar el inicio:

Incremento riesgo IO.

Riesgo de muerte aumentado o disminución de supervivencia.

Tratamiento TBC Y TARGA

Actualmente, el momento optimo esta por definir.

Se sugiere:

CD4 <100:	**≥ 2 semanas**
CD4 100-200:	**8 semanas**
CD4 >200:	**durante el mantenimiento.**
CD4 >350	**al finalizar.**

Control microbiológico y clínico similar a pacientes no VIH.

Table 5.1 **Initiating first-line antiretroviral therapy in relation to starting anti-TB treatment**[a]

CD4 cell count	ART recommendation	Timing of ART in relation to the start of anti-TB treatment
CD4 <200 cells/mm^3	Recommend ART[b]	Between 2 and 8 weeks[c]
CD4 200–350 cells/mm^3	Recommend ART	After 8 weeks
CD4 >350 cells/mm^3	Defer ART	Re-evaluate patient at 8 weeks and at the end of anti-TB treatment
CD4 not available	Recommend ART[e]	Between 2 and 8 weeks

[a] Adapted from *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*, 6th revision. Geneva, World Health Organization, 2006.

[b] A regimen containing efavirenz is the preferred first-line regimen; alternative regimens include nevirapine and triple NRTIs based on regimens using tenofovir disoproxil fumarate or abacavir. For nevirapine-containing regimens, alanine aminotransferase should be checked at 4, 8 and 12 weeks, and directed by symptoms thereafter.

[c] Start ART as soon as anti-TB treatment is tolerated.

[d] If other non-TB stage 3 or 4 events are present, start ART.

[e] For some TB diagnoses that generally respond well to anti-TB treatment (e.g. TB of the lymph nodes, uncomplicated pleural effusion), consider deferring ART.

TABLE 10.2 **Timing of ART in the ART-naive patient starting antituberculosis therapy for DR-TB**

CD4 CELL COUNT	ART RECOMMENDATIONS	TIMING OF ART IN RELATION TO START OF DR-TB TREATMENT
CD4 <200 cells/mm^3	Recommend ART	At two weeks or as soon as DR-TB treatment is tolerated
CD4 between 200 and 350 cells/mm^3	Recommend ART	After eight weeks[a]
CD4 >350 cells/mm^3	Defer ART[b]	Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every three months during DR-TB treatment.
Not available	Recommend ART[c]	Between two and eight weeks

[a] Clinical evaluation may prompt earlier initiation of ART.

[b] ART should be started if other non-TB stage 3 or 4 events are present.

[c] This recognizes that some patients may be prematurely placed on life-long ART.

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

45 años varón español

Indigente.

Tabaquismo severo

Cocaína 2-3gr/día

Heroína 2 gr/día

Varios "Tranquimazines"/día

VHC positivo

VIH negativo

Tos+expectoración verdosa

Perdida de peso.

BK positivo / Rx tórax patológica

Aislamiento respiratorio

2HRZE, alta y abandono

Cultivo positivo *M tuberculosis*

Abandono-TDO

*** Tratamiento supervisado se refiere a la ayuda a los pacientes para tomarse la medicación regular y completamente.**

*** Tratamiento directamente observado -TDO- es el método recomendado de supervisión.**

*** Sujeto a mucho debate pues una revisión sistemática concluyo que no mejoraba los resultados, pero en otras publicaciones TDO se asociaba a altas frecuencias de cura y finalización del tratamiento.**

Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews*, 2007, (4)(4):CD003343.

Rusen ID et al. Cochrane systematic review of directly observed therapy for treating tuberculosis: good analysis of the wrong outcome. *International Journal of Tuberculosis and Lung Disease*, 2007, 11:120−121.

9 meses después reingresa.

BK positivo.

Resistente a H.

Aislamiento respiratorio hospital

2RZELfx (34 Kg)+ Metadona + Benzodiazepinas.

Interacciones

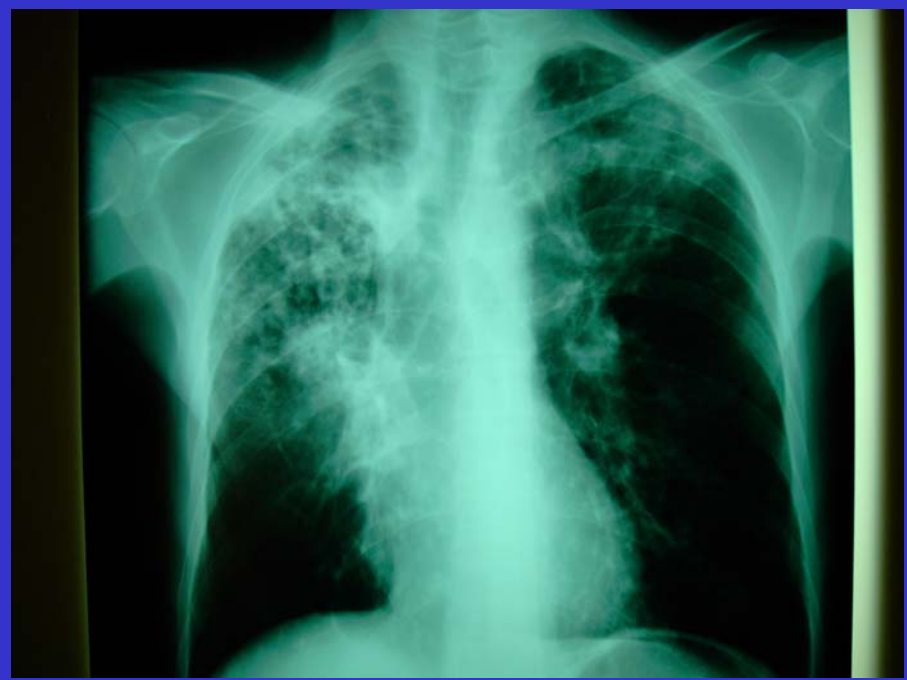
Alta con 7RZE + TDO + piso acogida.

