Appling Drug Information Skills on Adverse Drug Reaction Evaluation

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Outline

- Evaluation of Adverse Drug Reaction (ADR)
  - Causality
  - Severity
  - Preventability
- Data collection points
- Drug Information Resources of ADR
- Example
  - Phenytoin induced Steven-Johnson Syndromes
- Exercise
  - Amiodarone induced pulmonary fibrosis

Objectives

- After the current lecture you should be able to
  - Speak out all of the three aspects of ADR evaluation
  - Write down four important drug information resources of ADR (must include three textbooks)
  - Speak out at least five items to collect from ADR literature

Taiwan ADR Reporting System

Adverse Drug Reaction Evaluation

Severity of ADR

Level	Description
Minor	No antidote, therapy or prolongation of hospitalization is required
Moderate	Requires a change in drug therapy, specific treatment, or an increase in hospitalization
Severe	Potentially life-threatening causes permanent damage or requires intensive medical care
Fatal	Directly or indirectly contributes to the death of the patient

Naranjo Causality Scale

Item	Y	N	U
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse reaction event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs at any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score			

Definite ADR $\geq$ 9 Probable ADR 5-8 Possible ADR 1-4 Doubtful $\leq$ 0

Category of DILI

- Liver injuries are classified in three categories and defined

Category of DILI	Defined
Hepatocellular Liver injuries	**ALT > 2 N or R ≥ 5**
Cholestatic liver injuries	**ALP > 2 N or R ≤ 2**
Mixed liver injuries	**ALT > 2 N and** **An increase in ALP and 2 < R <5**

1.DILI: drug induced liver injury 2.N: normal range

3.R: ratio serum activity ALT/ALP 4.Data measured together at time of recognition.

J Hepatol *1990;11:272-6*

J Clin Epidemiol *1993;46:1323-30*

Causality Assessment of Drug-induced Liver Disease

Hepatocellular Type Injury (RUCAM)-1

Item	Description		Score
1. Time to onset			
Incompatible	Before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)		Unrelated
Unknown	When information is not available to calculate		ID
*From the beginning of the drug	Initial Treatment	Subsequent Treatment	
Suggestive	5~90 days	1~15 days	+2
Compatible	<5 or >90 days	> 15 days	+1
*From cessation of drug			
Compatible	≤ 15 days	≤ 15 days	+1
2. Course	Difference between the peak of ALT and ULN		
After cessation of the drug			
Highly suggestive	Decrease ≥50% within 8 days		+3
Suggestive	Decrease ≥50% within 30 days		+2
Compatible	*Not applicable*		+1
Inconclusive	No information or Decrease ≥50% after the 30th days		0
Against the role of the drug	Decrease <50% after the 30th days or recurrent increase		-2
If the drug is continued or inconclusive	All situations		0
3. Risk factors			
Ethanol Presence			+1
Absence			0
Age ≥55 years			+1
Age <55 years			0

ID = Insufficient documentation; ULN = Upper limit of normal

Causality Assessment of Drug-induced Liver Disease

Hepatocellular Type Injury (RUCAM)-2

Item	Description	Score
4.Concomitant drug(s)		
None or no information or concomitant drug with incompatible time to onset		0
Concomitant drug with compatible or suggestive time to onset		-1
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset		-2
Concomitant drug with evidence for its role in this case		-3
5.Search for non drug causes		
*Gr I(6 causes): HAV, HBV, HCV, biliary obstruction, alcoholism, acute hypotension	Rule out Gr I&II	+2
	Rule out 6 of Gr I	+1
*Gr II: CMV, EBV, Herpes virus infection, other underlying disease	Rule out 5 or 4 of Gr I	0
	Rule out <4 of Gr I	-2
	Non drug cause highly Probable	-3
6. Previous information of hepatotoxicity of the drug		
Reaction labeled in the product characteristics		+2
Reaction published but unlabelled		+1
Reaction unknown		0
7. Rechallenge		
Positive	Doubling of ALT with the drug alone	+3
Compatible	Doubling of ALT with the drugs given at the time of the 1st reaction	+1
Negative	Increase of ALT but <ULN in the same condition as for the 1st reaction	-2
Not done or not interpretable	Other situations	0
8. Plasma concentration as toxic		+3
9. Validated lab. Test	Positive	+3
	Negative	-3
	Not interpretable or not available	0

*≤0: excluded * 1~2: unlikely * 3~5: possible * 6~8: probable *>8: highly probable **Total:**_____

