抗结核药物性肝损伤

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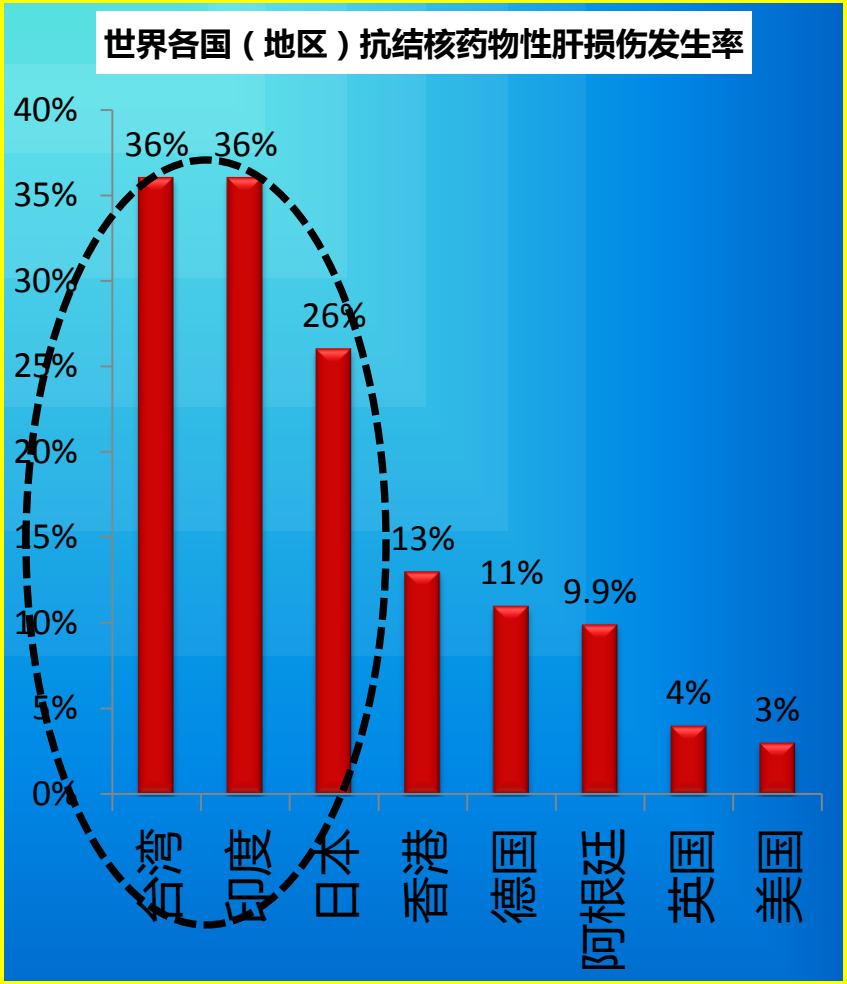
抗结核药物性肝损伤

- 发生率：3%～15%
- 病死率：0.40% ～ 1.50%

降低了患者的依从性
影响了结核病的防治效果



发生频率

- 发生多的药物

RFP PZA Eto TB1 PAS

- 发生少的药物

INH

- 基本不发生的药物

SM KM CM VM EMB CS

来自日本的资料

发生频率

- 常见

(-)

- 不常见

INH RFP PZA TB1 PAS

- 罕见

EMB

- 不发生

SM

来自IUATLD的资料

发生频率

关于药物联用

- INH+RFP

0.8%

- INH+RFP+PZA

2.8%

药物联用可增加肝损的风险

来自WHO的资料

Chang KC, Leung CC, Yew WW, et al. Hepatotoxicity of pyrazinamide :cohort and case-control analysis. Am J Respir Crit Care Med, 2008,177（12）:1391 - 1396

药肝的分型

- **肝细胞损害型**

ALT≥2ULN，ALT/ALP ≥5，临床表现不典型

- **胆汁淤积型**

ALP≥2ULN or ALT/ALP≤2，分为毛细胆管型及肝毛细胆管型

- **混合型**

ALT/ALP=2~5，临床介于肝细胞损伤型与胆汁淤积型之间

RUCAM评分标准分类

抗结核药物性肝损的类型

- 肝细胞损害型

25%

- 胆汁淤积型

35%

- 混合型

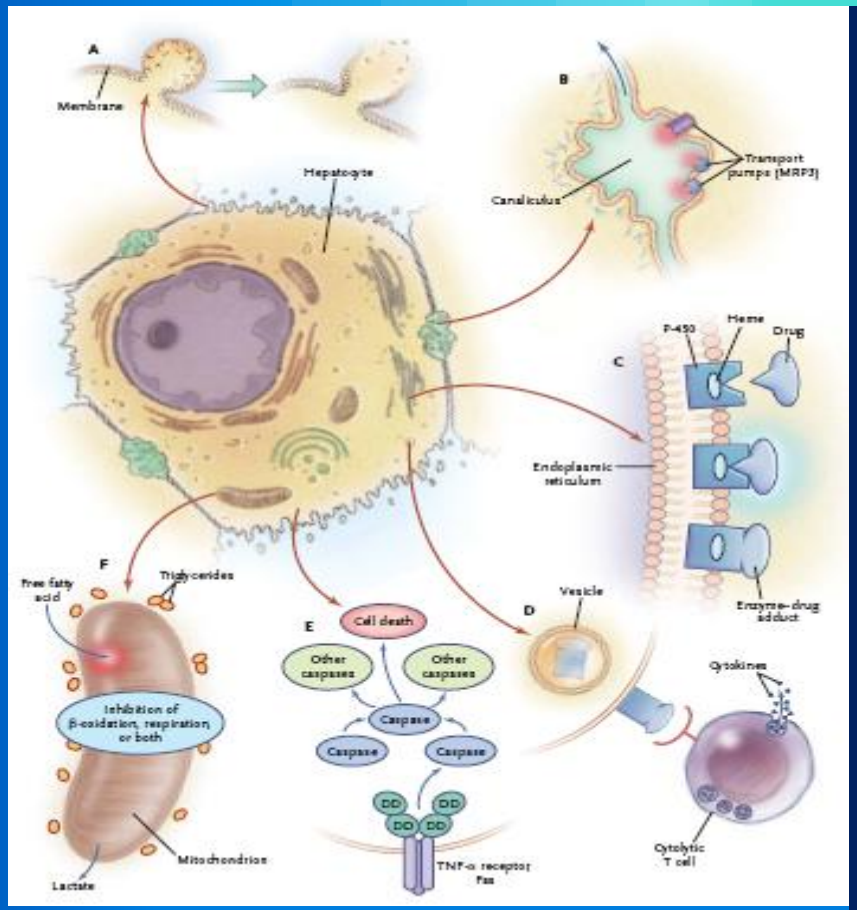
40%

王晓丽, 虞朝辉, 陈韶华, 厉有名. 药物性肝病临床特征及预后分析. 中华内科杂志, 2008, 47(5): 385 – 388

药物性肝损的机制

- 代谢产物调节毒性
- 超敏反应/自身免疫调节
- 胆汁分泌受阻
- 小胆管的自身免疫性破坏
- 脂蛋白分泌减少
- 脂肪酸线粒体β氧化受阻
- 溶酶体磷酸酶阻滞
- 肝星状细胞激活

