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REVIEW ARTICLE

Antituberculosis drug-induced non-blistering systemic severe reactions: A 10-year (2012-2022) literature review

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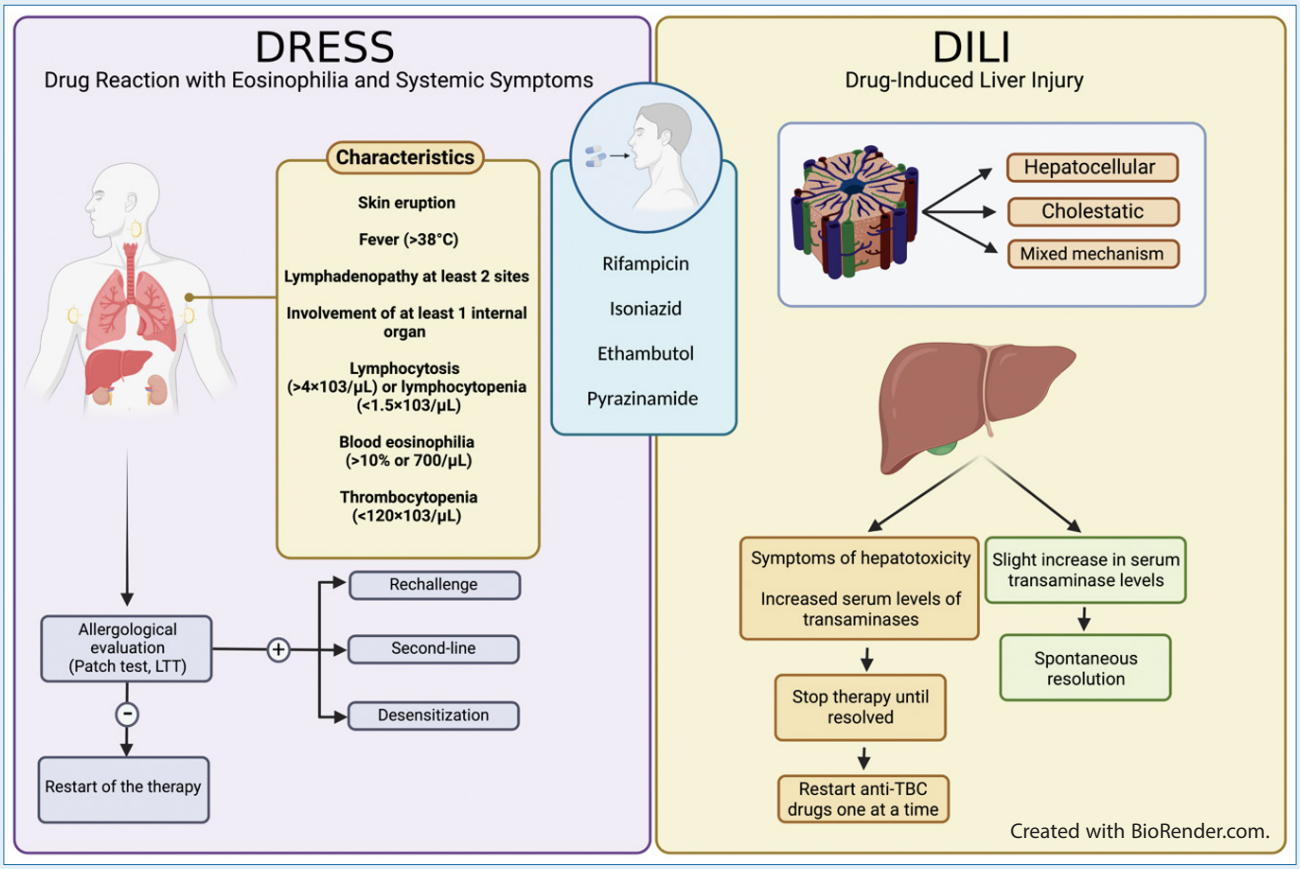
Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) and drug-induced liver injury (DILI) can hamper therapeutic strategy, contribute to multiple drug resistance and serious public health burden. Diagnosis (including allergy assessment) and management of these two severe hypersensitivity reactions in clinical practice are somewhat difficult and published scientific evidence is rather weak and limited. The first step is always represented by stopping all anti-tuberculosis (TB) drugs, treating reaction with systemic corticosteroids, and identifying the offending drug, even if it is often complicated by the patient's simultaneous intake of antibiotics. Patch tests and in vitro tests, such as lymphocyte transformation test, could bridge this diagnostic gap, but the available data are scarce and their sensitivity low. The re-challenge test is often necessary but places patients at risk for serious adverse reactions. The desensitization protocols are quite varied and not universally accepted. In this narrative review, we provide an update to the literature data on the management of DRESS and DILI with particular attention to the allergological work-up in the last decade.



Key words: Antituberculosis drugs, systemic severe reactions, Drug Reaction with Eosinophilia and Systemic Symptoms, drug-induced hypersensitivity syndrome, Drug-Induced Liver Injury, T-cell-mediated hypersensitivity, allergological management, re-challenge, desensitization

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Introduction

In 2016, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of guidelines on the treatment of drug-sensitive tuberculosis (TB), which was also approved by the European Respiratory Society (ERS) and the US National Tuberculosis Controllers Association (NTCA).[1] Individual patient care and minimization of the transmission of Mycobacterium tuberculosis to other people are the goals of TB treatment.

In particular, the primary objectives of drug therapy of tuberculosis are (1) to rapidly reduce the number of actively growing bacilli in the patient, allowing to limit the severity of the disease, prevent death and stop the transmission of *M. tuberculosis*; (2) eradicating persistent bacilli populations to achieve lasting cure after completion of therapy; and (3) preventing the acquisition of drug resistance during therapy.

Height decades of scientific literature have become the mainstays of multi-agent drug treatment to achieve these treatment goals, minimize drug toxicity and maximize the likelihood of treatment completion.[2–6]

The success of pharmacological treatment, however, depends on many factors including the onset of hypersensitivity reactions that can influence the therapeutic strategy adopted. Severe drug eruption, characterized by high fever, erythematous rash and inflammation of internal organ(s), include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)[7] and Drug-Induced Liver Injury (DILI).[8]

This review reports an update from the last decade on severe systemic hypersensitivity reactions to anti-TB drugs with particular emphasis on allergological management.

Methods

In order to describe the most recent reports of severe non-blistering systemic reactions (DRESS, DIHS, DILI) induced by anti-tuberculosis drugs, a review of literature was carried out. PubMed and Web of science were searched up from 2012 to September 2022.

Primary screening was performed using the following MeSH headings and keywords: "antitubercular agents", "antitubercular drugs", "anti-tuberculosis agents", "anti-tuberculosis drugs" and "antibiotics, antitubercular". Secondary screening was performed using terms such as "drug hypersensitivity syndrome", "drug reaction with eosinophilia and systemic symptoms syndrome", "DRESS syndrome" and "chemical and drug induced liver injury".

Criteria for inclusion were as follows: full-text case reports, classical articles, clinical studies, letters, and observational studies available online. Criteria for exclusion were as follows: duplicate publications, unavailability of full-text, language other than English, and review articles.

From each report, we retrieved data regarding time of onset of clinical manifestations, culprit drug and allergological diagnostic tests (skin prick test (SPTs), intradermal tests (IDTs), patch tests, lymphocyte transformation tests (LTTs).

Results

1. DRESS and antitubercular drugs

DRESS or drug-induced hypersensitivity syndrome (DIHS) is a potential life-threatening severe adverse drug reaction characterized by an extensive skin rash in association with visceral organ involvement, lymphadenopathy, eosinophilia and other hematologic abnormalities.[9] The latency between drug exposure and the disease onset is generally between 2-8 weeks.[10] The incidence of DRESS is estimated between 1 in 1000 and 1 in 10,000 drug administrations with a mortality rate of up to 10%.[11] The diagnosis of DRESS is performed usually following European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) group criteria.[12]

RegiSCAR criteria let to classified patients with suspected DRESS into definite, probable, possible or no cases, basing on following characteristics: 1) skin eruption, 2) fever (>38°C), 3) lymphadenopathy at least 2 sites, 4) involvement of at least 1 internal organ, 5) lymphocytosis ($> 4 \times 10^3/\mu L$) or lymphocytopenia ($< 1.5 \times 10^3/\mu L$), 6) blood eosinophilia (> 10% or 700/μL), and 7) thrombocytopenia ($< 120 \times 10^3/\mu L$).[12] Mizukawa et al. have developed a scale useful to evaluate the severity of DRESS based on the collection of clinical and anamnestic data. This scale includes fixed and variable parameters that ranges from -1 to 3. When the drug responsible for the reaction is allopurinol, 1 starting point is assigned, as this is recognized as a risk factor for severe disease and renal failure.