Causality Assessment of Drug-induced Liver Disease

Cholestatic or Mixed Injury (RUCAM)-1

Item	Description		Score
1. Time to onset			
Incompatible	Before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)		Unrelated
Unknown	When information is not available to calculate		ID
*From the beginning of the drug	Initial Treatment	Subsequent Treatment	
Suggestive	5~90 days	1~90 days	+2
Compatible	<5 or >90 days	> 90days	+1
*From cessation of drug			
Compatible	≤ 30 days	≤ 30 days	+1
2. Course	Difference between the peak of ALP (or T.Bil) and ULN		
After cessation of the drug			
Highly suggestive	*Not applicable*		+3
Suggestive	Decrease ≥50% within 180 days		+2
Compatible	Decrease <50% within 180 days		+1
Inconclusive	Persistence or increase or no information		0
Against the role of the drug	*Not applicable*		-2
If the drug is continued inconclusive	All situations		0
3. Risk factors			
Ethanol or Pregnancy Presence			+1
Absence			0
Age ≥55 years			+1
Age <55 years			0

ID = Insufficient documentation; ULN = Upper limit of normal

Causality Assessment of Drug-induced Liver Disease

Cholestatic or Mixed Injury (RUCAM)-2

Item	Description	Score
4.Concomitant drug(s)		
None or no information or concomitant drug with incompatible time to onset		0
Concomitant drug with compatible or suggestive time to onset		-1
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset		-2
Concomitant drug with evidence for its role in this case		-3
5.Search for non drug causes		
*Gr I(6 causes): HAV, HBV, HCV, biliary obstruction, alcoholism, acute hypotension	Rule out Gr I&II	+2
	Rule out 6 of Gr I	+1
*Gr II: CMV, EBV, Herpes virus infection, other underlying disease	Rule out 5 or 4 of Gr I	0
	Rule out <4 of Gr I	-2
	Non drug cause highly probable	-3
6. Previous information of hepatotoxicity of the drug		
Reaction labeled in the product characteristics		+2
Reaction published but unlabelled		+1
Reaction unknown		0
7. Rechallenge		
Positive	Doubling of ALP (or T. Bil) with the drug alone	+3
Compatible	Doubling of ALP (or T. Bil) with drugs given at the time of the 1st reaction	+1
Negative	Increase of ALP (or T. Bil) but <**N** in the same condition as the 1st reaction	-2
Not done or not interpretable	Other situations	0
8. Plasma concentration as toxic		+3
9. Validated lab. Test	Positive	+3
	Negative	-3
	Not interpretable or not available	0

*≤0: excluded * 1~2: unlikely * 3~5: possible * 6~8: probable *>8: highly probable **Total:**

A Causal Relation between the Drug and Thrombocytopenia

Description	Criterion
(1) Therapy with the candidate drug preceded thrombocytopenia and (2) recovery from thrombocytopenia was complete and sustained after therapy with the drug discontinued	1
(1) The candidate drug was the only drug used before the onset of thrombocytopenia or (2) other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count	2
Other causes for thrombocytopenia were excluded	3
Re-exposure to the candidate drug resulted in recurrent thrombocytopenia	4

Definition	Level of evidence
Definite: criteria 1, 2, 3, and 4 met	**I**
Probable: criteria 1, 2, and 3 met	**II**
Possible: criteria 1 met	**III**
Unlikely: criteria 1 not met	**IV**

Definite DIT	Probable DIT	Possible DIT	Unlikely DIT	Level:	

DIT: Drug induced thrombocytopenia

Ann Intern Med 1998; 29(11): 886-90.

Preventability of ADR

	Item	Y	N
1	Was the drug involved in the ADR considered **not** considered **appropriate** for the patient's clinical condition?	Y	N
2	Was the **dose, route, and frequency** of administration **not appropriate** for the patient's age, weight and/or disease state?	Y	N
3	Were required **therapeutic drug monitoring** or other necessary laboratory tests not performed?	Y	N
4	Was there a history of **allergy or previous reactions** to the drug?	Y	N
5	Was a **drug interaction** involved in the reaction?	Y	N
6	Was a **toxic** serum level documented?	Y	N
7	Was **poor compliance** involved in the reaction?	Y	N

Result: Preventable

Unpreventable

Classification of Adverse Drug Reactions

Type of reaction	Mnemonic	Features	Examples	Management
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants	• Reduce dose or withhold • Consider effects of concomitant therapy
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)	• Withhold and avoid in future
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	• Reduce dose or withhold; withdrawal may have to be prolonged
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia	• Often intractable
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)	• Reintroduce and withdraw slowly
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	• Increase dosage • Consider effects of concomitant therapy

SSRIs=serotonin-selective reuptake inhibitors.