药物性肝损的机制



药物对肝脏毒性损害

- 直接损害

对肝细胞及细胞器无选择性

- 间接损害

免疫介导、线粒体失能、肝星状细胞、巨噬细胞放大药物肝毒性等

药物性肝损的机制

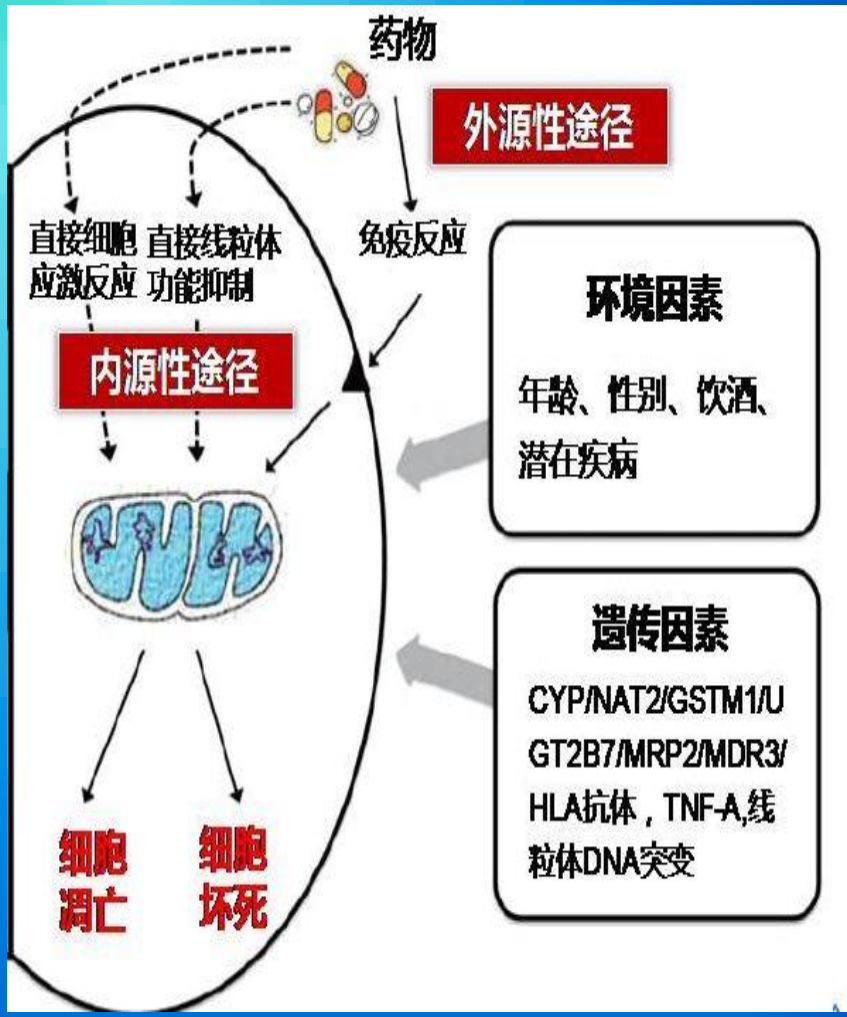
机体对药物特异质

- 遗传因素

如乙酰化快型或乙酰化慢型与INH的肝损害

- 获得性因素

年龄、性别、营养状态、妊娠、慢型酒精滥用、药物相互作用、自体合并的肝脏疾病或肝外疾病、炎症反应等



抗结核药物肝损伤

诊断、治疗、预防

Diagnosis, management and prevention of drug-induced liver injury

S Verma,[1] N Kaplowitz[2]

[1] Department of Medicine, Brighton and Sussex Medical School, Brighton, UK; [2] USC Research Centre for Liver Diseases, Keck School of Medicine, University of Southern

ABSTRACT

Drug-induced liver injury (DILI) is increasingly being recognised as a significant cause of both acute and chronic liver disease. The most commonly implicated agents are paracetamol, antimicrobials, non-steroidal anti-

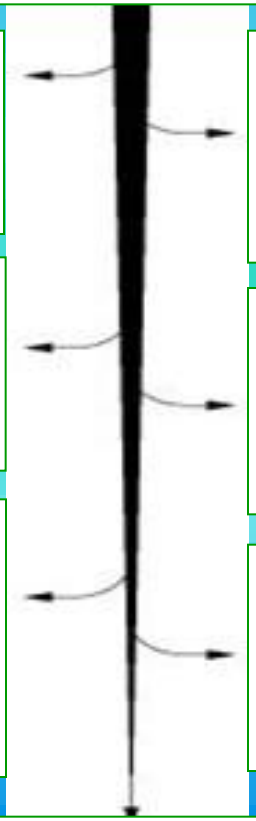
ADRs were reported by a 3 year French prospective community study where the global crude annual incidence rate was 13.9 (SD 2.4) per 100 000 inhabitants.[10] A more recent French impatient study observed the incidence of DILI to be 1.4%.[11]

抗结核药物肝损伤

诊断依据

- 应用有损肝脏的抗结核药物
- 有肝损伤症状和/或体征
- 肝功能异常达到肝损标准
- 除外其他原因引起的肝损伤
- 关联性评价

药物性肝损伤的排除诊断法



肝损伤

胆系异常

（超声、CT、MRI、MRCP）

自身免疫性疾病

(ANA,抗平滑肌抗体,γ球蛋白)

代谢 遗传

（铁水平、铁蛋白、总铁结合率、血清铜蓝蛋白、ALT水平）

病毒性肝炎

抗HAV-IgM、抗HEV –IgM

抗HCV、HBsAg

酒精

（饮酒史、饮酒量、AST/ALT＞2:1）

血液动力学

（高血压、休克、心衰、血管闭塞）

可能为药物相关性肝毒性

药物性肝炎诊断标准

指标	评分
1、药物治疗与症状出现的时间关系	
（1）初次治疗5-90天；后续治疗1-15天	+2
（2）初次治疗<5天或>90天；后续治疗>15天	+1
（3）停药时间≤15天	+1
2、病程特点	
（1）停药后8天内ALT从峰值下降≥50%	
（2）停药后30天内ALT从峰值下降≥50%	+3
（3） 持续用药ALT下降水平不确定	+2 0
3、危险因素	
（1）饮酒或妊娠	+1
（2）无饮酒及妊娠	0
（3）年龄≥55岁	+1
（4）年龄＜55岁	0
4、伴随用药	
（1）伴随用药与发病时间符合	
（2）已知伴随用药的肝毒性且与发病时间符合	-1
（3）有伴随用药导致肝损伤的证据（如再用药反应等）	-2 -3
5、除外其他非药物因素	
6个主要因素：甲型、乙型或丙型病毒性肝炎；胆道阻塞；酒精性肝病（AST/ALT≥2）;近期高血压病或心脏病发作史。	
其他因素：潜在其他疾病；CMV、EBV或HSV感染	+2
（1）除外以上所有因素	+1
（2）可除外4~5个因素	-2
（3）可除外1~4个因素	-3
（4）高度可能为非药物因素	
6、药物肝毒性的已知情况	
（1）在说明书中已注明	+2
（2）曾有报道但未在说明书中注明	+1
（3）无相关报告	0
7、再用药反应	
（1）阳性（单纯用药后ALT升高＞2倍正常值）	+2
（2）可疑阳性（ALT＞2倍正常值，但同时伴有其他因素）	+1
（3）阴性（ALT升高＜2倍正常值）	-2
（4）未再用药	0