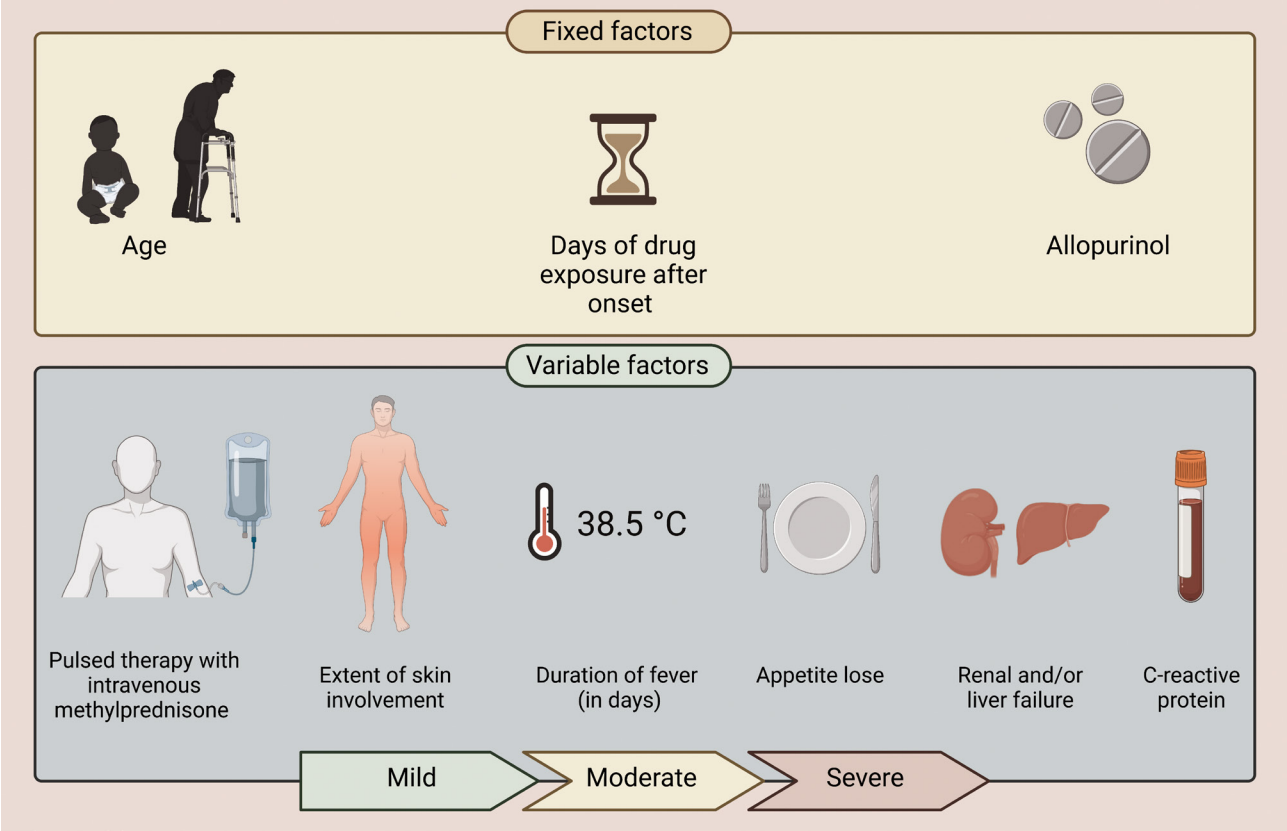

Figure 1. Risk factors can be fixed or variable. Each parameter ranges from -1 to 3 and the results allows to assess the degree of severity of the disease. The clinical history of allopurinol intake before and during the onset of the manifestations is considered a risk factor (1 point). Score < 1 describes mild disease, in this case therapy is not required. Scores between 1 and 3 describe moderate disease. Finally, levels ≥ 4 describe severe disease. This latter condition requires a high-dose corticosteroid therapy.[13] Based on the compound score proposed by Mizukawa et al.[13]
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The final score, resulting from this scale, allows to assess the disease severity and to drive therapeutic strategies, since it represents a useful indicator of therapeutic response.[13]

The pathogenesis of DRESS is multifactorial and not deeply understood, probably due to an interaction among genetic and environmental factors such as a genetic deficiency of detoxifying enzyme, human leukocyte antigen (HLA) haplotypes predisposing, virus–drug interactions (HHV-6).[14] However, the pathogenesis involves a delayed type hypersensitivity reaction, where T-helper type 2 cells play an important role.[14]

In the skin and involved organ, biopsies reveal CD4+ and CD8+ T cells, responsible for the production of Th2 proinflammatory cytokines and chemokines such as *thymus and activation-regulated chemokine* (TARC) and *macrophage-derived chemokine* (MDC).[15,16]

Innate immunity is also involved. In fact, IL-5 secreting innate lymphoid cell 2 (ILC2s) are involved in the immunopathogenesis of DRESS favoring the recruitment and activation of eosinophils. The increase in TNF-α and INF-γ levels suggest an overlap with the Th1 pattern.[16] Furthermore, in the early stages of DRESS, there is an expansion of the Tregs with consequent state of Treg-mediated immunosuppression, responsible for the reactivation of the herpes viruses (**Figure 2**).[14]

The most frequent involved culprit drugs include anticonvulsant, allopurinol, antibiotics, and antiretroviral drugs. Antitubercular drugs are uncommonly reported cause of DRESS, probably underdiagnosed or delay diagnosed. Most DRESS reactions described in literature occurred during first line (FL) anti-TB drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) (**Table 1**). In a case-control pharmacogenetic study, HLA Cw*0401 is reported as possible risk factor for antitubercular-associated DRESS development.[17] DRESS syndrome onset during antitubercular treatment represents a serious complication may lead to therapy discontinuation, high-dose of systemic corticosteroids use and second-line therapy.

1.1 Culprit antitubercular drugs

Among antitubercular drugs, rifampicin is most involved drug following by isoniazid in development of DRESS though often the patients undergo an antibiotics combination protocol, and the identification of culprit drug is difficult to realize. Analyzing French pharmacovigilance database, Allouchery et al.[18] reported the largest series of antitubercular drug-associated DRESS describing 67 cases. They recorded rifampicin and isoniazid as the most involved drugs with a median time of symptoms onset of 24 days of treatment.

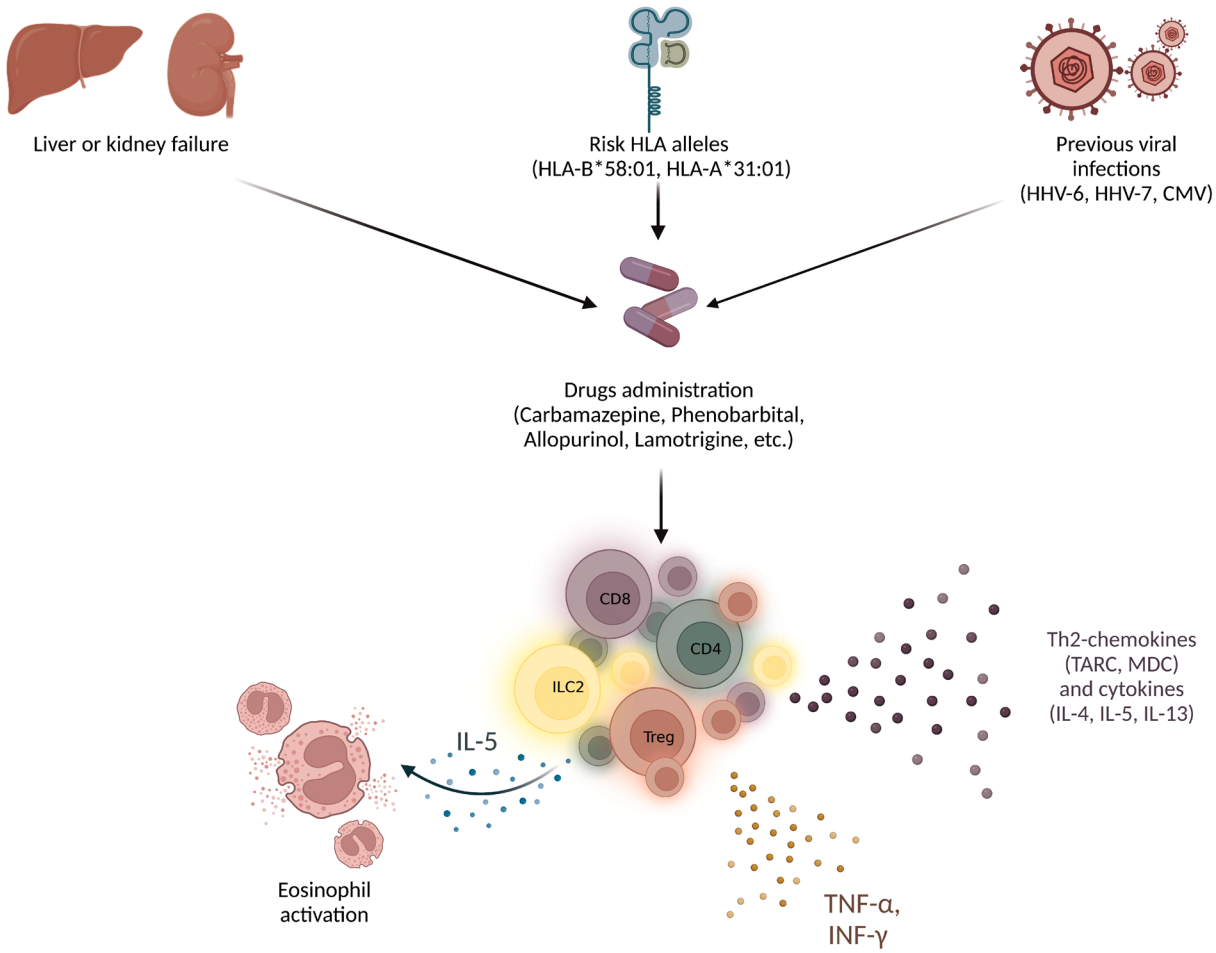

Figure 2. A genetic predisposition and some acquired factors, such as herpes virus infections or a reduced drug metabolism, are involved in the development of DRESS. In these patients, the administration of specific pharmacological classes could induce the activation of T cells (CD4 and CD8), ILC2, and Tregs. Tregs could favor the reactivation of herpes viruses.[14-16]
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In their case series, a drug allergy evaluation was performed in 11 patients (10 patch test and 1 intradermal/prick test with delayed readings) and was positive in 8 cases. Two patients died from DRESS. Overall, rifampicin seems to be most suspected because of its larger indications while isoniazid is associated with a deeper allergy investigation that indicated it as culprit drug,[19] less cases are related to ethambutol,[20] none with pyrazinamide alone.

A recent large Turkish study[21] found a global prevalence of drug hypersensitivity reactions to antituberculosis drugs of 7.8%. About a third of patients developed Type IV hypersensitivity reactions, most frequently represented by maculopapular eruption. Rifampicin was the most frequently responsible drug for developing Type IV hypersensitivity reactions, followed by pyrazinamide, isoniazid, and ethambutol.

Identification of culprit drug is often complicate in clinical practice by the possibility of a multiple drug hypersensitivity (MDH) in these patients.

DRESS is the severe cutaneous adverse reaction most frequently associated with MDH, which can be presented up to 18% of cases of DRESS.[22] The most accredited hypothesis sees transient immunosuppression and the costimulatory signals provided by viral reactivation and/or sensitization to the first drug as cofactors capable of increasing the stimulation of an immune response to other drugs and leading to the development of hypersensitivity to different classes of medications.[22] In this regard, Toujani et al.[23] attempted a rechallenge with a separate and sequential reintroduction of the involved drugs (HRZE) with positive results for all of them. Systemic symptoms reappeared with each reintroduction and the time to onset of symptoms was variable (3-7 days).

Carneiro-Leão L et al.[24] demonstrated a MDH in patient treated in the 15 last days, at first with piperacillin/tazobactam and vancomycin for community-acquired pneumonia and then with HRZE for tuberculosis infection. In this case,

Table 1. DRESS: allergological management. Update of reports from literature.