No expectora.

Tratamiento completado.

Rx tórax final tratamiento.

Declaración Salud Publica.



Rifampicin substantially reduces the concentration and effect of the following drugs

anti-infectives (including certain antiretroviral drugs discussed in section 5.6.1, mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol);
hormone therapy,[1] including ethinylestradiol, norethindrone, tamoxifen, levothyroxine;
methadone;
warfarin;
cyclosporin;
corticosteroids;
anticonvulsants (including phenytoin);
cardiovascular agents including digoxin (among patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprorol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone;
theophylline;
sulfonylurea hypoglycaemics;
hypolipidaemics including simvastatin and fluvastatin;
nortriptyline, haloperidol, quetiapine, benzodiazepines (including diazepam, triazolam), zolpidem, buspirone.

9 meses después reingresa.

BK positivo.

Resistente a H.

Aislamiento respiratorio hospital

2RZELfx (34 Kg)+ Metadona + Benzodiazepinas.

Interacciones

Alta con 7RZE + TDO + piso acogida.

No expectora.

Tratamiento completado.

Rx tórax final tratamiento.

Declaración Salud Publica.

Monorresistencia

Definiciones

Resistencia entre casos nuevos y casos previamente tratados.

Monorresistencia: Resistencia a un solo fármaco.

Polirresistencia: Resistencia a mas de un fármaco pero que no sean isoniacida y rifampicina juntas.

Hay que tratar bien las monorresistencias y polirresistencias…….

para no llegar a las multirresistencias

TABLE 8.1 **Suggested regimens for mono- and poly-drug resistance[a] (when further acquired resistance is not a factor and laboratory results are highly reliable)**

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF OF TREATMENT (MONTHS)	COMMENTS
H (± S)	R, Z and E	6–9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
H and E	R, Z and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.

Treatment of tuberculosis: guidelines, 4 th ed WHO/HTM/TB/2009.420

R	H, E, fluoroquinolones, plus at least 2 months of Z	12–18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)	H, Z, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
R and Z (± S)	H, E, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
H, E, Z (± S)	R, fluoroquinolones, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

[a] Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians* (3)

34 años varón español.

Varios meses con tos, expectoración verdosa, astenia, anorexia, perdida de peso. (antibióticos)

Vive solo.

Antiguo contacto de paciente con TBC-MR. (HRZES)

Ingreso aislamiento respiratorio.

Rx tórax / 2BK +/ test rápido HR resistentes.

Declaración Salud Pública urgente y estudio de contactos.

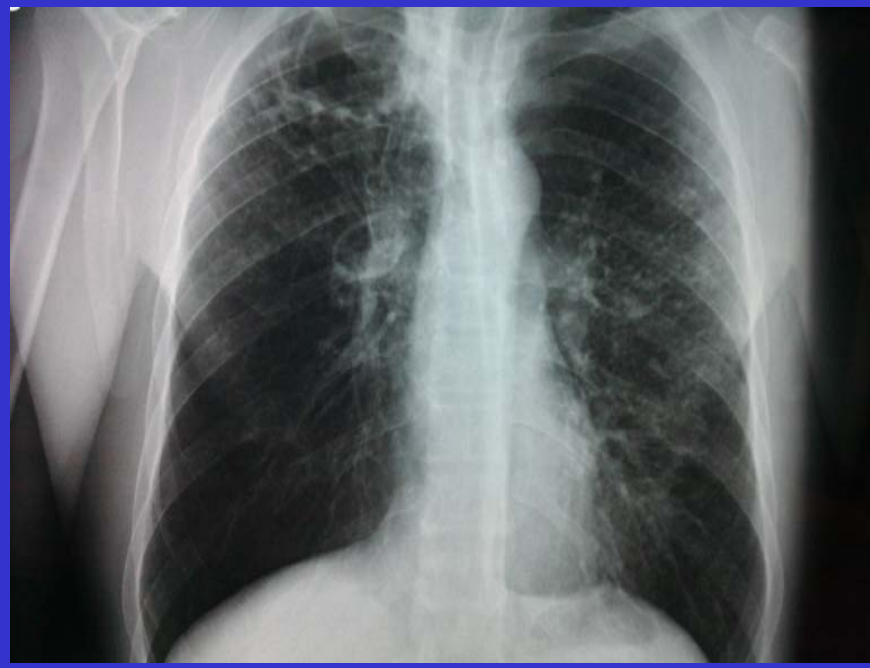
Am, Lfx, Eto, Cs, Lzd+ B6

Cultivos mensuales.

Control efectos adversos.

Evaluación clínica y radiológica.

Informe final y Declaración EDO.



Multirresistencia

TBC MR y XDR

Definiciónes

Multiresistencia (MR) se define como resistencia a Isoniacida (H) y Rifampicina (R) con o sin resistencia a otras drogas.

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

Definiciónes

Tuberculosis XDR (extenxive drug resistant): Resistencia a H / R / mas cualquier fluorquinolona y al menos un fármaco inyectable (capreomicina, kanamicina y amikacina)

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

Definiciónes

Tuberculosis totalmente resistente

¿Por qué unas guías urgentes?

Situación resistencias

Problema global en el mundo.

Zonas calientes: países pobres o en desarrollo.