判断标准: >8:非常可能；6~8：很可能；3~5：可能；1~2：不象；≤0：无关。

抗结核药物肝损伤

诊断难点

- 外周嗜酸性粒细胞升高、肝组织嗜酸性粒细胞浸润及肉芽肿形成，或合并过敏反应
- 患者停药8天内ALT下降50%
- 鉴别诊断困难时可行肝穿刺活检
- ……

抗结核药物肝损

• 存在问题

- 诊断药物性肝损的常用量表，如Maria评分表，RUCAM评分表，DDW-J诊断标准，已广泛地被消化、肝病科采用，但未被结核科采用

抗结核药物肝损伤

药物确定

抗结核药物为多药联用

确认方法有2类

- 直接鉴别法
- 间接鉴别法

抗结核药物肝损伤

药物直接鉴别法

- 发生肝损后停用全部抗结核药物，待肝损害恢复后，开始试用一种药物，若有肝损反应，则该药为肝损的药物，如无肝损反应，再试用另外一种药物
- 用于重症患者

抗结核药物肝损伤

药物间接鉴别法

- 出现肝损后，开始只停用一种肝损可疑药物，如肝损害反应消失，即可明确肝损药物，如不消失，再停用另外一种药物，直至明确肝损药物
- 用于轻症患者

抗结核药物肝损伤

治疗原则

- 停用并防止重新给予引起肝损害的药物
- 早期清除和排泄体内药物
- 密切检测，是否急性肝衰竭？是否有进展为慢性肝衰竭的征象？

提高预后评估水平

多因素logistic回归分析以下4项指标是影响药肝预后的主要因素

- 血清白蛋白（Alb）
- 总胆汁酸（TBA）
- 直接胆红素（DBil）
- 凝血酶原时间（PT）

Alb值越低，预后差的可能性越高，而TBA、DBil、PT值越高则预后差的可能性越大

王晓丽, 虞朝辉, 陈韶华, 厉有名. 药物性肝病临床特征及预后分析. 中华内科杂志, 2008, 47(5): 385 – 388

Treatment of tuberculosis

GUIDELINES

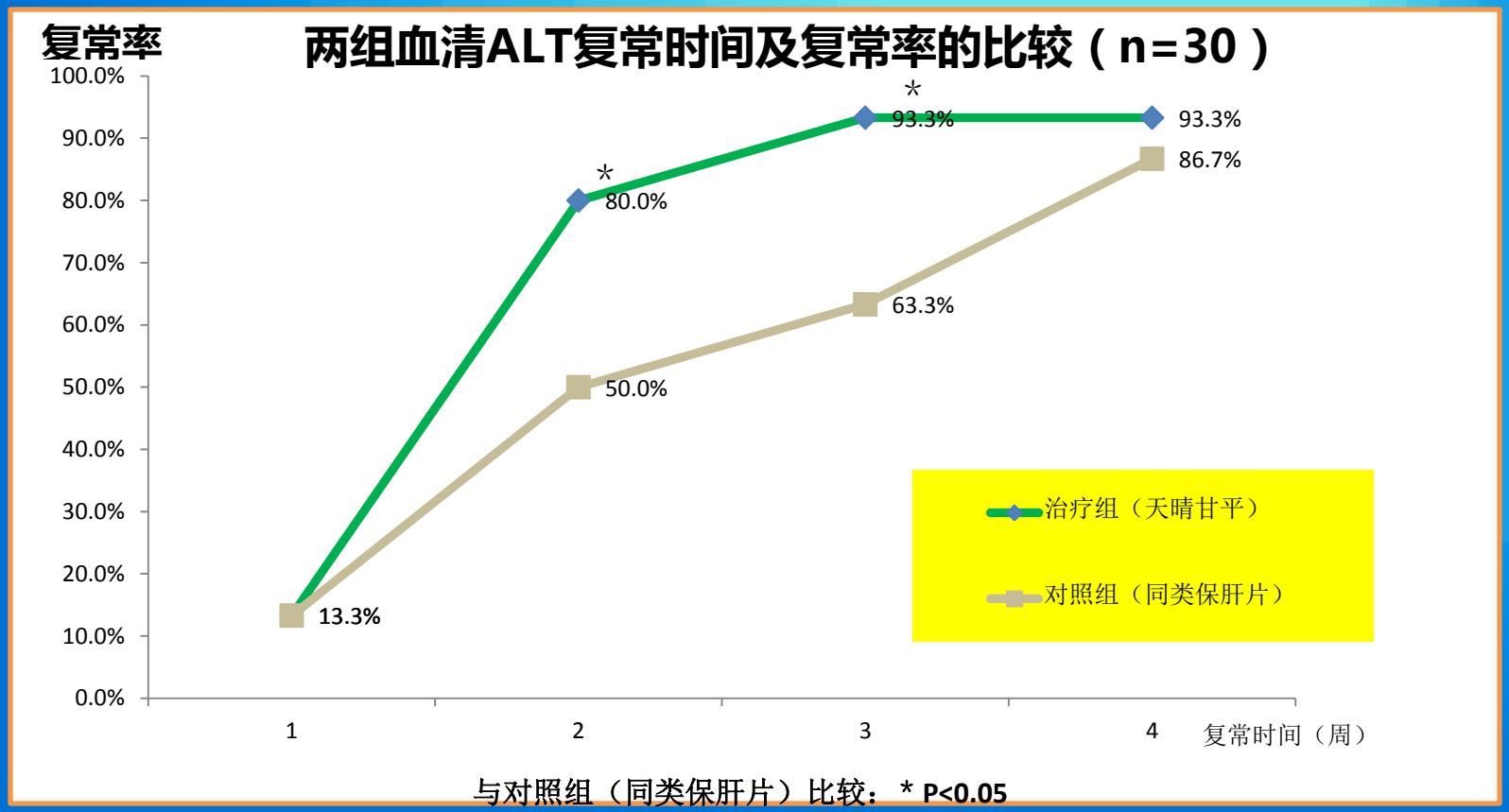
Fourth edition

The management of hepatitis induced by TB treatment depends on:

- whether the patient is in the intensive or continuation phase of TB treatment;
- the severity of the liver disease;
- the severity of the TB; and
- the capacity of the health unit to manage the side-effects of TB treatment.

护肝治疗肝损伤2周复常率达80%

部分病人可维持原化疗方案，避免不必要的停药或改药



顾 瑾,肖和平.甘平胶囊治疗抗结核药物所致肝功能异常的疗效[J].临床肺科杂志,2006,11(5):587-588.

重症药物性肝炎与肝功能衰竭

- 停用全部肝损的药物
- 维持水电解质热量平衡
- 促进肝细胞再生
- 静脉输注鲜血、蛋白
- 胰高糖素-胰岛素疗法
- 促肝细胞生长素、前列腺素E
- 补充生理性代谢物质ATP、辅酶A等

- 改善微循环
- 控制出血
- 纠正氨基酸代谢紊乱
- 预防和控制肝性脑病
- 继发感染控制
- 低血糖及肾功能不全治疗
- 人工肝支持治疗
- 部分患者需要肝移植

Recent advances in clinical practice

Diagnosis, management and prevention of drug-induced liver injury

S Verma,[1] N Kaplowitz[2]

[1] Department of Medicine, Brighton and Sussex Medical School, Brighton, UK; [2] USC Research Centre for Liver Diseases, Keck School of

ABSTRACT

Drug-induced liver injury (DILI) is increasingly being recognised as a significant cause of both acute and chronic liver disease. The most commonly implicated

ADRs were reported by a 3 year French prospective community study where the global crude annual incidence rate was 13.9 (SD 2.4) per 100 000 inhabitants.[10] A more recent French inpatient

In the US, as well 500 deaths.[4] This exceeds by at least 3-fold the number of deaths related to all idiosyncratic hepatic drug reactions combined.[5] In the UK, paracetamol overdose accounts for 200–500 deaths, and 20–40 liver transplants annually.[6 7]

抗结核药物肝损的处理

预防

- 原有肝损害患者抗结核药物的选择
- 抗结核药物性肝损害的预防

原有肝损患者的抗结核治疗

肝损伤的原因

- 传染性肝病
- 肝硬化
- 肝癌
- 全身疾病的继发等

心衰，缩窄性心包炎等

针对已有肝损患者的药物分类

- 可用药物

SM KM AMK CM VM CS EMB

- 慎用药物

INH 莫西沙星、左氧氟沙星、氯法齐明、克拉霉素、阿莫西林/克拉维酸 利奈唑胺

- 忌用药物

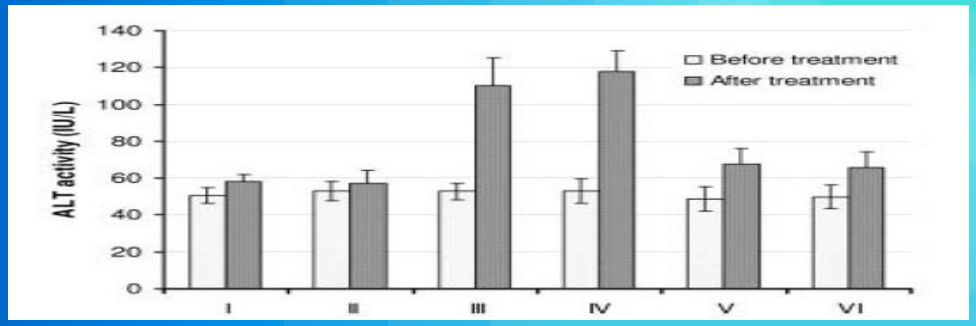
RFP、PZA、Pto、PAS、TB1

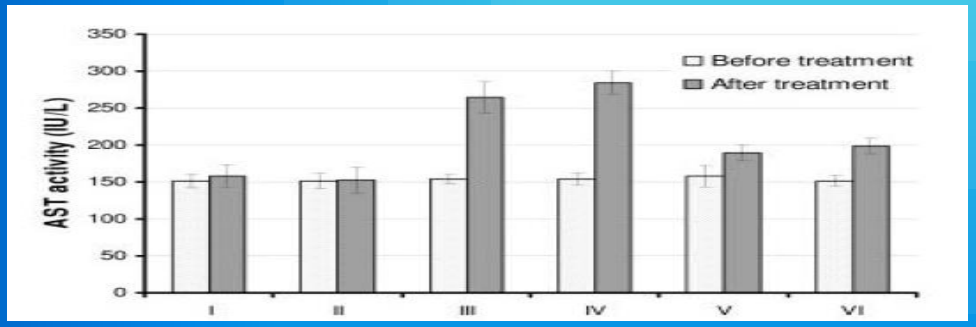
抗结核药物分类法之一

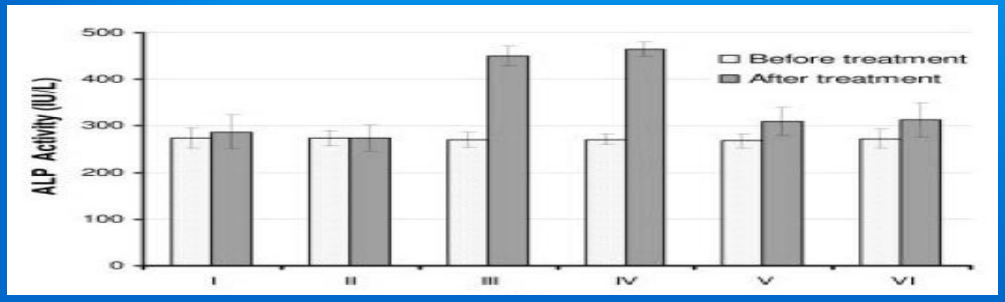
抗结核药物肝损的处理

- 原有肝损患者抗结核药物的选择
- 抗结核药物性肝损的预防

预防有效性的动物试验研究








Nutrition & Metabolism
BioMed Central
Research
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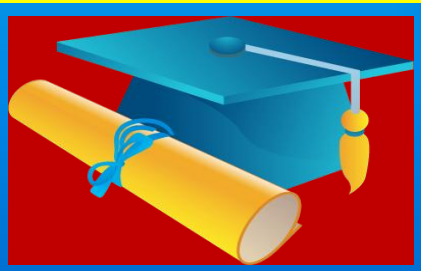
Silymarin protects liver against toxic effects of anti-tuberculosis drugs in experimental animals