Study	N° of Pts[1]	Time of onset symptoms (days)	ATDs[2]	SPT[3]/ IDT[4]	Patch test	LTT[5]	Culprit drug/s	Re-challenge	DS
Allouchery M et al.[18]	67	24 (median)	Various	-	5/10: pos. H, 2/10: pos. E, 1/10 R	-	H: 32/67 R: 60/67 Z: 25/67 E: 23/67	Various results	-
Arruti N et al.[19]	1	30	HRZE	pos.: H	pos.: H	pos.: H	H	Neg.: Z, E	- (2nd ATDs: S, Lvx)
Jamel EIG et al.[20]	1	49	HRZE	-	E: pos	-	E	H: neg, R: neg,	
Toujani S et al.[23]	1	34	HRZE	-	-	-	HRZE	Pos: HRZE	- (2nd ATDs: Eth, S and ciprofloxacin)
Carneiro-Leão L et al.[24]	1	7	piperacillin/tazobactam (14 days) + vancomycin (10 days) + HRZE (7 days)	-	H: pos	Pos: all drugs	DRESS induced by piperacillin/tazobactam or vancomycin and complicated by HRZE (MDHS)	H: pos, E: pos	- (2nd ATDs: Z, Lvx, and linezolid)
Ogawa K et al.[25]	1	14	HRZE	-	pos: H	pos: H	H, allopurinol	Neg.: R, E	-
Rodríguez R et al.[26]	1	14	HRZE	Neg	Neg	-	HRZE	Pos.: H, R, Z, E	-
Jung ES et al.[27]	1	28	HRZE	-	-	-	RE	Pos.: R, E Neg.: H, Z	- (2nd ATDs: Lvx and S)
Cheng J et al.[28]	1	28	R, Z, E	-	Neg (while on steroids)	-	R, Z, E	-	-
Draz N et al.[29]	1	21	HRZE	-	-	-	HRZE	pos.: H, E, rifabutin	-
Kaswala DH et al.[30]	1	7-10	HRZE	-	-	-	HRZE	-	- (2nd ATDs: Cs and Mfx)
Palmero D et al.[31]	11	33.5 ± 15.1	9/11: HRZE 1/11: Km, Z, E, Cs, Mfx, 1/11: Cs, E, PAS, Mfx	-	-	-	Of the 8/11 with favourable outcome: 6/8: R 5/8: H 3/8: E 2/8: Z	H: 3/8 R: 2/8 E: 6/8	- (2nd ATDs: LVX: 8/8, S: 6/8, Cs: 5/8, Eth: 1/8, Km: 1/8)
Lee JH et al.[32]	1	28	HRZE	-	-	-	H	Neg.: R, Pos.: H, No rechallenge for E, Z	- (2nd ATDs: S, Mfx)
Zhang SN et al.[33]	1	60	HRZE	-	-	-	H	-	-
Blair PW et al.[34]	1	28	E, rifabutin, clarithromycin	-	-	-	E	-	-
Mancano MA et al.[35]	1	60	HRZE	-	-	-	H	Neg.: R Pos.: H	-

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Table 1. (Continued)

Study	N° of Pts[1]	Time of onset symptoms (days)	ATDs[2]	SPT[3]/ IDT[4]	Patch test	LTT[5]	Culprit drug/s	Re-challenge	DS
Kim H et al.[36]	1	-	HRZE	-	-	-	HRZE, Mfx, Cs, Eth, PAS	Pos: HRZE, Mfx, Cs, Eth, PAS	Patient died
Kim JH et al.[37]	1	21	Km, Mxf, Cs, PTH, PAS	-	-	-	PTH, PAS	Pos: PTH, PAS Neg: Km, Mfx, Cs	- (Mfx, Cs, Km)
Lehloenya RJ et al.[38]	6	-	HRZE	-	-	-	R (6/6)	Pos: R, H (2/6); Pos: R, Mfx (3/6); Pos: R, Z, and/or Ter and/or E (1/6)	- 6/6: rifabutin to replace R
Yoshioka Y et al.[39]	1	15	HRZE	-	pos.: E neg.: R	Neg.	E	-	-
Gest N et al.[40]	1	77	HRZE	-	E: pos, R: neg, Z: neg	-	E	E: pos, R: neg, Z: neg	Mfx
Kapur A et al.[41]	1	35	HRZE + Streptomycin	-	-	-	E	E: pos, HRZ: neg	- (2nd ATDs: Lvx)
Shrestha R et al.[42]	1	60	HRZE	-	-	-	R	R: pos, HZE: neg	-
Urbonas V et al.[43]	1	90	HRZE + pyridoxine	-	pos: HR	-	HR	-	-
Permatasari A et al.[44]	1	28	HRZE	-	-	-	-	E: neg	- (2nd ATDs: S, Lvx)
Shebe K et al.[46]	1	28	HRZE	neg	pos: R	-	R	Neg.: H, Z, E	-
Ye YM et al.[48]	4	30/30/12/60	HRZE	-	1: pos H, E, R 2: - 3: neg, 4: neg	1: pos HRZE 2: pos H 3: pos H, 4: pos HRZE	RHE/H/RHZ	1: pos.: HRE/neg.: Z 2: -, 3: pos.: HRE 4: pos.: HRZ	-
Coster A et al.[49]	2	36-90	HRZE	2: Neg: R	1: pos: HZE, neg: R 2: pos: H, doubtful: E, neg: R	-	1: pos: R, 2: pos: Z neg: R	1: HRZE 2: HZE	
Thong BY et al.[60]	6	30 ± 30	HRZE	-	-	-	6/6 H, 6/6 R, 3/6 Z, 5/6 E	Successful 5/6: H Successful 2/6: R Successful 2/6: Z Successful 2/6: E	
Oh JH et al.[63]	27	28 (median)	21/27 HRZE	-	performed in 9/27: multiple drugs pos	-	1st and 2nd ATDs	9: change all drug, 5: graded challenge	13 (11 pts with 1st ATDs and 2 pts with 2nd ATDs). Success in 9/11 pts.

[1]N° of pts = number of patients; [2]ATDs = anti tuberculosis drugs; [3]SPT = skin prick test; [4]IDT = intradermal test; [5]LTT = lymphocyte transformation test; [6]DS = desensitization; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; Lvx = levofloxacin; S = streptomycin; Km = kanamycin; Cs = cycloserin; PAS = para-aminosalicylic acid; Eth = ethionamide; Mfx = moxiflox-acin; PTH = prothionamide; MDHS = Multiple-drug hypersensitivity syndrome.

patch test resulted positive for isoniazid and lymphocyte transformation tests (LTTs) were positive to all drugs involved confirming MDH. However, on the basis on higher stimulation index for rifampicin and isoniazid rather than other anti-TB drugs, Authors readministered ethambutol and pyrazinamide without adverse effects. Furthermore, anti-TB could often be associated with other drugs known to induce DRESS (such as allopurinol) making it more difficult to identify the exact cause of DRESS. In fact, Ogawa et al[25] report a case of allopurinol-induced DRESS complicated by isoniazid hypersensitivity confirmed by patch and LTTs.

Table 1 summarizes the characteristics of the other cases reported in the literature.[26–44]

1.2 Allergological evaluations

Identifying the culprit drug is critical to restoring effective therapy quickly and safely. Therefore, an allergological in vivo or in vitro tests may prove useful to recognize the culprit drug. Preferably, an allergological work-up should be done after at least to 4-6 weeks after a complete remission of clinical manifestations of DRESS syndrome. In published cases, this time is often shortened to rapidly restore a therapy for these patients.

The diagnostic tool available does not seem to have high sensitivity and specificity and they do not often used in the clinical practice. Intradermal and skin prick tests are rarely performed and not standardized. Patch test can be useful in case of DRESS with a high specificity and a sensitivity reported between 32-64% depending on the drugs.[45] Interestingly, Shebe et al.[46] reported a case of systemic reaction (pruritus, eosinophilia, hepatitis, facial oedema, conjunctivitis, hemorrhagic cheilitis and erythematous tender palms) after rifampicin patch test application in a patient affected by HIV suggesting a possible life-threatening drug reactions associated with allergological evaluations in these patients.

LTTs are in vitro test helpful for the diagnosis of DRESS. LTT measures the uptake of a DNA precursor, tritiated thymidine, by lymphocytes after exposure to an antigen. Drug-induced LTT has a limited sensitivity ranging between 23-57% depending on considered drug, higher for isoniazid, but 93-98% of specificity that might aid in identifying the culprit drug.[47] Ye et al.[48] recorded a specific T cell response to isoniazid and rifampicin in patients with antituberculosis drug-induced DRESS syndrome or maculopapular exanthema. In their experience, LTT results agreed with oral provocation test while often were not associated with patch test results. Although LTT does not present any risk to the patient, compared to other allergy tests, and can be performed immediately after reactions, it is not routinely performed, especially in those countries where tuberculosis is currently widespread.

1.3 Rechallenge, retreatment and cross-reactivity

The management of anti-TB - related DRESS foresees the immediate withdrawing all drugs involved and starting topical and/or systemic corticosteroid therapy. Once clinical resolution is obtained, after 4-6 weeks, an allergological work-up is necessary to identify the culprit drugs and drive the reintroduction of other FL-anti-TB, but it is not always performed or reliable. Several Authors adopt a sequential reintroduction of FL antituberculosis drugs (e.g., one drug every 3-5 days) in increasing doses.[49] Nevertheless, the exact dose escalation and the order of drugs to be readministered, as well as the use of concomitant autoreactive therapy remain heterogenous and debated. Although sometimes it can reveal as a diagnostic aid, this approach should be performed carefully because often complicated by DRESS resumption, potentially life-threatening. Second-line antituberculosis drugs, such as aminoglycosides (streptomycin, amikacin, kanamycin) and quinolones (levofloxacin, moxifloxacin, ofloxacin, ciprofloxacin), can be administrated alternately or added to patients' therapy. These drugs represent safer option but generally less effective. For these reasons, rechallenge should only be considered when the risks associated with suboptimal therapy outweigh those of a possible reaction and only in a specialized environment. Moreover, concerning the alternative treatment, although ethionamide and isoniazid have structural analogues, the risk of cross-reactivity seems low.[50] Several findings also suggest the lack of cross-reactivity between rifampicin and rifabutin,[51–53] but the absence of such cross-reactivity remains to be confirmed by further evidences.

1.4 Desensitization

Desensitization (DS) consists in a stepwise administration until reaching a therapeutic dose of culprit drug inducing a temporary tolerance and allowing the patient to complete an uninterrupted course of medication safely. The exact mechanism behind desensitization is not completely understood but it could provoke an increase of T-reg that could downregulated T-cell activated by antigen. DS is generally not recommended in serious adverse reaction following drugs administration.[54] However, a desensitization protocol can be a reasonable option for patients with anti-TB drug-related DRESS to resume anti-TB medication. Antituberculosis drug desensitization data have been described in the literature.[55–57] To date, the only institutional protocol, a 16-day slow desensitization protocol, proposed by the Japanese Society for Tuberculosis in 1997[58] was effectively tested for the first time in nineteen patients between August 1998 and March 2000 by Kobashi Y. and coworkers.[59] Furthermore, the authors highlighted correlated factor with the success, such as the longer period from the discontinuation to the desensitization therapy and lower doses of drugs at starting desensitization.[59]

In the recent years, some Authors tried desensitization protocols in cases where benefit of therapy outweighed the risk of a severe reaction to procedure.[60–62] These studies recorded anti-TB DS success rate of 62.5-63.6%[61,62] in DRESS cases. Regarding breakthrough reactions during DS, Ban GY et al.[62] demonstrated that the drugs identified during allergological work-up showed significantly high reactions rates (p = 0.014), although this was not correlated with desensitization failure rate. Recently, Oh et al.[63] proposed a desensitization protocol as a safe and well-tolerated option after anti-TB DRESS, especially when there are no effective alternative drugs, compared with graded challenges or complete changing drugs regimes.