Estimaciones:

- **50 millones de personas infectadas.**
- **500.000 enfermos nuevos cada año.**
  - ***solo 50.000 en tratamiento.**
  - ***alrededor de 10% son XDR.**

OMS 2009

Resistencias en el Mundo: Problema global

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD WHO REPORT Nº 4: 2002-2007.

Resistencia entre casos nuevos:

Cualquier resistencia:	**17.0%**
Resistencia Isoniazida :	**10.3%**
Multirresistencia:	**2.9%**

Resistencias en el Mundo: Problema global

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD WHO REPORT Nº 4: 2002-2007.

Resistencia entre casos previamente tratados:

Cualquier resistencia:	**35.0%**
Resistencia Isoniazida :	**27.7%**
Multirresistencia:	**15.3%**

Resistencias en el Mundo: Problema global

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD WHO REPORT Nº 4: 2002-2007.

Resistencia entre todos los casos :

Cualquier resistencia:	**20%**
Resistencia Isoniazida :	**13,3%**
Multirresistencia:	**5.3%**

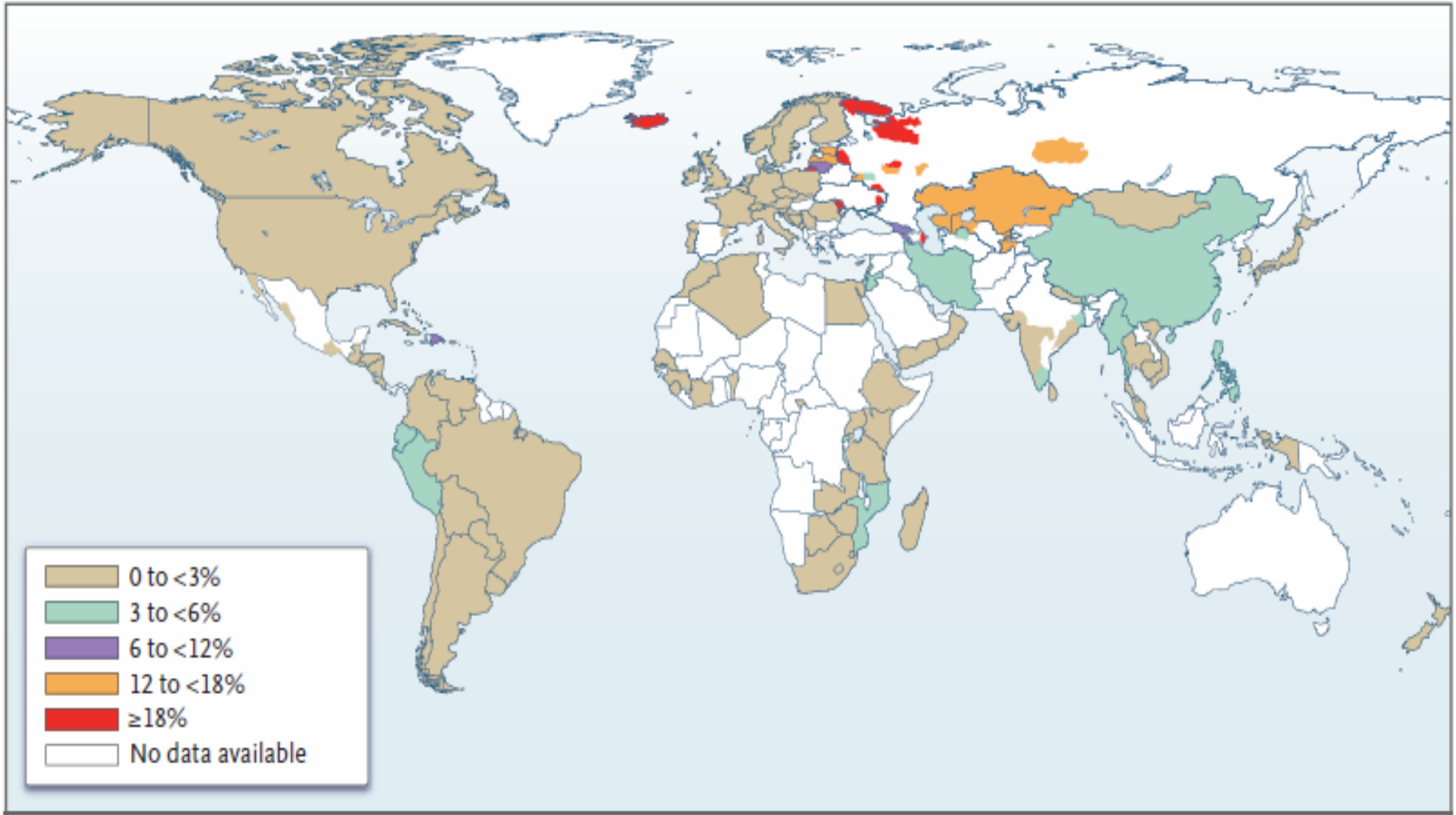


Figure 1. Distribution of the Proportion of Cases of MDR Tuberculosis among New Cases of Tuberculosis, 1994–2009.

The following 27 countries are responsible for 85% of the world's estimated cases of MDR tuberculosis and are classified as countries with a high burden of MDR tuberculosis: China, India, Russia, Pakistan, Bangladesh, South Africa, Ukraine, Indonesia, Philippines, Nigeria, Uzbekistan, Democratic Republic of Congo, Kazakhstan, Vietnam, Ethiopia, Myanmar, Tajikistan, Azerbaijan, Moldova, Kyrgyzstan, Belarus, Georgia, Bulgaria, Lithuania, Armenia, Latvia, and Estonia. Adapted from the 2010 report on MDR and XDR tuberculosis from the WHO.[1]

MAP 7 Distribution of countries and territories reporting at least one case of XDR-TB as of January 2010

Situación resistencias

En España no hay datos oficiales actualizados.