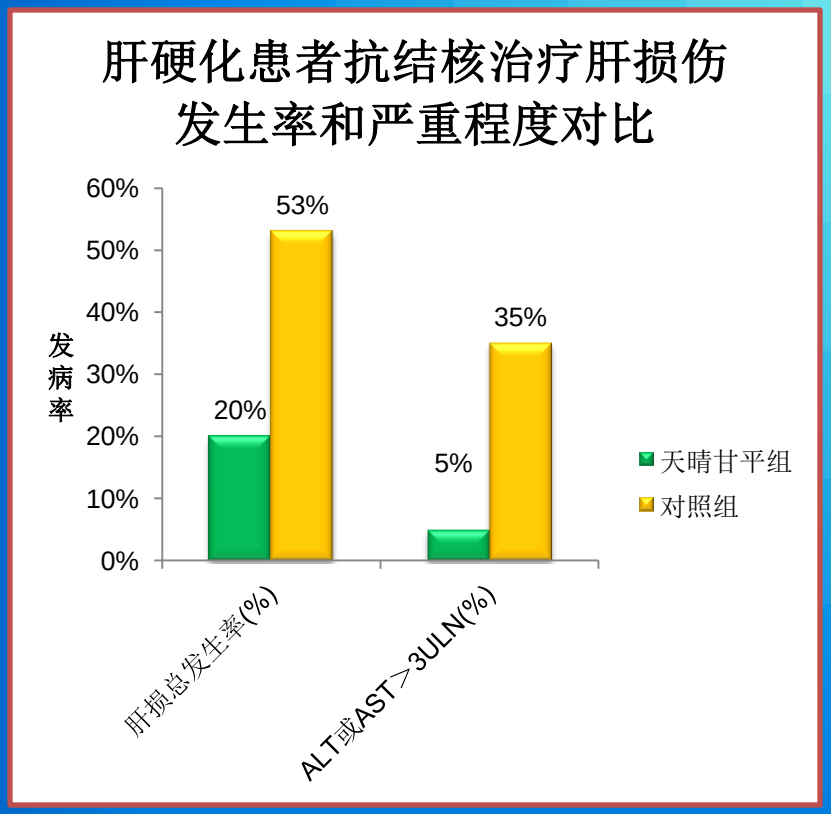
Sude Eminzade*[1], Fikriye Uras[2] and Fikret V Izzettin[1]

- I: Control
- II: Silymarin control
- III: INH+RIF
- IV: INH+RIF+PZA
- V: INH+RIF+Silymarin
- VI:INH+RIF+PZA+Silymarin



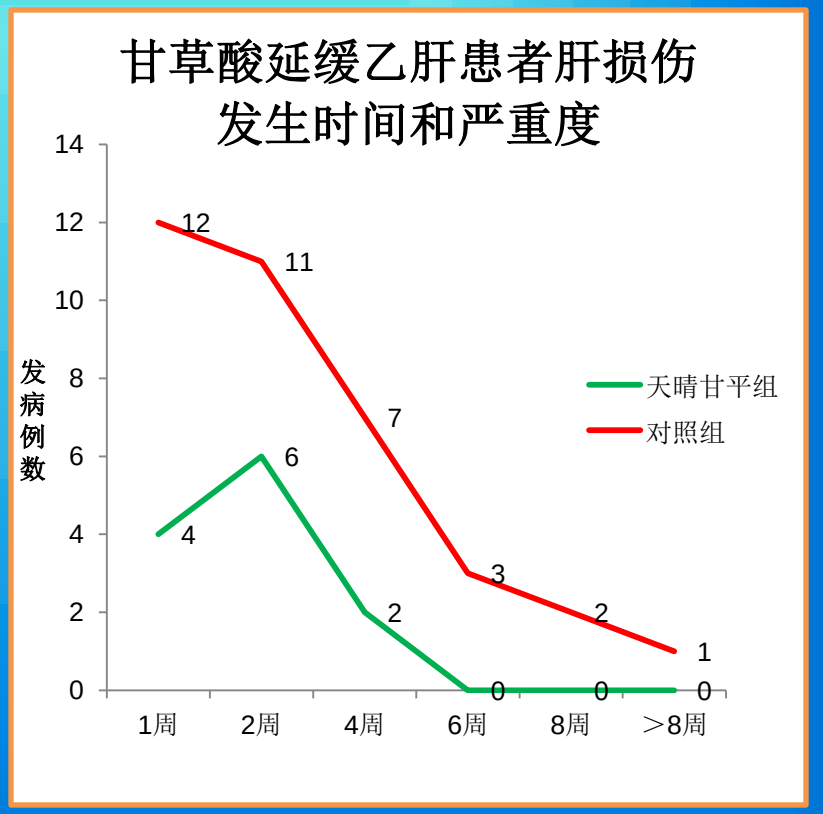
预防保肝的临床研究:发生时间、频率、程度

减少药物性肝损伤发生率、降低程度



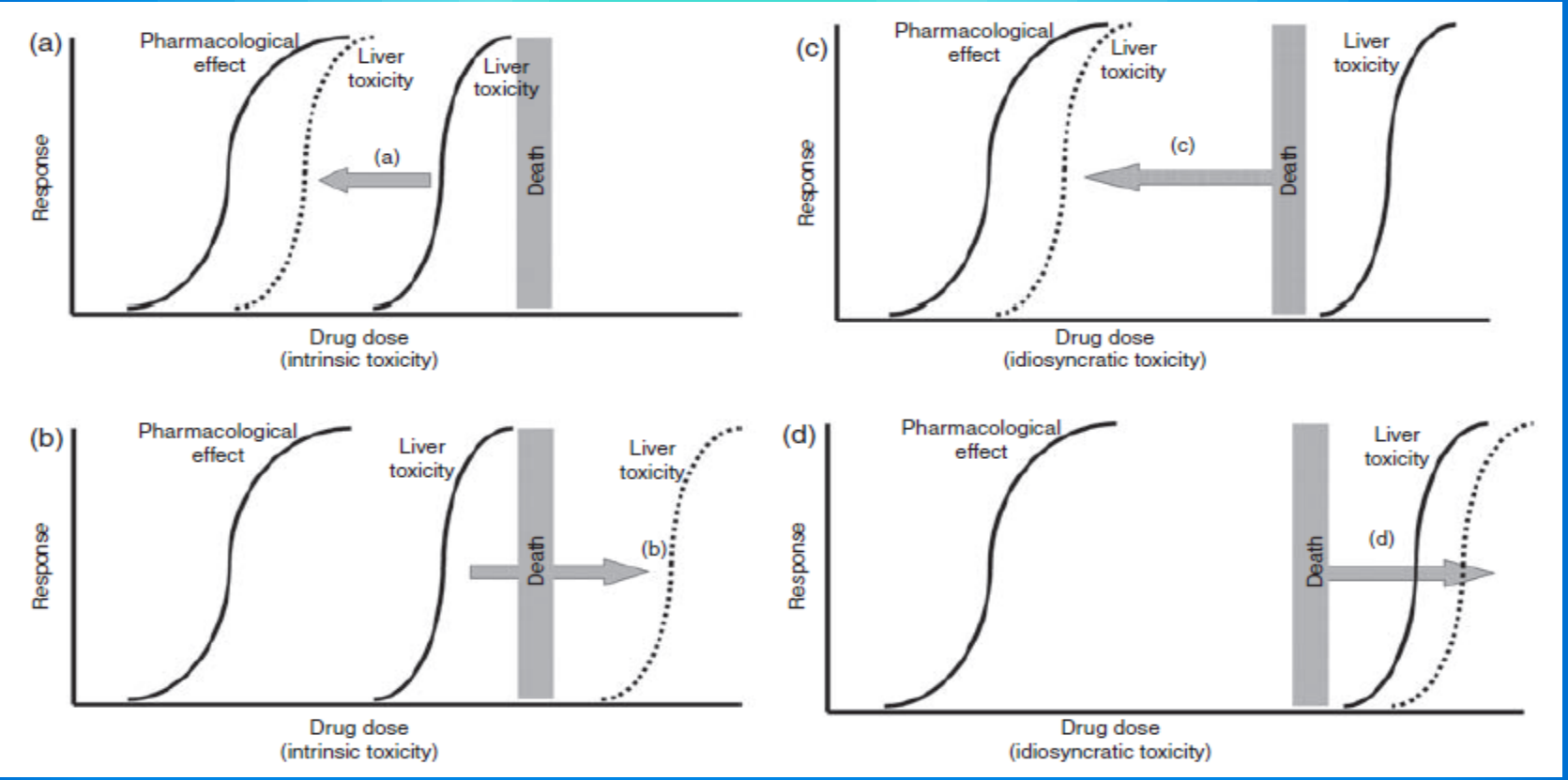
邱邦东.甘草酸二铵脂质复合物预防酒精性肝硬化患者抗结核治疗致肝损害20例[J].中国药业,2010,19(19):80-81.

延缓药物性肝损伤发生时间、减少发生率



冯宗欣.甘草酸二铵肠溶胶囊防治抗结核药物性肝损害的临床观察[J].医学信息,内.外科版,2009,22(9):792-794.