The utilization of antihistamines and corticosteroids as premedication for desensitization also remains controversial with limited evidence in literature. Scherer and colleagues[54] reported no difference between patients who took anti-reactive therapy daily during desensitization and those who did not. Such premedication seems rather more useful for relieving allergic symptoms in patients with skin diseases or a history of adverse drug reactions.

However, further data are necessary to assess the actual safety, tolerability, and effectiveness of desensitization protocols.

2. Drug-induced liver injury (DILI) and anti-tubercular drugs

DILI is a liver disease that commonly occurs 5-90 days after drug ingestion. Its clinical spectrum ranges from only biochemical abnormalities to an acute liver insufficiency.[64] Traditionally, DILI is classified into intrinsic (dose-related, predictable, and short latency to onset) and idiosyncratic (not dose-related, unpredictable, and variable latency to onset). Idiosyncratic DILI (IDILI) can be sub-classified into genetically mediated IDILI and immune-mediated IDILI (that can manifest with hypersensibility or drug-induced autoimmune injury). DILI is histopathologically classified into three groups: hepatocellular, cholestatic and mixed according to the Council for International Organizations of Medical Sciences (CIOMS).[65] Hepatocellular damage occurs when alanine aminotransferase (ALT) is ≥ 3 ULN (upper limit of normality) or the ratio (R) between ALT and alkaline phosphatase (ALP) is ≥ 5 (R = ALT serum activity / ALP serum activity). Hepatocellular type injury is more severe than cholestatic or mixed types. ALP ≥ 2 ULN or R ≤ 2 occurs in cholestatic type injury, while mixed type is defined by ALT ≥ 3 ULN, ALP ≥ 2 ULN and 2 < R < 5. Cholestatic and mixed type appear to occur more in patients with chronic disease.[65–67] Vascular liver injury is a rare histopathological alteration mainly due to radio-chemotherapy and pyrrolizidine alkaloid-based herbs (e.g., gynura segetum).[68,69] From a study published in 2006 on a small population of DILI patients at a center in Singapore, anti-TB drugs appear to be the second cause after herbal medicines.[70] It has been shown that isoniazid, rifampicin and pyrazinamide (metabolized by the liver) can cause DILI,[71] while for ethambutol or streptomycin it has not been clearly described.

DILI due to anti-tuberculosis drugs is a diagnosis of exclusion: personal medical history, physical examination and liver biochemistry are crucial in the diagnosis while imaging and liver biopsy should be discussed based on clinical presentation. For this reason, it is difficult to establish the exact incidence. Studies have shown a variable incidence between 2% and 28%.[7,72–84]

A study on the Chinese population found a 2.55% incidence of DILI with an asymptomatic rate of 33%; 70% of patients had to change their therapeutic regimen.[85] In a Malaysian study of 473 TB patients, 9.7% developed hepatitis,[86] and in a Sri Lankan study of 783 patients, the incidence was 9.5%.[87] On the other hand, in Tanzania, the incidence is lower than expected.[88]

A study on 47,594 patients identified a DILI incidence of 0.03% per year, and 80% of these were related to anti-TB.[89]

Advanced age, female sex, pregnancy, malnutrition, chronic ethanol consumption appear to be the major risk factors.[84,87,90,91] Furthermore, HIV infection, concomitant use of anti-retroviral drugs, decreased CD4 counts,[92] and extrapulmonary TB infection are associated with an increased risk of developing hepatitis.[86]

Over the years, many authors have also evaluated the possible genetic predisposition to develop liver damage with anti-TB intake. It has been hypothesized that mutations in genes involved in drug metabolism may promote liver damage. It has been known for many years that the detection of a slow NAT2 acetylation phenotype represents a significant risk factor for Isoniazid-induced toxicity.[84,93] Higuchi et al. demonstrated that the frequency of a variant haplotype, NAT2 6A, was significantly increased in patients with hepatotoxicity while the frequency of a wild-type haplotype NAT2 4, was significantly lower.[94] These data have also been recently confirmed.[95]

Evaluation of cytochrome P450 2E1 (CYP2E1) polymorphisms could be a useful diagnostic tool.[96]

In 2010, Wang et al. investigated the association between the genetic polymorphism of cytochrome P450 2E1 (CYP2E1) and glutathione S-transferase mu 1 (GSTM1) with the risk of developing DILI from anti-TB therapy. Their results demonstrated that the CYP2E1 RsaI c1/c1 genotype is a risk factor for the development of DILI in these patients, while the GSTM1 RsaI null genotype appears to increase susceptibility.[97]

DILI clinical severity is classified into five grades: from grade 0 (no liver injury) to grade 5 (death) (**Table 2**).[98]

Table 2. DILI clinical severity grading.

Grade	Comment	Laboratory	Clinical manifestations
0	No liver injury	None	None
1	Mild liver injury	↑ ALT[1] and/or ALP[2] and TBIL[3] < 2.5 mg/dL and INR[4] < 1.5	Fatigue, nausea, asthenia, jaundice, rashes, pruritus, right upper abdominal pain
2	Moderate liver injury	↑ ALT and/or ALP and TBIL ≥ 2.5 mg/dL or INR ≥ 1.5 without Hyperbilirubinemia	Symptoms like grade 1 but with more severity
3	Severe liver injury	↑ ALT and/or ALP and TBIL ≥ 2.5 mg/dL with or without INR ≥ 1.5	Patient needs to be hospitalized
4	Acute Liver Failure	↑ ALT and/or ALP and TBIL ≥ 2.5 mg/dL and at least 1 of the following: 1) Prolonged jaundice and symptoms beyond 3 months, or 2) Signs of hepatic decompensation (INR ≥ 1.5, ascites, encephalopathy), or 3) Other organ failure believed to be related to drug induced liver injury	Encephalopathy, ascites, DILI-related dysfunction of other organs
5	Lethal		Death/transplantation

[1]ALT = alanine aminotransferase; [2]ALP = alkaline phosphatase; [3]TBIL = total bilirubin; [4]INR = international normalized ratio.

2.1. Isoniazid

Isoniazid inhibits the formation of the mycobacterial cell wall. It is cleared mainly by the liver and its hepatotoxicity appears to be idiosyncratic[99] and caused by its toxic metabolites. The hepatic enzyme N-acetyltransferase 2 (NAT2) metabolizes the majority of isoniazid into acetylisoniazid and only a small part of isoniazid is hydrolyzed into isonicotinic acid and hydrazine; this pathway seems to be predominant in slow acetylators,[100,101] which develop hepatic injury more often and more severely than fast acetylators. This behaviour suggests hydrazine and its toxic metabolites (acetylated hydrazine, hydrazones and nitrogen gas) hepatotoxicity. CYP 2E1 c1/c1 genotype increases CYP 2E1 activity and appears to be involved to a higher hepatotoxins production.[84,96,102,103]

Bhatia et al. described a case of recurrent DILI in a child treated with isoniazid and rifampicin.[104] Isoniazid has been defined as responsible for pruritus episodes of liver damage, and according to the authors, in cases of recurrent DILI, fluoroquinolones may be preferred.[104] According to Branco Caetano et al, the hepatotoxic effect of isoniazid would be enhanced by anti-epileptic therapy and the ketogenic diet. The author reported two cases of DILI in patients diagnosed with epilepsy undergoing anti-TB treatment.[105]

2.2 Rifampicin

Rifampicin can rarely induce a dose-dependent hepatotoxicity due to an interference with bilirubin uptake, causing an unconjugated hyperbilirubinemia by inhibiting the bile salt exporter pump.[106,107]

2.3 Pyrazinamide

The mechanism of pyrazinamide hepatotoxicity is unknown. Since pyrazinamide is only used in combination therapy, its toxicity is unclear to date. In 2001, the Centers for Disease Control and Prevention (CDC) reported two episodes of severe hepatitis associated with the combination of rifampin and pyrazinamide in New York and Georgia.[108]

Wang et al. reported the case of a 78-year-old man with biopsy-confirmed liver injury secondary to pyrazinamide therapy. Upon suspension of the therapy, the liver damage regressed, and a new cycle with ethambutol and levofloxacin was started.[95] The patient had a NAT2 slow acetylator phenotype, which may be implicated in pyrazinamide toxicity by unknown mechanisms.[95] Ruslami et al. reported 4 cases of pyrazinamide-related hepatotoxicity.[109]

2.4 Ethambutol and streptomycin

To date, no hepatotoxicity is described.

2.5 Management

One in five patients shows an increase in serum transaminase levels when treated with standard anti-TBC regimen and resolves spontaneously.[71,73,110] Routine transaminase monitoring is unnecessary if no risk factors or underlying liver disease coexist.[111] Some authors suggest monitoring liver function in the first eight weeks of treatment in patients treated with anti-TB.[112] British Thoracic Society (BTS) suggest monitoring liver function only of patients with known chronic liver disease for the first 2 months.[113]

American Thoracic Society (ATS) guidelines suggest a baseline liver function testing in at risk patients. If hepatotoxicity occurs, after stopping the treatment, ATS guidelines suggests restarting anti-TBC drugs one at a time.[114] For BTS, in the case of DILI, the treatment must be suspended, and once liver function normalizes, the drugs can be reintroduced sequentially in the order: isoniazid, rifampicin, pyrazinamide; these patients should be monitored daily for clinical condition and liver function.[113] In 2014, Zuberi et al. compared the two main guidelines for the treatment of tuberculosis. According to the authors, there are no substantial differences in the treatment of DILI between the ATS and BTS guidelines.[115] Sharma et al. evaluated with good results the reintroduction of the three main drugs (isoniazid, rifampicin, and ethambutol) simultaneously and at full dosage, with advantages on patients with bilateral pulmonary tuberculosis or for life-threatening patients.[116]

There is no evidence on correct approaches for reintroducing anti-TB therapy in pediatric patients with comorbidities (meningitis, HIV infection, cardiac disease), and standardized guidelines would be needed.[117]

2.6 What literature adds about the diagnostic evaluation?

According to the most recent studies, the dosage of bilirubin, the MELD score, creatinine, albumin, and INR can be markers of the severity of liver damage.[118,119] According to some authors, these markers and signs of encephalopathy, ascites, and jaundice are associated with poor prognoses.[118,120,121]

Hepatitis B and cirrhosis are important risk factors, and the Child-Pugh score should be evaluated before starting treatment.[122]

There are conflicting results in the literature. Saha et al. found no statistically significant risk factors.[123] Given the high incidence of DILI in patients on anti-TB therapy, according to Abbara et al., it would be helpful to monitor liver damage enzymes in the first eight weeks of treatment.[112]

Cao et al.,[124] evaluating urinary metabolites, found that tricarboxylic acid circulation, arginine and proline metabolism and purine metabolic pathways were affected by anti-tuberculosis treatment. Potential diagnostic markers such as mean eosinophilic volume (MEV) and mean eosinophilic volume and size variability (MEV-SD) were described by Shen et al.[125] Changes in serum values of these biomarkers were present in patients who had undergone antituberculosis therapy. To date, no allergy tests are reported in the literature to correctly diagnose or predict drug-induced liver injury due to ADTs. The only diagnostic procedure also described by the current guidelines provides for the suspension and subsequent reintroduction of the drugs involved.