DoTS Classification of ADR

- Relation to dose
- Time course
- Susceptibility factors

(1) Relation to Dose

Items	Reactive dose
Toxic reactions	Supra-therapeutic doses
Collateral reactions	Standard therapeutic doses
Hyper-susceptibility reaction	Sub-therapeutic dose in susceptable individuals

(2) Time Course

Items	Reactive timing
Time independent	Any time during the course
Time dependent	
Immediate or rapid reactions	Occur when drug administered too rapidly
First-dose reactions	Occur after 1st dose
Early reactions	Occur early after therapy begin
Intermediate reactions	Occur after a period of time, then less risk during long-term therapy
Late reactions	Occur with continued or repeated exposure
Withdrawal reactions	Occur when, after a long-term treatment, a drug is withdrawn or the dose is reduced
Delayed reactions	Occur some time after exposure or even if the drug is stopped

(3) Susceptibility Factors

Items	Reactive factors
Gender	
Age	Age related enzyme activity loss
Genetic	Inheritable enzyme deficiency
Physiological variation	
Exogenous factors	Drug-drug interactions, Drug-food interactions, smoking
Disease	Comorbidity

What data should we collect from adverse drug reaction literature?

Data to Collect

- Incidence, risk factors
- Clinical manifestation
  - Outcome, symptoms
  - Time course: onset / duration
  - Dose relation
- Mechanism
- Management
  - Treatment, monitoring parameter
- Strength of evidence

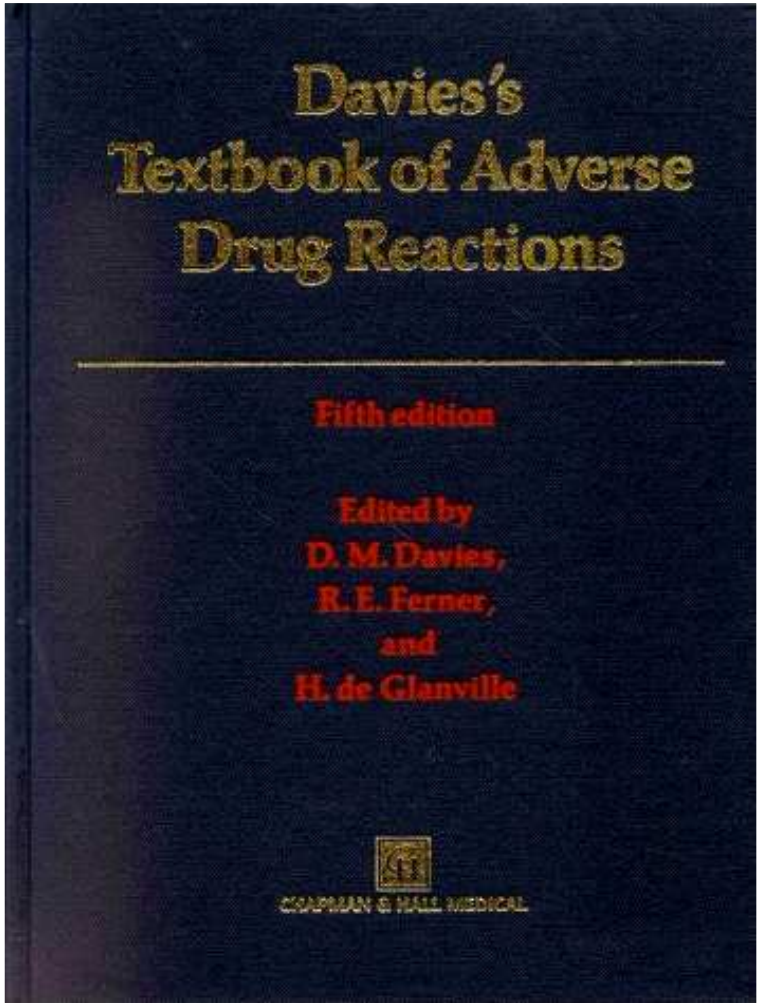
Adverse Drug Reaction Literature Resources