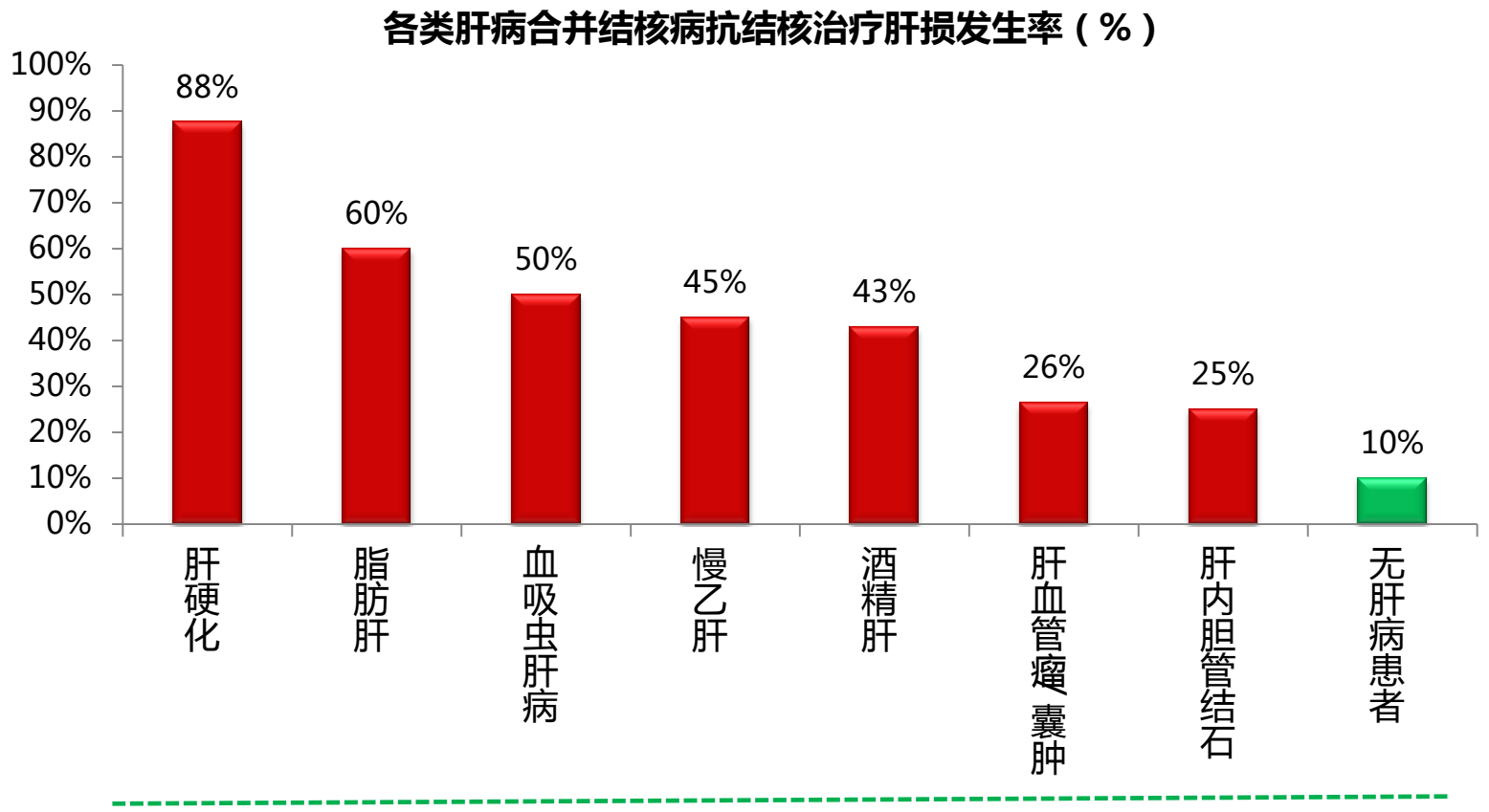
危险因素研究



危险因素： 1)年龄>50岁：2)慢性肝病变 丙肝或乙肝：3)其它药物：4)基础AST／ALT升高；5) 慢性酒精中毒：6)营养不良。*与对照组相比$P<0.001$。肝毒性：血清转氨酶>3倍的正常上限值；严重肝毒性：血清转氨>10倍的正常上限值；

（INT J TUBERC LUNG DIS 8(12)：1499-1505@ 2OO4 IUATLD）

危险因素研究



李春香.中国医师杂志,2002,4(5):538.
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黄汉平,张丽. 临床内科杂志,2007,5(24):310-312.
郭虹.北华大学学报.2005，6：425.

抗结核药物肝损的处理

预防治疗的对象

- 老年女性
- 曾经出现肝损
- 合并使用可导致肝损药物
- 免疫缺陷综合症
- 乙型肝炎或丙型肝炎等
- 饮酒、营养不良等
- 存在遗传易感性等

抗结核药物性肝损预防

- 肝功能、HBVM监测
- HBV阳性者慎用RFP等
- 老年、女性、营养不良、糖尿病、嗜酒等患者慎用RFP、PZA
- 高龄老人：减量及“非R非Z”方案
- 注意个体差异
- 预防性治疗

抗结核药物肝损的处理

预防性治疗

- 相关文献众多
- 缺乏循证依据的数据

抗结核药物性肝损预防

生物标志物引导下预防措施

Eur J Clin Pharmacol (2013) 69:1091–1101
DOI 10.1007/s00228-012-1429-9

PHARMACOGENETICS

NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy

Junichi Azuma · Masako Ohno · Ryuji Kubota · Soichiro Yokota · Takayuki Nagai · Kazunari Tsuyuguchi · Yasuhisa Okuda · Tetsuya Takashima · Sayaka Kamimura · Yasushi Fujio · Ichiro Kawase · Pharmacogenetics-based tuberculosis therapy research group

Received: 29 July 2012 / Accepted: 4 October 2012 / Published online: 14 November 2012

Abstract
Objective This study is a pharmacogenetic clinical trial designed to clarify whether the *N*-acetyltransferase 2 gene (*NAT2*) genotype-guided dosing of isoniazid improves the tolerability and efficacy of the 6-month four-drug standard

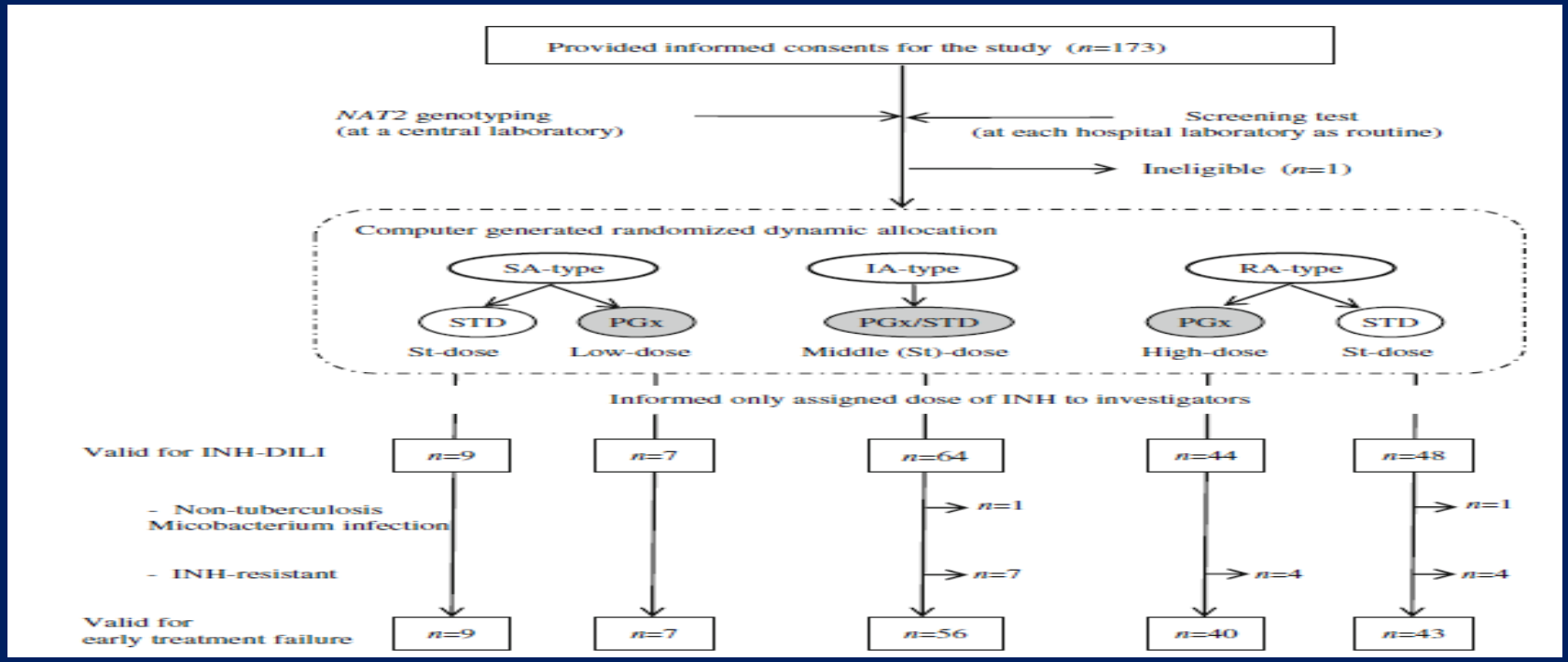
patients heterozygous for *NAT2*4*: intermediate acetylators; 2.5 mg/kg, patients without *NAT2*4*: slow acetylators). The primary outcome included incidences of 1) isoniazid-related liver injury (INH-DILI) during the first 8 weeks of therapy, and 2) early treatment failure as indicated by a persistent