Estudio del Grupo Español de Micobacterias:

(Rev Esp Quimioter 2008;21(1):22-25.)

Datos de 2006:

Resistencia a cualquier fármaco: 8,3%
Resistencia Isoniacida: 4,9%
Multirresistencia: 1,3%

¿Por que y como se hacen las resistencias ?

Mecanismo

- La resistencia a drogas es casi siempre causado por un inadecuado tratamiento.

- Incluye:
  - ► Errores en el paciente.
  - ► Errores de prescripción del médico.
  - ► Fallo en el sistema sanitario en proporcionar fármacos.
  - ► Malabsorción de fármacos.

TABLE 1.1 **Causes of inadequate antituberculosis treatment** (*1*)

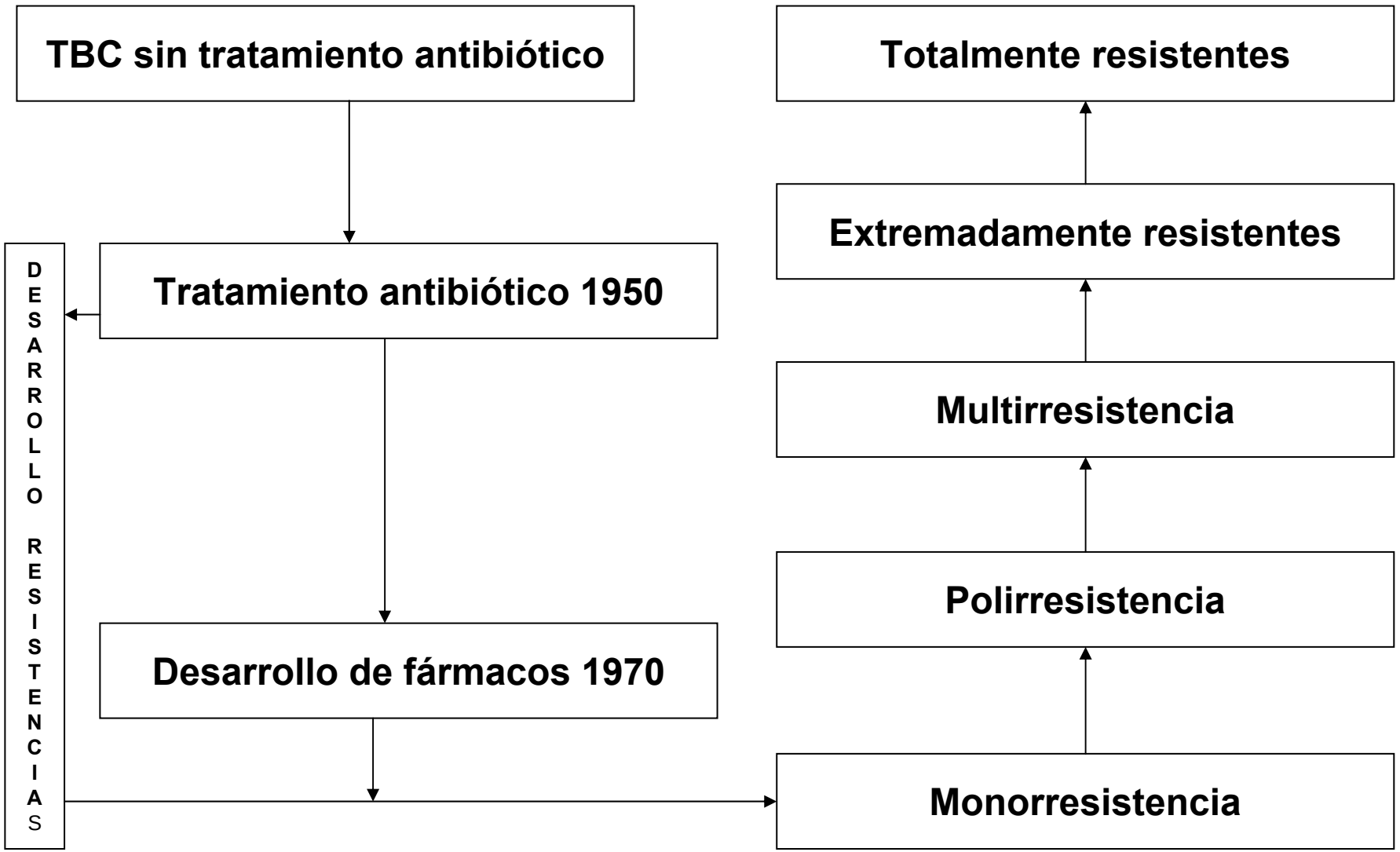
HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY OR QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

La resistencia a fármacos tuberculostáticos es cromosómica, definitiva e irreversible.

La resistencia a fármacos esta en relación inversa con buenos programas de control TBC: TDO, uso de fármacos asociados……..

Lo que ha ocurrido y puede ocurrir



¿ En quien sospechamos que tiene una tuberculosis multirresistente?

Historia de TBC previa y/o abandonos.
VIH.
Inmigrantes de zonas prevalentes.
Contactos de pacientes MR.
Indigentes.
Drogadicción activa.
Ingresos penitenciarios.
Grandes lesiones cavitárias.

¿Cómo se diagnostican las resistencias?

Test fenotípicos: Es el test clásico y de referencia. Sobre cultivo positivo, detección de inhibición de crecimiento en medios sólidos. Requiere entre 4-8 semanas. Mal estandarizados para fármacos de segunda línea.