Drug Information Resources

Textbook

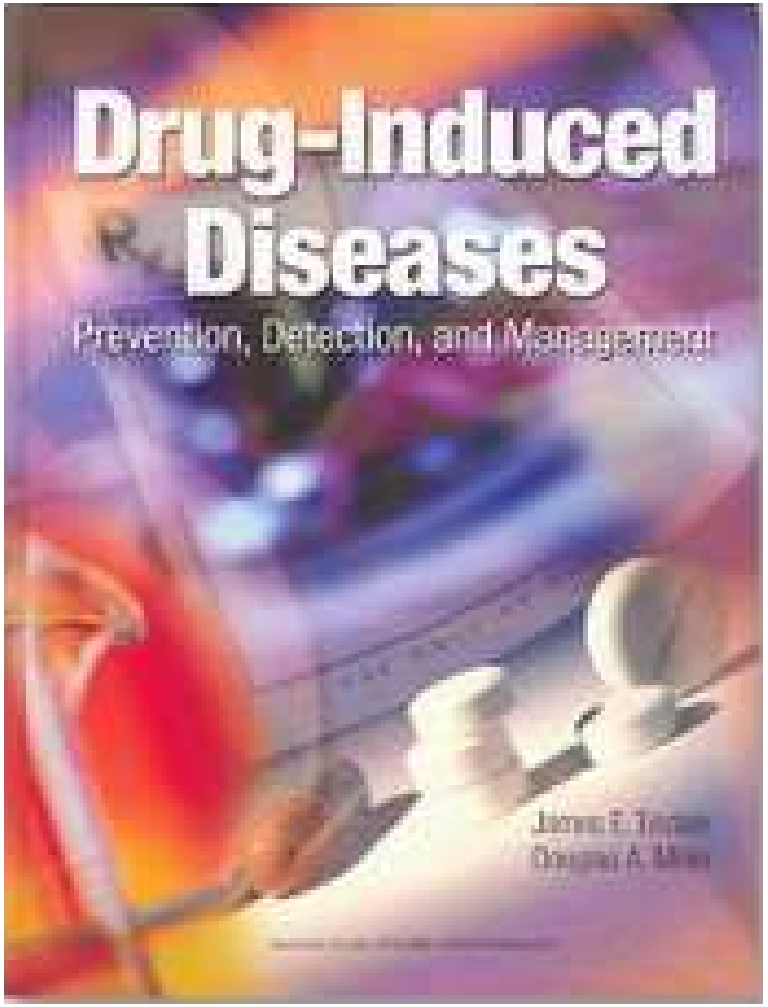
Davies's Textbook of Adverse Drug Reactions

- Most current edition
  - Publisher
    - Chapman and Hall Medical
  - 5th Edition, 1998
  - ISBN: 0412824809
  - Contents by "*affected organ*"



Drug-Induced Diseases: Prevention, Detection, and Management

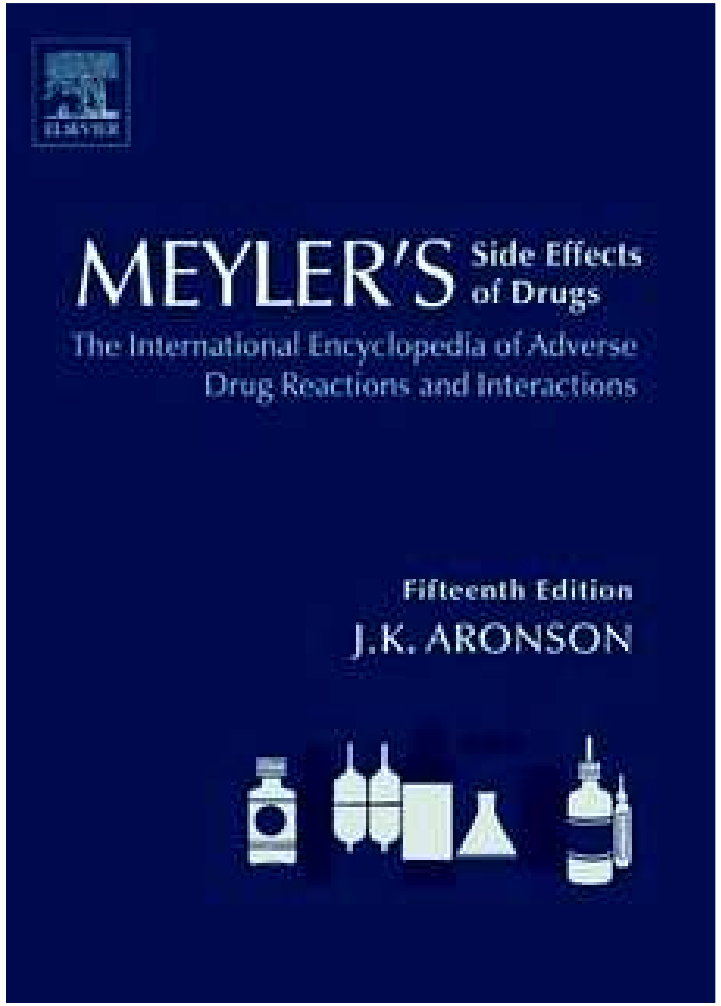
- Most current edition
  - Publisher: American Society of Health-System Pharmacists (ASHP)
  - 1st edition, 2005
  - ISBN: 1585280860
  - Contents by "*affected organ*"