NAT2 genotype

Junichi Azuma & Masako Ohno & Ryuji Kubota, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy Eur J Clin Pharmacol (2013) 69:1091–1101

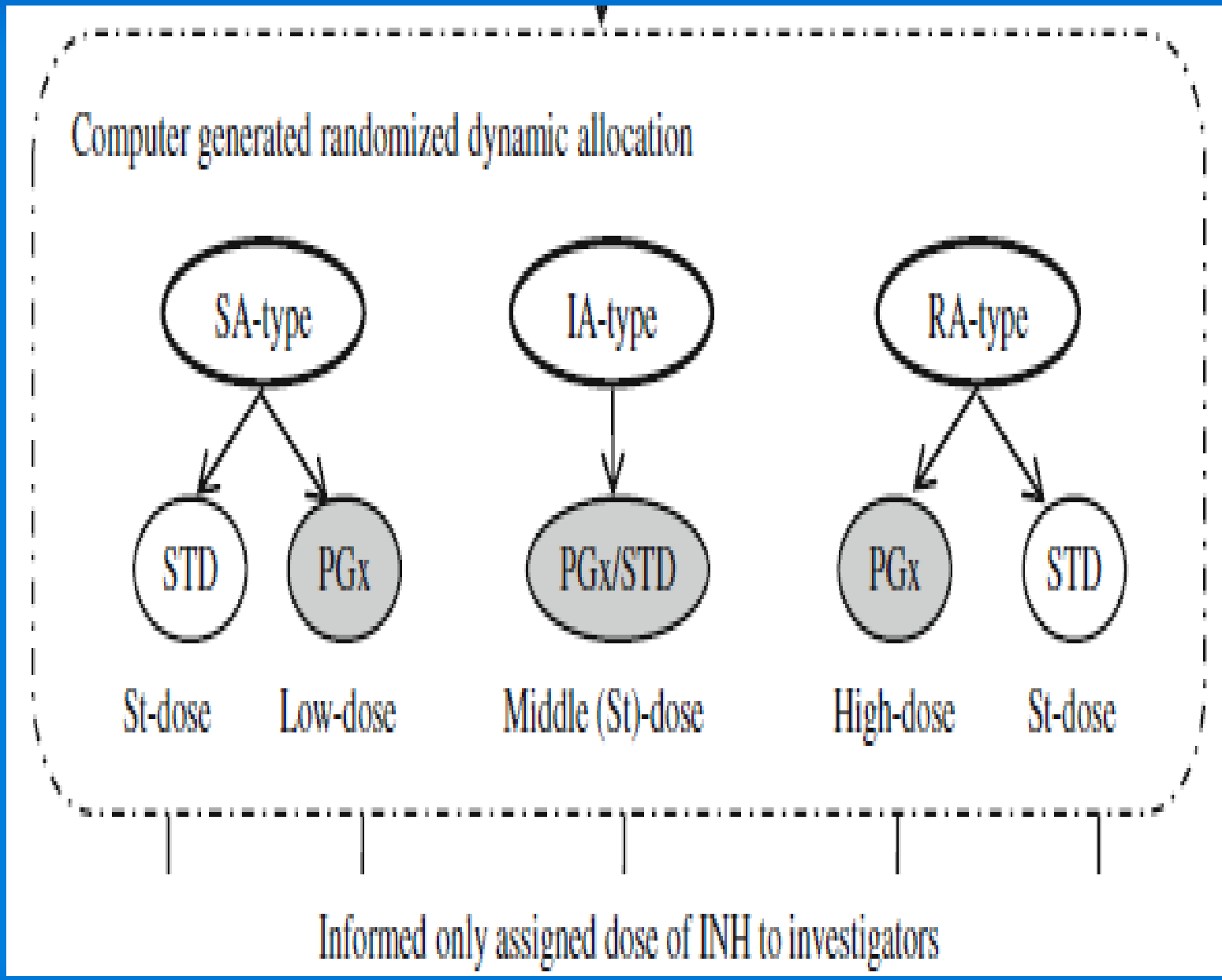
抗结核药物性肝损预防

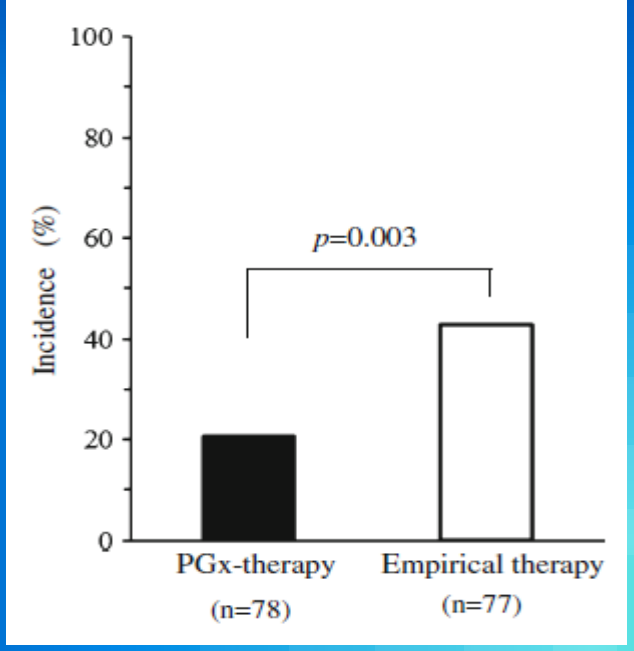
生物标志物引导下的预防措施

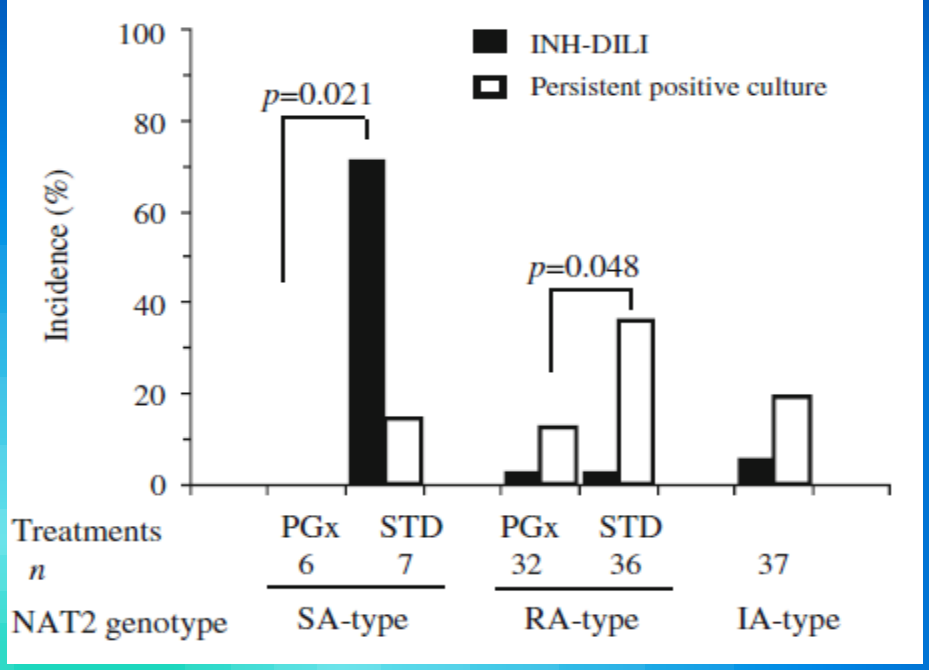


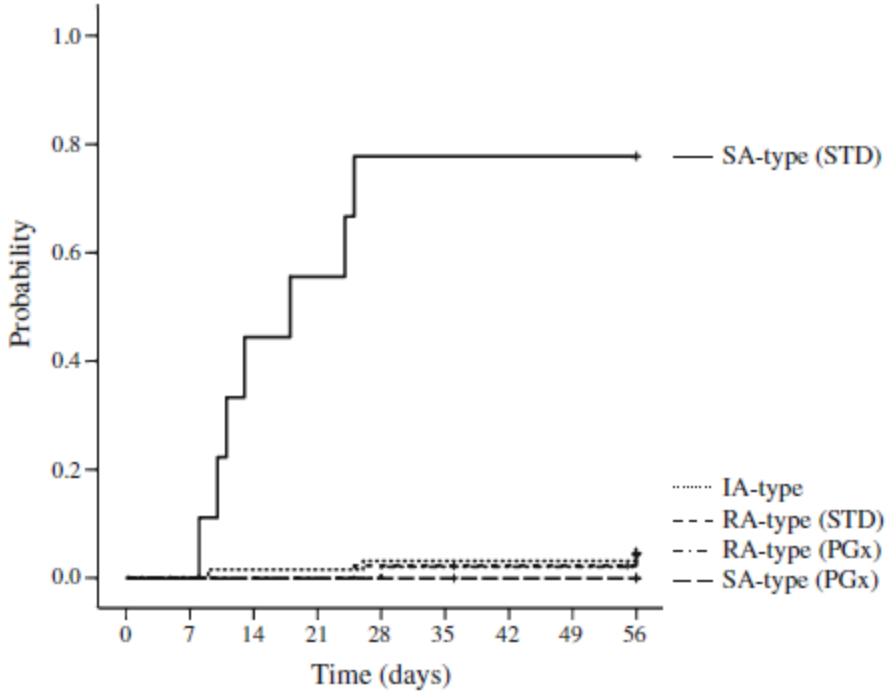
NAT2 genotype

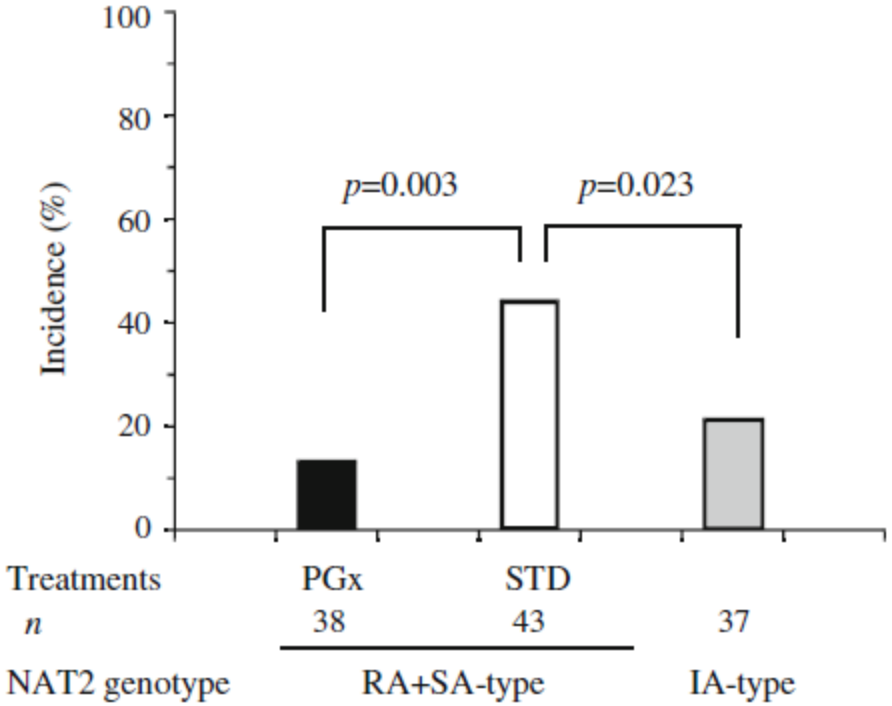
Junichi Azuma & Masako Ohno & Ryuji Kubota, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy Eur J Clin Pharmacol (2013) 69:1091–1101


Computer generated randomized dynamic allocation
SA-type
IA-type
RA-type
STD
PGx
PGx/STD
PGx
STD
St-dose
Low-dose
Middle (St)-dose
High-dose
St-dose
Informed only assigned dose of INH to investigators


100
80
60
40
20
0
Incidence (%)
p=0.003
PGx-therapy
(n=78)
Empirical therapy
(n=77)


INH-DILI
Persistent positive culture
100
80
60
40
20
0
Incidence (%)
p=0.021
p=0.048
Treatments
PGx
STD
PGx
STD
n
6
7
32
36
37
NAT2 genotype
SA-type
RA-type
IA-type


1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
7
14
21
28
35
42
49
56
Time (days)
SA-type (STD)
IA-type
RA-type (STD)
RA-type (PGx)
SA-type (PGx)


100
80
60
40
20
0
Incidence (%)
p=0.003
p=0.023
Treatments
PGx
STD
n
38
43
37
NAT2 genotype
RA+SA-type
IA-type

抗结核药物性肝损预防

生物标志物引导下预防措施

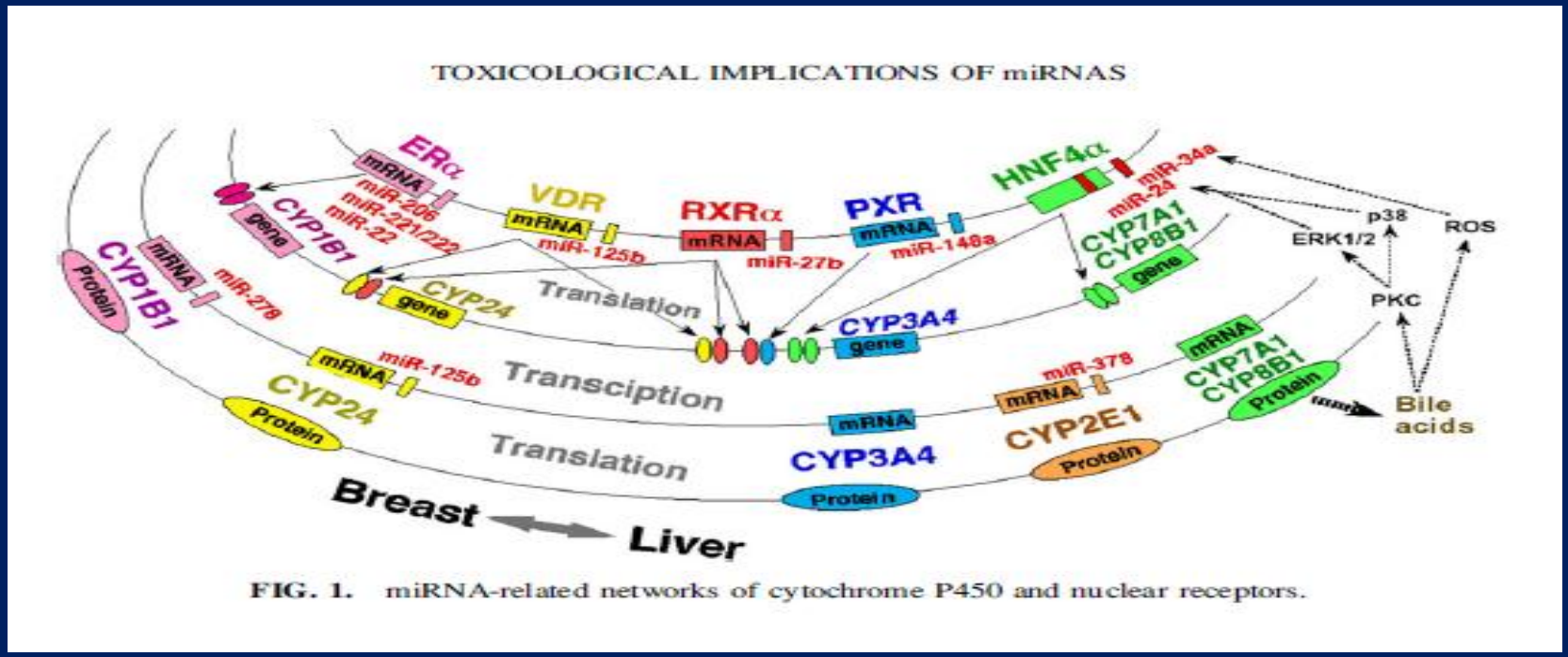


FIG. 1. miRNA-related networks of cytochrome P450 and nuclear receptors.

micRNA, p450

Tsuyoshi Yokoi1 and Miki Nakajima. Toxicological Implications of Modulation of Gene Expression by MicroRNAs TOXICOLOGICAL SCIENCES 123(1), 1–14 (2011)

抗结核治疗过程中预防性保肝治疗指征的研究

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- 01 上海市公共卫生临床中心（组长）
- 02 江西省胸科医院
- 03 天津海河医院
- 04 浙江杭州师范大学附属医院
- 05 黑龙江省第四医院
- 06 辽宁沈阳市胸科医院
- 07 山东省胸科医院
- 08 新疆维吾尔自治区胸科医院
- 09 四川成都市传染病医院
- 10 西安市结核病胸部肿瘤医院
- 11 福建省福州肺科医院
- 12 江苏镇江市第三医院
- 13 湖北武汉市结核病防治所
- 14 云南昆明市第三人民医院
- 15 广西南宁市第四人民医院

组织单位：**中华医学会结核病学分会**

中国疾控中心结核病防治临床中心

1200例，多中心、随机、空白对照临床研究

肝功能恢复后的抗结核治疗

- 恢复后的抗结核治疗

Challenges in Reintroducing Tuberculosis Medications after Hepatotoxicity

Jussi Saukkonen

Department of Medicine, Pulmonary Center, Boston University School of Medicine

(See the article by Sharma et al, on pages 833–839.)