Test genotípicos: determinan resistencia genética en dos pasos: PCR para *M tuberculosis* y amplificación con detección de mutaciones que correlacionan con resistencias. Sensibilidad 95% y especificidad de 100%.Los test rápidos para detectar resistencia a rifampicina son los que mas se están desarrollando.

	Description and comments	Manufacturer
Culture		
Microscopic observation drug-susceptibility assay*	Early detection of *Mycobacterium tuberculosis* in liquid culture media with an inverted light microscope; highly accurate, quick, and cheap	A standardised version under development with PATH
Thin-layer agar	Early growth detection on selective thin-layer agar with light microscopy or colorimetric detection; cheap, accurate, and easy to use	A standardised version under development with FIND
Nitrate reductase assay*	Early growth detected through a colour change mediated by the ability of *M tuberculosis* to reduce nitrate to nitrite (Griess reaction) in selective media; accurate and cheap	No standardised version available
Colorimetric redox indicator assays*	Growth detected by reduction of a coloured indicator added to a selective culture medium; accurate and cheap	No standardised version available
Nucleic acid amplification tests		
Line-probe assay*	PCR amplification of a segment of *rpoB* with hybridisation of the biotin-labelled amplicons to oligonucleotide probes on a membrane strip (line probe); the GenoType MTBDRplus assay detects rifampicin and isoniazid resistance; MTBDRsl version detects resistance to fluoroquinolones, aminoglycosides, capreomycin, and ethambutol	GenoType MTBDRplus assay (Hain Lifescience); GenoType MTBDRsl (Hain Lifescience); INNO-LiPA Rif.TB (Innogenetics)
Xpert MTB/RIF	Multiplex PCR amplification of *rpoB* with real-time detection with a fluorescent signal (molecular beacons); preliminary outcome data show good performance	Cepheid
Other technologies		
Bacteriophage assays	Based on detection of progeny phages, which infect *M tuberculosis*, as lytic plaques on a lawn of *Mycobacterium smegmatis*; few data available for clinical specimens	FASTPlaque
High-resolution melt assays	Novel method using DNA melting temperature during PCR to scan for mutations; no clinical data available	Experimental

PATH=Program for Appropriate Technology in Health. FIND=Foundation for Innovative New Diagnostics. MTBDR=*Mycobacterium tuberculosis* drug resistance. MTB=*Mycobacterium tuberculosis*. RIF=rifampicin. *Endorsed by WHO for use as a diagnostic test for drug-resistant tuberculosis.[11]

Table 2: **New and emerging technologies for diagnosis of drug-resistant tuberculosis[100]**

Lancet 2010; 375:1830-43

¿ Como organizamos el tratamiento de un paciente con tuberculosis multirresistente ?

- **No existen estudios randomizados controlados comparando diferentes fármacos y pautas.**

- **Recomendaciones basadas por tanto en principios generales, extrapolaciones y opiniones de expertos.**

• Hospitales con unidades apropiadas de aislamiento y médicos con experiencia.

• Los cuidados estarán centrados en el paciente como indican los estándar internacionales de calidad.

Control de la Infección

Medidas administrativas
(reducen exposición)

*Diagnostico precoz
    *Tos > 3 semanas
    *Clínica sospecha
    *Grupos de riesgo
    *Contactos
*Separación y aislamiento.
*Test rápidos de diagnostico
*Inicio de tratamiento efectivo

Medidas Ambientales
(reducen concentración)

*Ventilación estándar
*Presión negativa
*Filtros HEPA
*Rayos ultravioleta

Protección personas
(reducen inhalación)

*Mascaras respiratorias de alta protección >96%

WHO policy on TB infection control in health-care facilities, congregate settings and households. WHO/HTM/TB/2009.419.

- **Coordinación con laboratorio de microbiología y centros de referencia donde se realizaran los test a fármacos de segunda línea.**

- **Estrecha relación con servicio de epidemiología.**

- **Tratamientos estándar, empíricos o individualizados.**

- **Individualizado en base a la historia previa de fármacos utilizados y al antibiograma.**

TABLE 7.1 **Alternative method of grouping antituberculosis agents**

GROUPING	DRUGS
Group 1 – First-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb)[a]
Group 2 – Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 – Oral bacteriostatic second-line agents	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS)
Group 5 – Agents with unclear efficacy (not recom mended by WHO for routine use in MDR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H);[b] clarithromycin (Clr)

[a] Rifabutin is not on the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in many settings.

[b] High-dose H is defined as 16–20 mg/kg per day.

- **Iniciar con 5 o mas fármacos (no previamente utilizados) eligiendo de cada grupo.**

- **No añadir nunca un solo fármaco al régimen anterior.**

STEP 1

Use any available

Group 1: First-line oral agents

pyrazinamide
ethambutol

STEP 2

Plus one of these

Group 2: Injectable agents

kanamycin (or amikacin)
capreomycin
streptomycin

STEP 3

Plus one of these

Group 3: Fluoroquinolones

levofloxacin
moxifloxacin
ofloxacin

STEP 4

Pick one or more of

Group 4: Second-line oral bacteriostatic agents

p-aminosalicylic acid
cycloserine (or terizadone)
ethionamide (or protionamide)

STEP 5

Consider use of these

Group 5: Drugs of unclear role in DR-TB treatment

clofazimine
linezolid
amoxacillin/clavulanate
thioacetazone[b]
imipenem/cilastatin
high-dose isoniazid
clarithromycin

- **Mantener el inyectable al menos 6 meses y al menos 4 meses del 1º cultivo negativo.**

Recordar:

Conversión de esputo definido como dos set consecutivos de esputos negativos (BK y Cultivo) con un mes de separación.

La fecha del cultivo negativo se toma como punto entre fase de inducción o intensiva y mantenimiento.