Some authors have tried to associate traditional therapeutic schemes with supplements capable of reducing hepatotoxicity. Good results were obtained with silymarin,[126] with a mix of medicinal herbs[127] and cholecalciferol.[128]

Table 3 summarizes the main studies in the literature on DILI induced by anti-TB drugs. Due to the lack of clinical studies in the last decade, we have also included studies from previous years. Further data collection is needed to strengthen the evidence.

Table 3. DILI: reports from literature.

Study	N° of Pts[1]	ATDs[2]	Diagnostic evaluation	Culprit drug/s	Re-challenge	Comments
Studies before 2012*						
Wai CT (2006)[70]	4	HRZ	LFT	-	-	Evaluation of the main causes of DILI in a local liver center in Singapore. Anti-TB drugs are the second cause after medicinal herbs.
Pande JN et al. (1996)[84]	86	HRE (32) HREZ (39) HRZS (9) HRZ (6)	LFT	Z (?)	-	The authors analyze various risk factors for the development of DILI. Among these, only advanced age, hypoalbuminemia, high alcohol intake, slow acetylator phenotype, and extensive disease appear to be real risk factors for developing liver damage in patients undergoing a therapeutic regimen with anti-TB.
Shang P et al. (2011)[85]	106	HRZE	LFT	-	-	The cumulative incidence of liver injury is 2.55% in Chinese tuberculosis patients receiving HRZES treatment. One-third of patients with liver injury were asymptomatic, suggesting that liver function monitoring and identifying known risk factors are needed in patients undergoing therapy.
Marzuki OA et al. (2008)[86]	46	HRZS, HRZE or HZR	LFT	-	-	In a population of 473 patients suffering from tuberculosis and receiving anti-TB therapy, the prevalence of hepatitis was 9.7%. Concomitant HIV infection and signs of extrapulmonary tuberculosis were significant risk factors for developing DILI.
Senaratne WP et al. (2006)[87]	74	HRZE	LFT	R(?)	HRZE (60) HES (7) ESC (5)	Hepatitis in patients treated with anti-TB in Sri Lanka has an incidence of 9.5%. The incidence is highest among patients older than 60 and those weighing between 33 and 55 kg. Rifampicin overdose is also a predictor of liver injury. Standard treatment was resumed in 60 patients.
Tostmann A et al. (2010)[88]	1	HRZE	LFT	-	-	Data on the African population are limited. The authors measured liver enzymes in 112 patients receiving anti-TB therapy and found an incidence of 0.9%.
Treeprasertsuk S et al. (2010)[89]	68	HRZE	LFT	-	-	Incidence of DILI of 0.03% per year. 80% of DILI was induced by anti-TB.
Yimer G et al. (2008)[92]	34	HRZS (27) HRZE (3) HRZ (4)	LFT	-	-	The authors evaluated the possible role of HIV coinfection in developing DILI in tuberculosis patients treated with standard regimens. Subclinical hepatotoxicity has been shown to be associated with HIV coinfection, concomitant drug intake, and a decrease in CD4 count with statistically significant values. According to the scheme proposed and used by the authors, desensitization was successful in almost all patients.
Teixeira RL et al. (2011)[93]	26	HRZE	LFT	H (?)	-	Differences in isoniazid-induced toxicity have been attributed to genetic variability in NAT2, CYP2E1, GSTM1, and GSTT1, which code for enzymes involved in drug metabolism. In 167 patients with active tuberculosis, slow acetylators had a higher incidence of hepatitis than intermediate/fast acetylators. Slow acetylation status is the only independent risk factor for the occurrence of DILI during treatment with H.
Higuchi N et al. (2007)[94]	18	HR	LFT	-	-	The authors want to demonstrate the role of NAT2 in anti-TB drug-induced hepatotoxicity. Statistical analysis revealed that the frequency of a variant haplotype, NAT2 6A, was significantly increased in patients with hepatotoxicity while the frequency of a wild-type haplotype NAT2 4, was significantly lower. NAT2 4 and NAT2 6A are potential predictive biomarkers of anti-TB-induced hepatotoxicity.

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Table 3. (Continued)

Study	N° of Pts[1]	ATDs[2]	Diagnostic evaluation	Culprit drug/s	Re-challenge	Comments
Studies before 2012* (Continued)						
Vuilleumier N et al. (2006)[96]	35	H	LFT	H	-	There was a significant association between CYP2E1 *1A/*1A genotype and an increase of liver enzymes (OR: 3.4; 95%CI: 1.1-12; $p = 0.02$) but a nonsignificant trend for H-induced hepatitis (OR: 5.9; 95%CI: 0.69-270; $p = 0.13$) compared with other CYP2E1 genotypes. Genotyping of CYP2E1 polymorphisms may be a useful predictive tool to predict isoniazid-induced liver toxicity.
Wang T et al. (2010)[97]	104	HRZE	LFT	-	-	To investigate the association between the genetic polymorphisms of cytochrome P450 subtype 2E1 (CYP2E1) and glutathione S-transferase mu 1 (GSTM1) with the susceptibility to the development of DILI in patients with tuberculosis. The results indicate that the CYP2E1 RsaI c1/c1 genotype is a potential risk factor for DILI in patients on anti-TB therapy, while the GSTM1 RsaI null genotype could increase susceptibility.
Bhatia S et al. (2011)[104]	1	HR	LFT	H	EC	Case of recurrent DILI in a child treated with HRZ. Liver damage recurred after the addition of R during the rechallenge with H. For this reason, it was preferred to continue with E and C. A regimen containing fluoroquinolones may be preferred in case of recurrence of hepatotoxicity to first-line anti-TB drugs.
Centers for Disease Control and Prevention (2001)[108]	2	RZ	LFT	Z	-	Description of 2 cases of severe hepatitis induced by R and Z. One patient died of liver damage. He had not stopped the treatment.
Aziz S et al. (1990)[111]	47	HRZE	LFT, sputum			The anti-TB combinations are well tolerated, even in patients with anemia or malnutrition. There is a slight increase in bilirubin in the first two weeks. According to the authors, if there is no associated liver disease, routine evaluation of liver enzymes is not essential, as they do not appear sufficient to diagnose impending hepatitis early. All drugs should be discontinued at the first sign of toxicity (fever, rash, gastrointestinal discomfort). Upon normalization of liver function, the offending drug should be tested, and once identified, it should be eliminated.
Sharma SK et al. (2010)[116]	175	HRZ	LFT	-	HRZ at full dosage or ATS or BTS suggested reintroduction	All three potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) can be safely reintroduced simultaneously at full dosage in bilateral extensive pulmonary tuberculosis cases to stop disease transmission or for life-threatening patients.
Adhvaryu MR et al. (2008)[127]	29	HRZE (27) HRZE + HF (2)	LFT	-	-	The herbal formulation significantly prevents hepatotoxicity while improving patient outcomes and compliance without toxicity or side effects.

Table 3. (Continued)

Study	N° of Pts[1]	ATDs[2]	Diagnostic evaluation	Culprit drug/s	Re-challenge	Comments
Studies after 2012						
Gaude GS et al. (2015)[91]	150	HRZE → HR or HRZES → HR	LFT	in 12 patients were avoided R and Z	HRZE	Advanced age, hypoalbuminemia, alcoholism are independent risk factors for the development of DILI.
Wang YC et al. (2022)[95]	1	HRZE	LFT, liver biopsy	Z	EL	DILI related to Z; resolution after discontinuation of therapy for four months. New treatment with E + L. Detection of NAT2 slow acetylator phenotype. NAT2 is implicated in the metabolism of H.
Branco Caetano F et al. (2022)[105]	2	HRZEL HRZE	LFT	H	R PL → RL	The two patients being treated for tuberculosis were undergoing antiepileptic treatment and a ketogenic diet. In both cases, isoniazid toxicity appears to have occurred. It is probably a synergistic action between H, antiepileptic drugs and the ketogenic diet. All of these items are risk factors for DILI.
Ruslami R et al. (2021)[109]	4	HRZE	Plasma concentration–time profiles of the drugs, LFT, CSF drugs concentration	Z (?)	HR	After the development of liver damage, H, R, and Z were suspended while the therapy with ethambutol combined with streptomycin was continued (for two weeks). Upon normalization of liver enzymes, H and R were gradually reintroduced without any recurrence of DILI. Z was completely discontinued until the end of treatment.
Abbara A et al. (2017)[112]	105	HRZE	LFT	Z (?)	E → H → R	All patients on anti-TB therapy should be considered for liver monitoring during the first eight weeks of treatment.
Zuberi BF et al. (2014)[115]	34	HRZ	LFT	-	BTS suggested reintroduction (16) ATS suggested reintroduction (18)	The patterns of reintroduction of anti-TB therapy of BTS and ATS are compared. The study found no significant differences between the two main guidelines, but the ATS-recommended framework appears easier to follow.
Nataprawira HM et al. (2021)[117]	6	HRZ (2) HRZES (4)	LFT	HR H H (2) H HR	- R ES (2) EL HR	Description of 6 case reports of recurrent DALI in pediatric patients with complicated tuberculosis. HRZ therapeutic regimen, associated with E + S in patients with complications (meningitis, urinary tract tuberculosis, HIV infection, cardiac comorbidities). Standardized guidelines for the reintroduction of therapy in the pediatric age are needed.
Ou P et al. (2015)[118]	51	HRZ, HR, R or HZ	LFT	-	-	MELD score and albumin are independent predictors of outcome in DILI patients.
Sunil Kumar N et al. (2021)[119]	50	Not specified	LFT	-	-	Anti-TB drugs are the most common cause of DILI and DILI-related mortality among patients in this study. Variables such as MELD score, INR, bilirubin, albumin, and creatinine can be markers of severity of liver damage.