The potential for medications to cause hepatotoxicity has troubled clinicians treating tuberculosis (TB) for decades. Consequently, treatment-limiting biochemical thresholds and symptom screens have been used to forestall the development of severe TB drug–induced liver injury (TB-DILI). If treatment has been interrupted because of suspected hepatotoxicity, diagnostic studies are undertaken, and a period of time for hepatic biochemical normalization ensues. The clinician then rechallenges the patient with all or some of the drugs used in the initial regimen. These steps can take more than a month and require additional clinic visits with repeated clinical and biochemical monitoring. During this time, the patient may be treated with sub-optimal, alternative regimens. The time required to achieve neg-

The prospective study by Sharma et al [1] in this issue of *Clinical Infectious Diseases* assesses 3 strategies for rechallenge with TB medication after a hepatotoxic event. Of the 273 patients who were initially identified as having experienced TB medication–related hepatotoxicity, 58 patients who were pregnant, had a history of alcoholism or chronic liver disease, were taking concomitant hepatotoxic medication, or had human immunodeficiency virus infection were excluded. Four of these patients had died before rechallenge (3 due to liver failure and 1 due to progressive tuberculosis). Altogether, 175 patients with normalized liver biochemistry test results were randomized to either simultaneous rechallenge or one of 2 sequential rechallenge regimens, each lasting at least 2 weeks and including isoniazid, rifampin,

ter of identifying which TB drug caused the problem, either through actual rechallenge with all of the drugs that had been used initially or through successful reintroduction of all but 1 of the initial TB medications, which is then presumed to be the hepatotoxic agent. In practice, the clinician tries to determine whether alanine aminotransferase (ALT) level and/or total bilirubin increase to the same level as that achieved during the initial hepatotoxic event; to identify a particular drug as being hepatotoxic and to avoid it; and most critically, to find a regimen that the patient can tolerate.