- **Siempre bajo tratamiento directamente observado y con soporte psicológico.**

- **Duración de al menos 18 meses después de la conversión del cultivo.**

- **Habitualmente 24 meses.**

- **No utilizar pautas intermitentes excepto para aminoglicósidos en fase de mantenimiento.**
- **No utilizar fármacos resistentes si esta bien realizado el antibiograma.**
- **Siempre que se tolere utilizar dosis en una sola toma sobre todo Z,E y Q.**

- **Dosis determinadas por peso.**
- **Intentar iniciar con dosis plenas.**
- **Monitorizar efectos adversos.**

TABLE 11.2 **Frequency of common adverse effects among 818 patients in five DR-TB control programme sites (*1*)**

ADVERSE EVENT	NO. OF PATIENTS AFFECTED (%)
Nausea/vomiting	268 (32.8)
Diarrhoea	173 (21.1)
Arthralgia	134 (16.4)
Dizziness/vertigo	117 (14.3)
Hearing disturbances	98 (12.0)
Headache	96 (11.7)
Sleep disturbances	95 (11.6)
Electrolyte disturbances	94 (11.5)
Abdominal pain	88 (10.8)
Anorexia	75 (9.2)
Gastritis	70 (8.6)
Peripheral neuropathy	65 (7.9)
Depression	51 (6.2)
Tinnitus	42 (5.1)
Allergic reaction	42 (5.1)
Rash	38 (4.6)
Visual disturbances	36 (4.4)
Seizures	33 (4.0)
Hypothyroidism	29 (3.5)
Psychosis	28 (3.4)
Hepatitis	18 (2.2)
Renal failure/nephrotoxicity	9 (1.1)

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

TABLE 11.4 **Commonly used ancillary medications**

INDICATION	DRUG
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of flouroquinolones
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B_6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

- **Evaluación quirúrgica.**
- **TBC extrapulmonar igual.**
- **Terapia coadyuvante:**
  - **Soporte nutricional.**
  - **Vitamina B6.**
  - **Esteroides.**

¿ Y con las tuberculosis XDR-TB que hacemos ?

Figure 7.3 Management guidelines for patients with documented, or almost certain, XDR-TB

1. Use any Group 1 agents that may be effective.
2. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents, it is recommended to use one the patient has never used before.[a]
3. Use a later-generation fluoroquinolone such as moxifloxacin.
4. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
5. Use two or more agents from Group 5.
6. Consider high-dose isoniazid treatment if low-level resistance is documented.
7. Consider adjuvant surgery if there is localized disease.
8. Ensure strong infection control measures.
9. Treat HIV (as per Chapter 10).
10. Provide comprehensive monitoring (see Chapter 11) and full adherence support (see Chapter 12).

[a] This recommendation is made because, while the reproducibility and reliability of DST to injectables are good, there are little data on clinical efficacy of the test. Options with XDR-TB are very limited and some strains may be affected in vivo by an injectable agent even though they are testing resistant in vitro.

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402

¿ Cual es el pronóstico de estos pacientes?

Resultados OMS MR

* **Curación:** al menos 5 cultivos negativos consecutivos al final del 12º mes de tratamiento.

* Tratamiento completo.

* Muerte

* Fracaso.

* Abandono o perdida.

* Transferido

Los enfermos con cepas resistentes tienen menos probabilidades de curación (50-80% versus 95-97%), mas efectos adversos y son mas costosos (x 10-100).

Brotes de XDR en pacientes con VIH, elevada mortalidad (98%) y en pocas semanas (4-16).

Lancet, 2006, 368:1575−1580.

Meta-análisis de XDR, 43,7% resultado favorable, sobre todo los pacientes que tenían en su esquema de tratamiento fluorquinolonas de última generación (59,3% versus 30,6%).

CID 2010, 51: 6-14

¿ Como se valoran los contactos de pacientes con TBC MR ?

* Para la OMS es una situación de **emergencia** el estudio de contactos de los pacientes MR y XDR.

* Realizar de manera similar a pacientes con TBC no resistente.

* En los pacientes con el diagnostico de infección latente **no se recomienda** tratamiento pero si observación clínico-radiológica (evidencia C) al menos durante 2 años.

En pacientes inmunodeprimidos o niños < 5 años plantear:

- **3 drogas susceptibles por antibiograma.**
- **Si desconocido E+Z o FQ+Z**
- **Entre 6 a 12 meses.**


¿ Hay algo en el horizonte ?

Table 2. Drugs Currently in Development to Improve Tuberculosis (TB) Treatment

Drug	Mechanism of action	Activity in the mouse model of TB treatment	Clinical stage of development	Possible advantages	Limitations and/or cautions
High-dose rifampin	Inhibition of mycobacterial RNA-polymerase (rpoB gene)	May support shortening of treatment to 4 months	Enhanced activity demonstrated in monotherapy (EBA); phase 2B trials in development	Global system in place for manufacture and distribution; should be applicable to children and pregnant women	No activity against MDR-TB; drug interactions
Higher-dose and more frequently administered rifapentine	Inhibition of mycobacterial RNA-polymerase (rpoB gene)	Shortening of treatment to 3 months	Large trial under way of once-weekly therapy (with isoniazid) for latent TB infection; enhanced activity shown in monotherapy (EBA); initial phase 2B trial underway	Substantially greater potency than rifampin in the mouse model; should be applicable to children and pregnant women; age-specific dosing available (to age 2 years)	No activity against MDR-TB; drug interactions are likely to be similar to those of rifampin
Fluoroquinolones	Inhibition of mycobacterial DNA gyrase	Shortening of treatment to 4 months; active in models of MDR-TB treatment	Activity demonstrated as monotherapy (EBA); variable activity in phase 2B trials; phase 3 trials under way	Proven capacity for manufacture	Increasing rates of resistance in *Mycobacterium tuberculosis* in some parts of the world; uncertainties about safety during pregnancy and in children