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Table 3. (Continued)

Study	N° of Pts[1]	ATDs[2]	Diagnostic evaluation	Culprit drug/s	Re-challenge	Comments
Studies after 2012						
Devarbhavi H et al. (2013)[120]	269	HRZE	LFT, CSF	HRZ	-	DILI progresses to acute liver failure in a quarter of patients, with an overall mortality of 22.7%. Factors that increase mortality are the presence of jaundice, ascites, or encephalopathy.
Zhao H et al. (2020)[121]	140	HRZ (72%)	LFT	-	-	DILI is a more common adverse event in females. The H + R + Z combination and re-challenge are risk factors for severe DILI. Elevated total bilirubin, INR, MELD score, and onset of hepatic encephalopathy are associated with a poor prognosis.
Aminy RZ et al. (2022)[122]	1	HRE	LFT	-	EL	Hepatitis B and cirrhosis are risk factors for DILI in patients receiving anti-TB therapy. It is necessary to interrupt the therapy until resolved and then reset the treatment. Administration of anti-TB drugs should follow the stage of liver disease (Child-Pugh), considering liver tolerance.
Saha A et al. (2016)[123]	24	HRZ	LFT	Z	-	DILI was not significantly associated with known risk factors
Cao J et al. (2018)[124]	11	HRZE	LFT, urine metabolites	-	-	Circulating tricarboxylic acid, arginine and proline metabolism, and purine metabolic pathways were found to be affected by anti-TB drugs. The generation of superoxide may aggravate the hepatotoxic effects of HRZE anti-TB therapy.
Shen T et al. (2016)[125]	50	HRZE → HR	LFT, MEV, MEV-SD	-	-	In DILI patients, the MEV and MEV-SD increase was observed before the ALT increase, achieving sensitivities of 81% and 72% and specificities of 82% and 80%, respectively.
Luangchosiri C et al. (2015)[126]	10	HRZE + Silymarin (1) HRZE (9)	LFT, AOE dosage	-	-	Silymarin, a traditional medical herb extracted from milk thistle seeds (Silybum marinums), has been used in patients receiving anti-TB drugs to prevent liver damage. This double-blind placebo study demonstrated the efficacy of silymarin in preventing DILI. Silymarin could bring about the hepatoprotective effect by restoring superoxide dismutase.
Hasanain AFA et al. (2017)[128]	28	HRZE + cholecalciferol (8) HRZE (20)	LFT	-	-	Adjuvant cholecalciferol supplementation may be protective against DILI without additional adverse effects.

R = Rifampicin; H = Isoniazid; Z = Pyrazinamide; E = Ethambutol; S = Streptomycin; L = Levofloxacin; C = Ciprofloxacin; HF = Herbal formulation; MEV = mean eosinophilic volume; MEV-SD = mean eosinophilic volume and size variability; CSF = cerebrospinal fluid; AOE = antioxidative enzymes; LFT = liver function tests; ATS = American Thoracic Society; BTS = British Thoracic Society.
*Articles prior to 2012 were evaluated due to the lack of publications.

Conclusions

The World Health Organization Global Tuberculosis Report 2021 defines tuberculosis as the second infectious disease that causes sickness and death after SARS-CoV-2 infection and ranks it as the 13th among the global causes of death.[129] To date, the prevalence of the patients developing a hypersensitivity reaction against antituberculosis drugs is yet unknown. Patients should stop their antituberculosis treatment if any hypersensitivity reaction occurs against any of the drugs used. This situation not only delays the treatment but also represents a diagnostic and therapeutic challenge for clinician. Furthermore, adverse effects of the medication, in particular severe hypersensitivity reactions not properly managed, will also disrupt the patient's compliance with treatment and will weigh heavily on health care costs, requiring admission or prolongation of existing admission.[130] Known risk factors for adverse drug reactions are: genetic factors (some HLA sequences), women's lower body weight, advanced age, smaller organ sizes, greater body fat, gastric motility differences, and lower glomerular filtration rate, neo-diagnosis versus previous anti-tuberculous treatment.[21,61,74,82,131] The most common agents responsible for hypersensitivity reactions are rifampicin, isoniazid, and ethambutol. More and more frequent is the finding of multiple sensitivities against antituberculosis drugs.[132–134] The first step of the management of a hypersensitivity reaction is the interruption of suspected culprit drug, followed by antihistamine treatment, steroid treatment, or their combinations.[135] The next challenge for the clinician is identifying the drug responsible for hypersensitivity reaction before drug reintroduction.[135] Current diagnostic difficulties include: the limited availability of intravenous preparations for intradermal testing and the need for cutaneous manifestation recovery before testing,[45] the frequent need for ex vivo testing [such as IFN-gamma release enzyme-linked immunospot (ELISpot) assay], which can be a problem in low-income countries.[45,136–138]

In the spirit of nurturing research, overcoming roadblocks, and innovating the practice, eHealth technologies could be a way to enhance diagnosis procedures at each step of the management of patients with tuberculosis.[139,140] Through eHealth, the development of adverse reactions to antituberculosis drugs could be early intercepted with desirable reduction of morbidity and mortality.[141]

The Authors believe that future research should focus on: 1) diagnostic pathways based on clinical risk stratification and dual strategy involving sequential re-challenge and rapid drug desensitization,[142] 2) definition and constant up-date of well-phenotyped cohorts in order to uncover genomic predictors of hypersensitivity reactions.

Finally, a concerted international effort is needed to generate real-time data on hypersensitivity reactions to antitubercular drugs.

This global and multidisciplinary approach will improve the compliance of the patients to the antituberculosis treatment.

Key messages

- Anti-tuberculosis drugs may be responsible for severe delayed hypersensitivity reactions (DRESS and DILI).
- The main drugs involved are rifampicin, isoniazid, and ethambutol.
- These drugs are often administrated in combination; this approach potentially complicates the diagnostic work-up.
- Skin prick and intradermal tests are not conclusive. Patch tests with suspect drugs and lymphocyte transformation tests (LTTs) can be useful tools for diagnostic work-up, although sensitivity and specificity vary from drug to drug.
- A multidisciplinary approach, greater awareness of data collection and the search for standardized diagnostic tests are necessary pillars to ensure a correct diagnosis and a better compliance of the patient.

Conflicts of Interest

The authors declare no conflict of interest.

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Author Contributions

- Conceptualization, A.R., E.N. and R.I.
- Methodology, A.R. and R.I.
- Formal Analysis, R.I.
- Investigation, S.U., D.L. and L.G.
- Writing–Original Draft Preparation, A.R., S.U., D.L., F.M.L., L.G. and R.I.
- Supervision, E.N., G.G. and S.G.
- All authors have read and agreed to the published version of the manuscript.

References

1. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63:e147–95.
2. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999;3:S231-79.
3. Stanley S, Liu Q, Fortune SM. Mycobacterium tuberculosis functional genetic diversity, altered drug sensitivity, and precision medicine. Front Cell Infect Microbiol. 2022;12:1007958.
4. J LF, Yn D, N V, A S, Bb A. Design principles to assemble drug combinations for effective tuberculosis therapy using interpretable pairwise drug response measurements. Cell reports Medicine [Internet]. 2022 [cited 2022 Oct 29];3. Available from: https://pubmed.ncbi.nlm.nih.gov/36084643/
5. Mitchison D, Davies G. The chemotherapy of tuberculosis: past, present and future. Int J Tuberc Lung Dis. 2012;16:724–32.
6. Pontali E, Raviglione MC, Migliori GB, and the writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev. 2019;28:190035.
7. Sharifzadeh S, Mohammadpour AH, Tavanaee A, Elyasi S. Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review. Eur J Clin Pharmacol. 2021;77:275–89.