The authors found that there was no difference in the rate of recurrent hepatotoxicity among patients who underwent simultaneous challenge (13.8%) or sequential challenges (10.2% and 8.6%),

Treatment of tuberculosis

GUIDELINES

Fourth edition

If it is thought that the liver disease is caused by the anti-TB drugs, all drugs should

If it is thought that the liver disease is caused by the anti-TB drugs, all drugs should be stopped. If the patient is severely ill with TB and it is considered unsafe to stop TB treatment, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.

If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Some advise starting with rifampicin

If TB treatment has been stopped, it is necessary to wait for liver function tests to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing the anti-TB drugs. If it is not possible to perform liver function tests, it is advisable to wait an extra 2 weeks after resolution of jaundice and upper abdominal tenderness before restarting TB treatment. If the signs and symptoms do not resolve and the liver disease is severe, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started (or continued) for a total of 18–24 months (*7*).

duced, the last drug added should be stopped. Some advise starting with rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent (7, 8). After 3–7 days, isoniazid may be reintroduced. In patients who have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.

目前並無足夠的證據確認INH與RMP兩者引發藥物性肝炎的危險性孰高孰低。因此，當病人副作用消失或趨於正常而考慮逐一加入抗結核藥物時，除非有特殊的考量，否則INH應優先於RMP，理由有二：

1. 在所有抗結核藥物當中，INH具有最高的早期殺菌力（early bactericidal activity），可以迅速減少病人體內結核菌量，改善臨床症狀及降低傳染力。
2. 逐一加入抗結核藥物時，由於使用的藥物種類往往不足，因此最先使用的藥物，最有可能產生抗藥性。基於保護RMP，優先加入INH。

防疫學苑系列

結核病診治指引

Taiwan Guidelines for TB Diagnosis & Treatment

行政院衛生署疾病管制局　編

主　　編　陸坤泰

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（依姓氏筆畫排序）

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李品慧　林錫勳　姜義新

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蘇維鈞

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臺灣胸腔暨重症加護醫學會　臺灣內科醫學會　臺灣結核病醫學會

行政院衛生署疾病管制局　出版

2011 年 3 月

抗结核药物肝损的处理

- 治疗原则
- **治疗药物**
- 并发症处理

抗结核药物肝损伤

治疗药物

- 可选择的药物有抗氧化剂、保护性物质前体、阻止损伤发生过程的干预剂或膜损伤的修复剂等

治疗药物

- 多烯磷脂酰胆碱能使受损的肝功能和酶活力恢复正常，促进肝组织再生，调节肝脏的能量平衡，转化中性脂肪和胆固醇
- 甘草甜素类具有较强的抗炎，保护肝细胞膜及改善肝功能的作用
- 熊去氧胆酸有稳定细胞膜，免疫调节及线粒体保护作用，促进胆酸在细胞和胆小管的运输

治疗药物

- 还原性谷胱甘肽能加速自由基的排泄，有助于减轻毒副作用，保护肝脏的合成、解毒、灭活激素等功能，并促进胆酸代谢
- 腺苷蛋氨酸可通过转甲基作用，增加膜磷脂的生物合成，增加膜流动性，加快胆酸的转运，同时通过转硫基作用增加肝细胞的解毒作用和清除自由基的保护作用
- 前列腺素E作为一种抗氧化剂可用于药物型肝损害的辅助治疗
- 糖皮质激素在药物诱导的肝损害患者中可考虑使用，尤其有免疫高敏感性证据的患者

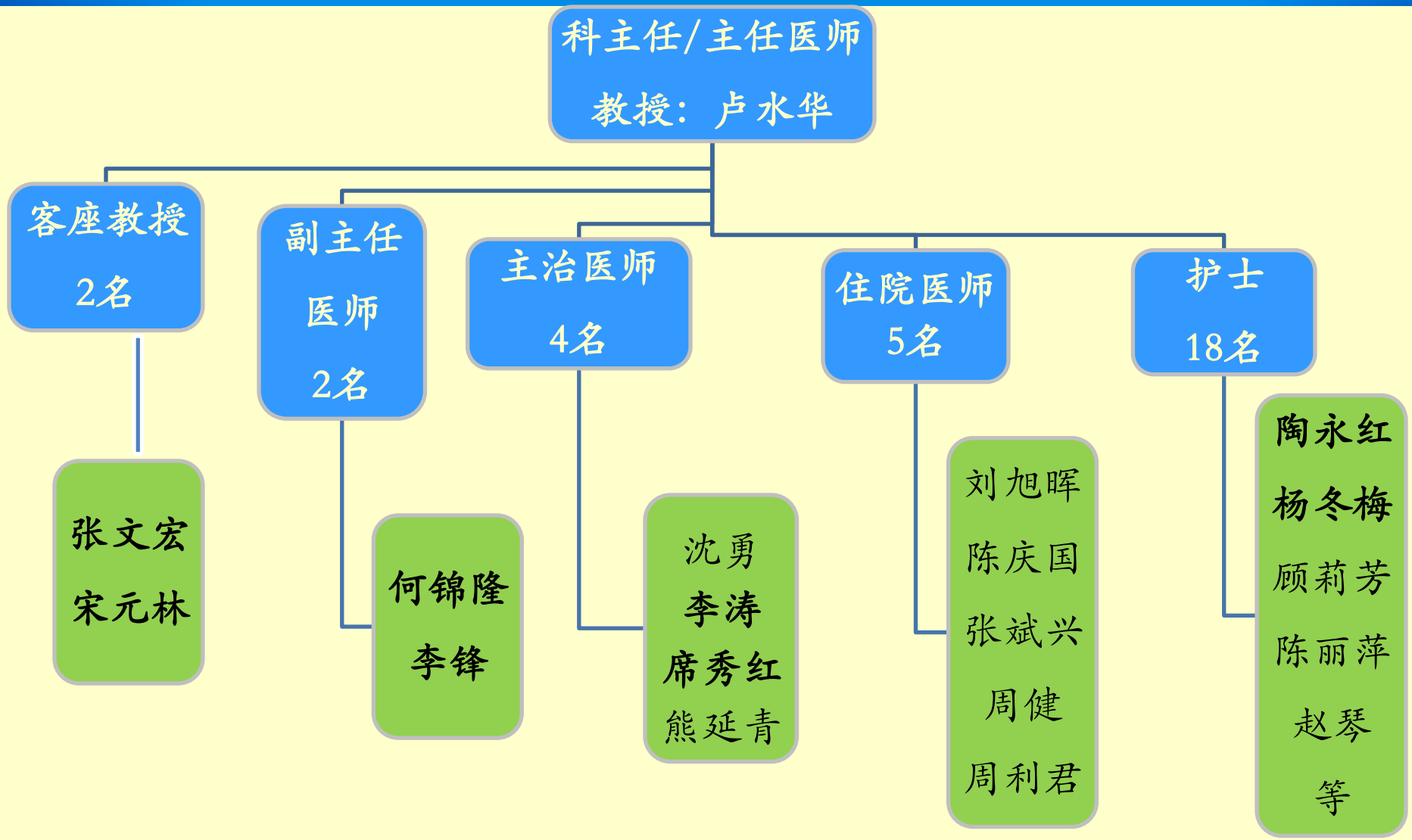
小结

抗结核药物性肝损

- 预防：抗结核药物调整；预防应用护肝药
- 诊断：排除性诊断；分级诊断；早期发现重病人
- 治疗：护肝药物可用于治疗；也可用于预防

谢谢关注

专业团队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教授：卢水华
客座教授
2名
副主任
医师
2名
主治医师
4名
住院医师
5名
护士
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- ✓ 1 Shuihua Lu* Yufang Zheng,Tao Li.et,al. Clinical Findings for Early Human Cases of Influenza A(H7N9) Virus Infection, Shanghai, China. Emerg Infect Dis [Internet]. 2013 Jul [*date cited*]. [Epub ahead of print]
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- ✓ 5 Hai-Nv Gao, Hong-Zhou Lu, Bin Cao, Bin Du, Hong Shang., Jian-He Gan,, Shui-Hua Lu, Clinical finding in 111 case of influenza A（H7N9) virus infection. N Engl J Med 2013. DOI: 10.1056/NEJMoa1305584_130613
- ✓ 6 Yuwen Hu, Shuihua Lu, Zhigang Song. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance . Lancet , www.thelancet.com Published online May 28, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61125-3

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