TMC207	Inhibition of mycobacterial ATP-synthetase	Shortening of treatment to 3 months; marked improvement in treatment of MDR-TB	Activity demonstrated in monotherapy (EBA) and in the initial stage of a pivotal trial in MDR-TB	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes	Very long tissue half-life raises concerns for toxicities; drug resistance; CYP3A4 metabolized; susceptible to interactions with rifampin and antiretroviral drugs
OPC67683	Inhibition of mycobacterial cell wall synthesis	Shortening of treatment to 3 months; marked improvement in treatment of MDR-TB	Activity shown in monotherapy (EBA); phase 2B dose-ranging trial under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes; low likelihood of having drug-drug interactions	Early in development, so data needed on dose, adverse effects, etc.
PA-824	Inhibition of mycobacterial cell wall synthesis	Treatment shortening to 3 months, marked improvement in treatment of MDR-TB	Activity demonstrated in monotherapy (EBA)	No cross-resistance with current drugs– may markedly improve MDR-TB treatment outcomes Low likelihood of having drug-drug interactions	Early in development, so data needed on dose, side effects, etc.
SQ-109	Inhibition of mycobacterial cell wall synthesis	May support shortening of treatment, but has not been rigorously evaluated in the standard model	Phase 1 studies of tolerability and pharmacokinetics among healthy volunteers under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes; low likelihood of having drug-drug interactions	Very early in development, so data needed on dose, adverse effects, etc.
PNU 100480	Inhibition of mycobacterial protein synthesis	Shortening of treatment to 3 months	Phase 1 studies of tolerability and pharmacokinetics among healthy volunteers under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes	Very early in development, so data needed on dose, adverse effects, etc.; possibility of toxicities similar to linezolid

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The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

WORKING GROUP on New TB Drugs

Stop TB Partnership

Working Group on new TB drugs

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VIEW ALL | HIT-TO-LEAD | LEAD-OPT | PRE-CLINICAL | PHASE I | PHASE II | PHASE III

Hit To Lead

Phenotypic Screening University of Illinois, TB Alliance	**M. tuberculosis Protein Kinase Inhibitors** Vertex Pharmaceuticals, Incorporated	**Fungal metabolites** Mycosynthetix, University of Illinois at Chicago
Actinomycete metabolites University of Illinois at Chicago, Myongji University	**DNA metabolism** AstraZeneca R and D Bangalore	**Hit to Lead Evaluation of novel compounds** The Lilly TB Drug Discovery Initiative
Phenotype screening AstraZeneca R and D Bangalore	**Combinatorial Biosynthetic Compounds** Shaw Environmental and University of Illinois at Chicago	**Folate Biosynthesis Inhibitors** AstraZeneca, TB Alliance
GSK Whole-Cell Screening GlaxoSmithKline, TB Alliance	**Malate Synthase Inhibitors** GlaxoSmithKline , Texas A&M University, TB Alliance	**Menaquinone Synthase Inhibitors** Colorado State University, TB Alliance

Lead Optimization

Nitroimidazoles TB Alliance, University of Auckland, University of Illinois	**New Generation Diarylquinoline** TB Alliance, Tibotec	**Riminophenazines** TB Alliance, Institute of Materia Medica, The Beijing Tuberculosis an...
InhA Inhibitors GlaxoSmithKline, TB Alliance	**LeuRS inhibitors** Anacor Pharmaceuticals	**Mycobacterial Gyrase Inhibitors** TB Alliance, GlaxoSmithKline
TL1 Inhibitors Sequella	**MTopo** AstraZeneca R and D Bangalore	**GyrB Inhibitors** AstraZeneca , TB Alliance

Pre-Clinical

CPZEN-45
Microbial Chemistry Research Foundation, Tokyo, Japan, Lilly TB Drug ...

New Respiratory Quinolone DC-159a
Japan Anti-Tuberculosis Association, JATA, Daiichi-Sankyo Pharmaceuti...

SQ609
Sequella

SQ641
Sequella

Benzothiozinones
New Medicines For Tuberculosis (NM4TB)

Q201-Novel anti-TB agent
Quro Science, Inc.

Phase I

Pfizer Oxazolidinone PNU-100480
Pfizer
NCE

Clinical Development of SQ109
Sequella,NIH
NCE

Clinical Development of AZD5847
Astrazeneca
NCE

Phase II

PA-824
TB Alliance
NCE

Clinical Development of TMC207 for Multi-Drug Resistant TB
Tibotec BVBA
NCE

Registration of TMC207 for Drug Sensitive TB
TB Alliance, Janssen Pharmaceutica N.V.
NCE

Clinical Development of OPC-67683
Otsuka Pharmaceutical Co., Ltd.
NCE

Low-Dose Linezolid for the Treatment of Multi-Drug Resistant Tuberculosis
TBTC, Pfizer

Rifapentine (TBTC study 29)
Information provided by WGND

TBTC Study 26
CDC, Sanofi-aventis

Phase III

Gatifloxacin
Information provided by WGND

Moxifloxacin in the shortening of Rx for drug sensitive pulmonary TB
University College London

En el futuro los biomarcadores de tuberculosis pueden tener un potencial importante en la duración del tratamiento y facilitar estudios clínicos como "surrogate endpoint" para las recaídas y la curación.