8. Devarbhavi H, Kurien SS, Raj S, Patil M, Gowda V, Kothari K, et al. Idiosyncratic Drug-Induced Liver Injury Associated With and Without Drug Reaction With Eosinophilia and Systemic Symptoms. Am J Gastroenterol. 2022;117:1709–13.
9. Stirton H, Shear NH, Dodiuk-Gad RP. Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS)/Drug-Induced Hypersensitivity Syndrome (DiHS)-Readdressing the DReSS. Biomedicines. 2022;10:999.
10. Cardones AR. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Clin Dermatol. 2020;38:702–11.
11. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010;146:1373–9.
12. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2006;155:422–8.
13. Mizukawa Y, Hirahara K, Kano Y, Shiohara T. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: A useful tool for assessing disease severity and predicting fatal cytomegalovirus disease. J Am Acad Dermatol. 2019;80:670-678.e2.
14. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int. 2019;68:301–8.
15. Miyagawa F, Asada H. Current Perspective Regarding the Immunopathogenesis of Drug-Induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (DIHS/DRESS). Int J Mol Sci. 2021;22:2147.
16. Hama N, Abe R, Gibson A, Phillips EJ. Drug-Induced Hypersensitivity Syndrome (DIHS)/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): Clinical Features and Pathogenesis. J Allergy Clin Immunol Pract. 2022;10:1155-1167.e5.
17. Kim SH, Lee SK, Kim SH, Park HW, Chang YS, Lee KW, et al. Antituberculosis drug-induced hypersensitivity syndrome and its association with human leukocyte antigen. Tuberculosis (Edinb). 2013;93:270–4.
18. Allouchery M, Logerot S, Cottin J, Pralong P, Villier C, Ben Saïd B, et al. Antituberculosis Drug-Associated DRESS: A Case Series. J Allergy Clin Immunol Pract. 2018;6:1373–80.
19. Arruti N, Villarreal O, Bernedo N, Audicana MT, Velasco M, Uriel O, et al. Positive Allergy Study (Intradermal, Patch, and Lymphocyte Transformation Tests) in a Case of Isoniazid-Induced DRESS. J Investig Allergol Clin Immunol. 2016;26:119–20.
20. Jamel EG, Ahmed S. DRESS Syndrome and Chronic Renal Failure Induced by Ethambutol. Am J Med Sci. 2019;358:e19.
21. Katran ZY, Bulut I, Babalik A, Keren M. Treatment and management of hypersensitivity reactions developed against anti-tuberculosis drug. Int J Mycobacteriol. 2022;11:309–17.
22. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013;168:555–62.
23. Toujani S, Zaiem A, Mjid M, Ouahchi Y, Ben Salah N, Louzir B, et al. Drug Rash with Eosinophilia and Systemic Symptoms to antituberculosis treatment. Tunis Med. 2015;93:590–3.
24. Carneiro-Leão L, Gomes I, Freitas C, Costa E Silva M, Viseu R, Cernadas J. Multiple Drug Hypersensitivity Syndrome to Antituberculosis Drugs: A Case Report. J Investig Allergol Clin Immunol. 2020;30:70–1.
25. Ogawa K, Morito H, Kobayashi N, Fukumoto T, Asada H. Case of drug-induced hypersensitivity syndrome involving multiple-drug hypersensitivity. J Dermatol. 2012;39:945–6.
26. Rodríguez R, Jover V, Orozco I, Domenech J. DRESS syndrome in a 19-year-old patient following the administration of first-line antituberculosis drugs. J Investig Allergol Clin Immunol. 2012;22:380–1.
27. Jung ES, Choi B, Choi HS, Kim BH, Ha M, Shin D, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Induced by Ethambutol and Rifampin. Infection & Chemotherapy. 2012;44:197–200.
28. Cheng J, Rawal S, Roberts A, Guttman OR. Drug reaction with eosinophilia and systemic symptoms syndrome associated with antituberculosis medications. Pediatr Infect Dis J. 2013;32:1388–90.
29. Draz N, Datta S, Webster DP, Cropley I. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome secondary to antituberculosis drugs and associated with human herpes virus-7 (HHV-7). BMJ Case Rep. 2013;2013:bcr2013010348.
30. Kaswala DH. Drug Rash with Eosinophilia and Systemic Symptoms Syndrome Due to Anti-TB Medication. J Family Med Prim Care. 2013;2:83–5.
31. Palmero D, Castagnino J, Musella RM, Mosca C, González Montaner P, de Casado GC. Difficult clinical management of anti-tuberculosis DRESS syndrome. Int J Tuberc Lung Dis. 2013;17:76–8.
32. Lee JY, Seol YJ, Shin DW, Kim DY, Chun HW, Kim BY, et al. A Case of the Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) Following Isoniazid Treatment. Tuberc Respir Dis (Seoul). 2015;78:27–30.
33. Zhang SN, He QX, Yang NB, Ni SL, Lu MQ. Isoniazid-induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Presenting as Acute Eosinophilic Myocarditis. Intern Med. 2015;54:1227–30.
34. Blair PW, Herrin D, Abaalkhail N, Fiser W. DRESS syndrome presenting after initiation of mycobacterium avium complex osteomyelitis treatment. BMJ Case Rep. 2015;2015:bcr2015210907.
35. Mancano MA. Bacteremia in Preterm Infants Receiving Probiotics; Throbbing Headache Associated with Enoxaparin Use; DRESS Reaction Following Isoniazid Treatment; SIADH Associated with Glimepiride; Mania Associated with Bortezomib Administration. Hosp Pharm. 2015;50:441–5.
36. Kim H, Bang ES, Lim SK, Lee JM. DRESS syndrome and acute generalized exanthematous pustulosis induced by antituberculosis medications and moxifloxacin: case report. Int J Clin Pharmacol Ther. 2016;54:808–15.
37. Kim JH, Jang SH, Kim DH, Park S, Kim DG, Jung KS. A case of DRESS syndrome induced by the antituberculosis drugs, prothionamide, and para-aminosalycilic acid. Ann Allergy Asthma Immunol. 2013;110:118–9.
38. Lehloenya RJ, Dlamini S, Muloiwa R, Kakande B, Ngwanya MR, Todd G, et al. Therapeutic Trial of Rifabutin After Rifampicin-Associated DRESS Syndrome in Tuberculosis-Human Immunodeficiency Virus Coinfected Patients. Open Forum Infect Dis. 2016;3:ofw130.
39. Yoshioka Y, Hanafusa T, Namiki T, Nojima K, Amano M, Tokoro S, et al. Drug-induced hypersensitivity syndrome by ethambutol: A case report. J Dermatol. 2016;43:971–2.
40. N G, S IHO, G G, M B, A H, S G, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome due to ethambutol. Medecine et maladies infectieuses [Internet]. 2018 [cited 2022 Nov 4];48. Available from: https://pubmed.ncbi.nlm.nih.gov/29602678/
41. Kapur A, Rehan HS. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome Associated with Ethambutol use: A Case Report. Curr Drug Saf. 2019;14:249–51.
42. Shrestha R, Jha SK, Bartaula J. Drug Reaction With Eosinophilia and Systemic Symptom (DRESS) Following Rifampicin Treatment: A Case Report. Cureus. 2021;13:e19223.
43. Urbonas V, Varnas D, Mociskiene K, Kvedariene V, Rudzeviciene O. Case Report: DRESS Syndrome Induced by Two Antituberculosis Drugs in an 8-Year-Old Girl. Front Pediatr. 2022;10:830611.
44. Permatasari A, Soegiarto G. Management of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a female Indonesian with pulmonary tuberculosis: A rare case report. Ann Med Surg (Lond). 2022;81:104512.
45. Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, et al. Controversies in drug allergy: Testing for delayed reactions. J Allergy Clin Immunol. 2019;143:66–73.
46. Shebe K, Ngwanya MR, Gantsho N, Lehloenya RJ. Severe recurrence of drug rash with eosinophilia and systemic symptoms syndrome secondary to rifampicin patch testing in a human immunodeficiency virus-infected man. Contact Dermatitis. 2014;70:125–7.
47. Sun Q, Sha W, Gui XW, Xiao YJ, Zeng WH, Sun WW, et al. Drug-induced lymphocyte stimulation test in the prediction of drug-induced hypersensitivity to antituberculosis drugs. Diagn Microbiol Infect Dis. 2015;82:172–6.

48. Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ, et al. Drug-specific CD4+ T-cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. Br J Dermatol. 2017;176:378–86.
49. Coster A, Aerts O, Herman A, Marot L, Horst N, Kenyon C, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by first-line antituberculosis drugs: Two case reports and a review of the literature. Contact Dermatitis. 2019;81:325–31.
50. Lehloenya RJ, Muloiwa R, Dlamini S, Gantsho N, Todd G, Dheda K. Lack of cross-toxicity between isoniazid and ethionamide in severe cutaneous adverse drug reactions: a series of 25 consecutive confirmed cases. J Antimicrob Chemother. 2015;70:2648–51.
51. Horne DJ, Spitters C, Narita M. Experience with rifabutin replacing rifampin in the treatment of tuberculosis. Int J Tuberc Lung Dis. 2011;15:1485–9, i.
52. Chien JY, Chien ST, Huang SY, Yu CJ. Safety of rifabutin replacing rifampicin in the treatment of tuberculosis: a single-centre retrospective cohort study. J Antimicrob Chemother. 2014;69:790–6.
53. Tattevin P, Revest M, Dupont M, Arvieux C, Michelet C. A regimen containing rifabutin for the treatment of tuberculosis in patients intolerant to rifampin. Clin Infect Dis. 2003;36:127–8.
54. Scherer K, Brockow K, Aberer W, Gooi JHC, Demoly P, Romano A, et al. Desensitization in delayed drug hypersensitivity reactions -- an EAACI position paper of the Drug Allergy Interest Group. Allergy. 2013;68:844–52.
55. Holland CL, Malasky C, Ogunkoya A, Bielory L. Rapid oral desensitization to isoniazid and rifampin. Chest. 1990;98:1518–9.
56. Kim JH, Kim HB, Kim BS, Hong SJ. Rapid oral desensitization to isoniazid, rifampin, and ethambutol. Allergy. 2003;58:540–1.
57. Rodrigues Carvalho S, Silva I, Leiria-Pinto P, Rosado-Pinto J. Rapid oral tolerance induction to isoniazid and pyrazinamide and controlled administration of ethambutol: clinical case. Allergol Immunopathol (Madr). 2009;37:336–8.
58. 有好近藤, 不蓋彌岸, 彰渡辺, 恒夫松宮, 雅子和田, 正雄荻原, et al. 抗結核薬の減感作療法に関する提言. 結核. 1997;72:697–700.
59. Kobashi Y, Okimoto N, Matsushima T, Abe T, Nishimura K, Shishido S, et al. [Desensitization therapy for allergic reactions of antituberculous drugs--evaluation of desensitization therapy according to the guideline of the Japanese Society for Tuberculosis]. Kekkaku. 2000;75:699–704.
60. Thong BYH, Chia FLA, Tan SC, Tan TC, Leong KP, Tan JWL, et al. A retrospective study on sequential desensitization-rechallenge for antituberculosis drug allergy. Asia Pac Allergy. 2014;4:156–63.
61. Siripassorn K, Ruxrungtham K, Manosuthi W. Successful drug desensitization in patients with delayed-type allergic reactions to anti-tuberculosis drugs. Int J Infect Dis. 2018;68:61–8.
62. Ban GY, Jeong YJ, Lee SH, Shin SS, Shin YS, Park HS, et al. Efficacy and tolerability of desensitization in the treatment of delayed drug hypersensitivities to anti-tuberculosis medications. Respir Med. 2019; 147:44–50.
63. Oh JH, Yun J, Yang MS, Kim JH, Kim SH, Kim S, et al. Reintroduction of Antituberculous Drugs in Patients with Antituberculous Drug-Related Drug Reaction with Eosinophilia and Systemic Symptoms. J Allergy Clin Immunol Pract. 2021;9:3442-3449.e3.
64. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. Expert Opin Drug Saf. 2007;6:673–84.
65. Drug-Induced Liver Injury • COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES [Internet]. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. [cited 2022 Oct 30]. Available from: https://cioms.ch/publications/product/drug-induced-liver-injury/
66. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11:272–6.
67. Andrade RJ, Lucena MI, Kaplowitz N, García-Muṇoz B, Borraz Y, Pachkoria K, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. Hepatology. 2006;44:1581–8.
68. Gao H, Li N, Wang JY, Zhang SC, Lin G. Definitive diagnosis of hepatic sinusoidal obstruction syndrome induced by pyrrolizidine alkaloids. J Dig Dis. 2012;13:33–9.
69. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol. 2014;4:332–46.
70. Wai CT. Presentation of drug-induced liver injury in Singapore. Singapore Med J. 2006;47:116–20.
71. Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle. 1978;59:13–32.
72. Døssing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis. 1996;77: 335–40.
73. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis. 1996;77:37–42.
74. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis. Am J Respir Crit Care Med. 2003;167:1472–7.
75. van Hest R, Baars H, Kik S, van Gerven P, Trompenaars MC, Kalisvaart N, et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. Clin Infect Dis. 2004;39:488–96.
76. Teleman MD, Chee CBE, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis. 2002;6:699–705.
77. Fernández-Villar A, Sopeña B, Fernández-Villar J, Vázquez-Gallardo R, Ulloa F, Leiro V, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis. 2004;8:1499–505.
78. Pukenyte E, Lescure FX, Rey D, Rabaud C, Hoen B, Chavanet P, et al. Incidence of and risk factors for severe liver toxicity in HIV-infected patients on anti-tuberculosis treatment. Int J Tuberc Lung Dis. 2007;11: 78–84.
79. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996;9:2026–30.
80. Breen R a. M, Miller RF, Gorsuch T, Smith CJ, Schwenk A, Holmes W, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax. 2006;61:791–4.
81. Huang YS, Chern HD, Su WJ, Wu JC, Chang SC, Chiang CH, et al. Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. Hepatology. 2003;37:924–30.
82. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med. 2002;166:916–9.
83. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, et al. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med. 1998;157:1871–6.
84. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax. 1996;51:132–6.
85. Shang P, Xia Y, Liu F, Wang X, Yuan Y, Hu D, et al. Incidence, clinical features and impact on anti-tuberculosis treatment of anti-tuberculosis drug induced liver injury (ATLI) in China. PLoS One. 2011;6:e21836.
86. Marzuki OA, Fauzi ARM, Ayoub S, Kamarul Imran M. Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. Singapore Med J. 2008;49:688–93.
87. Senaratne WV, Pinidiyapathirage MJ, Perera G a. MHE, Wickremasinghe AR. Anti-tuberculosis drug inducd hepatitis - a Sri Lankan experience. Ceylon Med J. 2006;51:9–14.
88. Tostmann A, van den Boogaard J, Semvua H, Kisonga R, Kibiki GS, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity is uncommon in Tanzanian hospitalized pulmonary TB patients. Trop Med Int Health. 2010;15:268–72.
89. Treeprasertsuk S, Huntrakul J, Ridtitid W, Kullavanijaya P, Björnsson ES. The predictors of complications in patients with drug-induced liver injury caused by antimicrobial agents. Aliment Pharmacol Ther. 2010; 31:1200–7.
90. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WCM, van der Ven AJAM, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23:192–202.
91. Gaude GS, Chaudhury A, Hattiholi J. Drug-induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. J Family Med Prim Care. 2015;4:238–43.