Lancet 2010;375:1920-37

About the Charter

***The Patients' Charter for Tuberculosis Care (The Charter)* outlines the rights and responsibilities of people with tuberculosis. It empowers people with the disease and their communities through this knowledge. Initiated and developed by patients from around the world, the *The Charter* makes the relationship with health care providers a mutually beneficial one.**

The Charter sets out the ways in which patients, the community, health providers (both private and public), and governments can work as partners in a positive and open relationship with a view to improving tuberculosis care and enhancing the effectiveness of the healthcare process. It allows for all parties to be held more accountable to each other, fostering mutual interaction and a "positive partnership."

Developed in tandem with the *International Standards for Tuberculosis Care* (http://www.worldcarecouncil.org/) to promote a "patient-centered" approach, *The Charter* bears in mind the principles on health and human rights of the United Nations, UNESCO, WHO, Council of Europe, as well as other local and national charters and conventions including the United Nations CESCR General Comment 14 on the right to health, WHO Ottawa Charter on health promotion, The Council of Europe Convention for the Protection of Human Rights and Dignity (biology and medicine), and the UNESCO Universal Draft Declaration on Bioethics and Human Rights (available at http://www.worldcarecouncil.org/).

The Patients' Charter for Tuberculosis Care practices the principle of Greater Involvement of People with Tuberculosis (GIPT). This affirms that the empowerment of people with the disease is the catalyst for effective collaboration with health providers and authorities and is essential to victory in the fight to stop tuberculosis. *The Charter*, the first global "patient-powered" standard for care, is a cooperative tool, forged from common cause, for the entire tuberculosis community.

Help turn these words into realities. Support the drive towards implementation in the community.

Sign online at http://www.wcc-tb.org or sign up by SMS text: +33 679 486 024

In common cause, with mutual respect, together we can raise the standards of care.

Comments warmly welcome: voices@wcc-tb.org

Thanks to the American Thoracic Society (http://www.thoracic.org) and the Open Society Institute (http://www.soros.org) for their support.

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THE PATIENTS' CHARTER FOR

Tuberculosis Care

PATIENTS' RIGHTS AND RESPONSIBILITIES

Patients' Rights

You have the right to:

Care

- The right to free and equitable access to tuberculosis care, from diagnosis through treatment completion, regardless of resources, race, gender, age, language, legal status, religious beliefs, sexual orientation, culture, or having another illness
- The right to receive medical advice and treatment which fully meets the now *International Standards for Tuberculosis Care*, centering on patient needs, including those with multidrug-resistant tuberculosis (MDR-TB) or tuberculosis-human immunodeficiency virus (HIV) coinfections and preventative treatment for young children and others considered to be at high risk
- The right to benefit from proactive health sector community outreach, education, and prevention campaigns as part of comprehensive care programs

Dignity

- The right to be treated with respect and dignity, including the delivery of services without stigma, prejudice, or discrimination by health providers and authorities
- The right to quality healthcare in a dignified environment, with moral support from family, friends, and the community

Information

- The right to information about what healthcare services are available for tuberculosis and what responsibilities, engagements, and direct or indirect costs are involved
- The right to receive a timely, concise, and clear description of the medical condition, with diagnosis, prognosis (an opinion as to the likely future course of the illness), and treatment proposed, with communication of common risks and appropriate alternatives
- The right to know the names and dosages of any medication or intervention to be prescribed, its normal actions and potential side-effects, and its possible impact on other conditions or treatments
- The right of access to medical information which relates to the patient's condition and treatment and to a copy of the medical record if requested by the patient or a person authorized by the patient
- The right to meet, share experiences with peers and other patients and to voluntary counseling at any time from diagnosis through treatment completion

Choice

- The right to a second medical opinion, with access to previous medical records
- The right to accept or refuse surgical interventions if chemotherapy is possible and to be informed of the likely medical and statutory consequences within the context of a communicable disease
- The right to choose whether or not to take part in research programs without compromising care

Confidence

- The right to have personal privacy, dignity, religious beliefs, and culture respected
- The right to have information relating to the medical condition kept confidential and released to other authorities contingent upon the patient's consent

Justice

- The right to make a complaint through channels provided for this purpose by the health authority and to have any complaint dealt with promptly and fairly
- The right to appeal to a higher authority if the above is not respected and to be informed in writing of the outcome

Organization

- The right to join, or to establish, organizations of people with or affected by tuberculosis and to seek support for the development of these clubs and community-based associations through the health providers, authorities, and civil society
- The right to participate as "stakeholders" in the development, implementation, monitoring, and evaluation of tuberculosis policies and programs with local, national, and international health authorities

Security

- The right to job security after diagnosis or appropriate rehabilitation upon completion of treatment
- The right to nutritional security or food supplements if needed to meet treatment requirements

Patients' Responsibilities

You have the responsibility to:

Share Information

- The responsibility to provide the healthcare giver as much information as possible about present health, past illnesses, any allergies, and any other relevant details
- The responsibility to provide information to the health provider about contacts with immediate family, friends, and others who may be vulnerable to tuberculosis or may have been infected by contact

Follow Treatment

- The responsibility to follow the prescribed and agreed treatment plan and to conscientiously comply with the instructions given to protect the patient's health, and that of others
- The responsibility to inform the health provider of any difficulties or problems with following treatment or if any part of the treatment is not clearly understood

Contribute to Community Health

- The responsibility to contribute to community well-being by encouraging others to seek medical advice if they exhibit the symptoms of tuberculosis
- The responsibility to show consideration for the rights of other patients and healthcare providers, understanding that this is the dignified basis and respectful foundation of the tuberculosis community

Show Solidarity

- The moral responsibility of showing solidarity with other patients, marching together towards cure
- The moral responsibility to share information and knowledge gained during treatment and to pass this expertise to others in the community, making empowerment contagious
- The moral responsibility to join in efforts to make the community tuberculosis free

¡Gracias por su atención!