92. Yimer G, Aderaye G, Amogne W, Makonnen E, Aklillu E, Lindquist L, et al. Anti-tuberculosis therapy-induced hepatotoxicity among Ethiopian HIV-positive and negative patients. PLoS One. 2008;3:e1809.
93. Teixeira RL de F, Morato RG, Cabello PH, Muniz LMK, Moreira A da SR, Kritski AL, et al. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. Mem Inst Oswaldo Cruz. 2011;106:716–24.
94. Higuchi N, Tahara N, Yanagihara K, Fukushima K, Suyama N, Inoue Y, et al. NAT2 6A, a haplotype of the N-acetyltransferase 2 gene, is an important biomarker for risk of anti-tuberculosis drug-induced hepatotoxicity in Japanese patients with tuberculosis. World J Gastroenterol. 2007;13:6003–8.
95. Wang YC, Chen KH, Chen YL, Lin SW, Liu WD, Wang JT, et al. Pyrazinamide related prolonged drug-induced liver injury: A case report. Medicine (Baltimore). 2022;101:e30955.
96. Vuilleumier N, Rossier MF, Chiappe A, Degoumois F, Dayer P, Mermillod B, et al. CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. Eur J Clin Pharmacol. 2006;62:423–9.
97. Wang T, Yu HT, Wang W, Pan YY, He LX, Wang ZY. Genetic polymorphisms of cytochrome P450 and glutathione S-transferase associated with antituberculosis drug-induced hepatotoxicity in Chinese tuberculosis patients. J Int Med Res. 2010;38:977–86.
98. Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM, et al. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int. 2017;11:221–41.
99. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003;349:474–85.
100. Mitchell JR, Zimmerman HJ, Ishak KG, Thorgeirsson UP, Timbrell JA, Snodgrass WR, et al. Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. Ann Intern Med. 1976;84:181–92.
101. Ellard GA, Gammon PT. Pharmacokinetics of isoniazid metabolism in man. J Pharmacokinet Biopharm. 1976;4:83–113.
102. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002;35:883–9.
103. Ohno M, Yamaguchi I, Yamamoto I, Fukuda T, Yokota S, Maekura R, et al. Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. Int J Tuberc Lung Dis. 2000;4:256–61.
104. Bhatia S, Tullu MS, Kannan S, Gogtay NJ, Thatte UM, Lahiri KR. An unusual recurrence of antitubercular drug induced hepatotoxicity in a child. J Postgrad Med. 2011;57:147–52.
105. Branco Caetano F, Milheiro Silva T, Gonçalves C, Dias AI, Brito MJ. Ketogenic Diet and Drug-Induced Hepatotoxicity During Tuberculosis Treatment. JPGN Rep. 2022;3:e216.
106. Grosset J, Leventis S. Adverse effects of rifampin. Rev Infect Dis. 1983; 5 Suppl 3:S440-50.
107. Dhiman RK, Saraswat VA, Rajekar H, Reddy C, Chawla YK. A guide to the management of tuberculosis in patients with chronic liver disease. J Clin Exp Hepatol. 2012;2:260–70.
108. Centers for Disease Control and Prevention (CDC). Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection--New York and Georgia, 2000. MMWR Morb Mortal Wkly Rep. 2001;50:289–91.
109. Ruslami R, Gafar F, Yunivita V, Parwati I, Ganiem AR, Aarnoutse RE, et al. Pharmacokinetics and safety/tolerability of isoniazid, rifampicin and pyrazinamide in children and adolescents treated for tuberculous meningitis. Arch Dis Child. 2022;107:70–7.
110. Sharifzadeh M, Rasoulinejad M, Valipour F, Nouraie M, Vaziri S. Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during antituberculosis [correction of antituberclosis] treatment. Pharmacol Res. 2005;51:353–8.
111. Aziz S, Agha F, Hassan R, Fairoz SA, Hassan K. Hepatotoxicity to different antituberculosis drug combinations. J Pak Med Assoc. 1990; 40:290–4.
112. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. BMC Infect Dis. 2017;17:231.
113. Joint T. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 1998;53:536–48.
114. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–52.
115. Zuberi BF, Zuberi FF, Bader N, Alvi H, Salahuddin J. Comparison of British Thoracic Society and American Thoracic Society reintroduction guidelines for anti-tuberculous therapy induced liver injury. J Pak Med Assoc. 2014;64:896–9.
116. Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010;50:833–9.
117. Nataprawira HM, Aliyannissa A, Febrianti SA. Unusual Recurrence of Antituberculosis Drug-Induced Hepatotoxicity in Children: A Case Series. Am J Case Rep. 2021;22:e930828.
118. Ou P, Chen Y, Li B, Zhang M, Liu X, Li F, et al. Causes, clinical features and outcomes of drug-induced liver injury in hospitalized patients in a Chinese tertiary care hospital. Springerplus. 2015;4:802.
119. Sunil Kumar N, Remalayam B, Thomas V, Ramachandran TM, Sunil Kumar K. Outcomes and Predictors of Mortality in Patients With Drug-Induced Liver Injury at a Tertiary Hospital in South India: A Single-Centre Experience. J Clin Exp Hepatol. 2021;11:163–70.
120. Devarbhavi H, Singh R, Patil M, Sheth K, Adarsh CK, Balaraju G. Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury. J Gastroenterol Hepatol. 2013;28:161–7.
121. Zhao H, Wang Y, Zhang T, Wang Q, Xie W. Drug-Induced Liver Injury from Anti-Tuberculosis Treatment: A Retrospective Cohort Study. Med Sci Monit. 2020;26:e920350.
122. Aminy RZ, Kholili U. Anti-tuberculosis drug-induced liver injury in patient with hepatitis B and cirrhosis: A case report. Ann Med Surg (Lond). 2022;80:104154.
123. Saha A, Shanthi F X M, Winston A B, Das S, Kumar A, Michael JS, et al. Prevalence of Hepatotoxicity From Antituberculosis Therapy: A Five-Year Experience From South India. J Prim Care Community Health. 2016;7:171–4.
124. Cao J, Mi Y, Shi C, Bian Y, Huang C, Ye Z, et al. First-line anti-tuberculosis drugs induce hepatotoxicity: A novel mechanism based on a urinary metabolomics platform. Biochem Biophys Res Commun. 2018;497: 485–91.
125. Shen T, Gu D, Zhu Y, Shi J, Xu D, Cao X. The value of eosinophil VCS parameters in predicting hepatotoxicity of antituberculosis drugs. Int J Lab Hematol. 2016;38:514–9.
126. Luangchosiri C, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. BMC Complement Altern Med. 2015;15:334.
127. Adhvaryu MR, Reddy N, Vakharia BC. Prevention of hepatotoxicity due to anti tuberculosis treatment: a novel integrative approach. World J Gastroenterol. 2008;14:4753–62.
128. Hasanain AFA, Zayed AAAH, Mahdy RE, Nafee AMA. Cholecalciferol for prophylaxis against antituberculosis therapy-induced liver disorders among naïve patients with pulmonary tuberculosis: A randomized, comparative study. Int J Mycobacteriol. 2017;6:149–55.
129. Global tuberculosis report 2021 [Internet]. [cited 2022 Nov 2]. Available from: https://www.who.int/publications-detail-redirect/9789240037021
130. Knight LK, Lehloenya RJ, Sinanovic E, Pooran A. Cost of managing severe cutaneous adverse drug reactions to first-line tuberculosis therapy in South Africa. Trop Med Int Health. 2019;24:994–1002.
131. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). Saudi Pharm J. 2014;22:83–94.
132. Shin HJ, Chang JS, Kim MS, Koh BG, Park HY, Kim TO, et al. Hypersensitivity reactions to multiple anti-tuberculosis drugs. PLoS One. 2021;16:e0246291.
133. Sharma RK, Verma GK, Tegta GR, Sood S, Rattan R, Gupta M. Spectrum of Cutaneous Adverse Drug Reactions to Anti-tubercular Drugs and Safe Therapy after Re-challenge - A Retrospective Study. Indian Dermatol Online J. 2020;11:177–81.
134. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents--a 6 year series from Chandigarh, India. J Postgrad Med. 2001;47:95–9.

135. Cabañas R, Ramírez E, Sendagorta E, Alamar R, Barranco R, Blanca-López N, et al. Spanish Guidelines for Diagnosis, Management, Treatment, and Prevention of DRESS Syndrome. J Investig Allergol Clin Immunol. 2020;30:229–53.
136. Copaescu A, Gibson A, Li Y, Trubiano JA, Phillips EJ. An Updated Review of the Diagnostic Methods in Delayed Drug Hypersensitivity. Front Pharmacol. 2020;11:573573.
137. Copaescu A, Mouhtouris E, Vogrin S, James F, Chua KYL, Holmes NE, et al. The Role of In Vivo and Ex Vivo Diagnostic Tools in Severe Delayed Immune-Mediated Adverse Antibiotic Drug Reactions. J Allergy Clin Immunol Pract. 2021;9:2010-2015.e4.
138. Trubiano JA, Strautins K, Redwood AJ, Pavlos R, Konvinse KC, Aung AK, et al. The Combined Utility of Ex Vivo IFN-γ Release Enzyme-Linked ImmunoSpot Assay and In Vivo Skin Testing in Patients with Antibiotic-Associated Severe Cutaneous Adverse Reactions. J Allergy Clin Immunol Pract. 2018;6:1287-1296.e1.
139. Margineanu I, Louka C, Akkerman O, Stienstra Y, Alffenaar JW. eHealth in TB clinical management. Int J Tuberc Lung Dis. 2022;26:1151–61.
140. The End TB Strategy [Internet]. [cited 2023 Mar 26]. Available from: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy
141. Kostin AA, Tsvetkov AI, Abramov AY, Kicha DI, Goloshchapov-Aksenov RS. [The effect of applying clinical organizational telemedicine technology management of anti-tuberculous care on dynamics of tuberculosis morbidity and mortality]. Probl Sotsialnoi Gig Zdravookhranenniiai Istor Med. 2023;31:60–4.
142. Bermingham WH, Bhogal R, Arudi Nagarajan S, Mutlu L, El-Shabrawy RM, Madhan R, et al. Practical management of suspected hypersensitivity reactions to anti-tuberculosis drugs. Clin Exp Allergy. 2022;52:375–86.