Meyler's Side Effects of Drugs

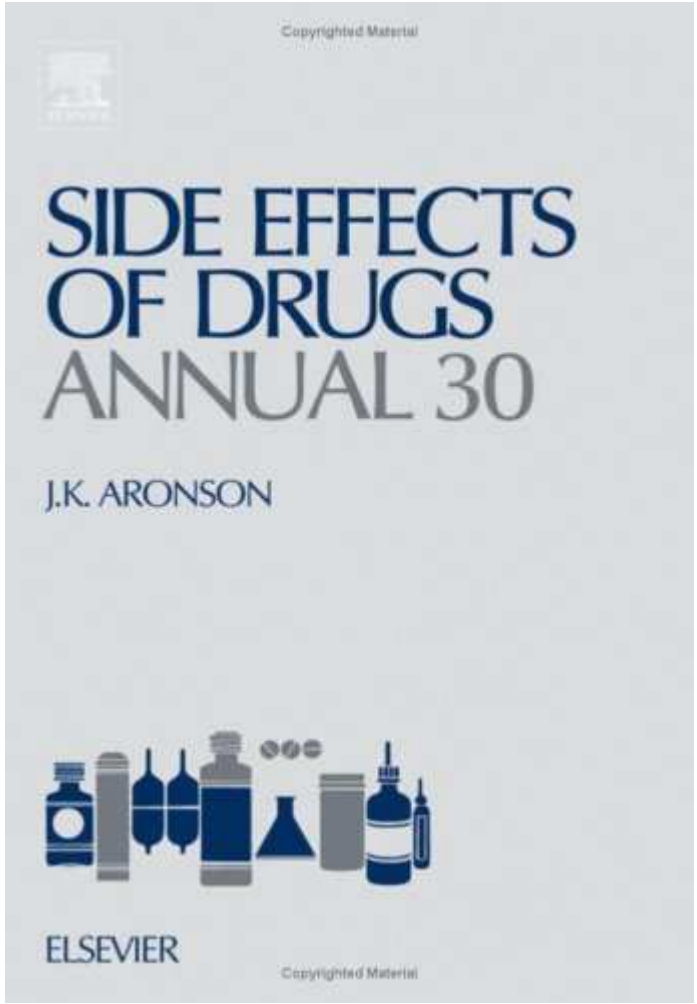
International Encyclopedia of Adverse Drug Reactions and Interactions

- Most current edition
  - Publisher: Elsevier Science
  - 15th Edition, 2006
  - ISBN: 0444509984
- Example edition
  - 14th Edition, 2000
  - ISBN: 0444500936
  - Contents by "*drug class*"



Side Effects of Drugs, Annual 30

- Abbreviation: SEDA-30
- Most current edition
  - Publisher: Elsevier
  - 30st edition, 2008 (annually)
  - ISBN: 978 0 444 52767 7
  - Contents by "*drug class*"
  - Reviewing publications of 2005



Drug Information Resources

Database

Micromedex—Health Care Series

- **DRUGDEX®** Evaluation
  - Cautions
    - Adverse reactions

Review Articles

Review Articles

- Journals with good review articles on adverse drug reactions
  - New England Journal of Medicine
  - Drug Safety

New England Journal of Medicine

- Official journal of *Massachusetts Medical Society*
  - Impact factor: 50.017 (JCR 2008)
  - Top 1% in “Medicine, general & internal”

The NEW ENGLAND JOURNAL of MEDICINE

Drug Safety

- Official journal of *International Society of Pharmacovigilance (ISoP)*
- Impact factor: 3.537 (JCR 2008)
  - Top 10.9% in “Toxicology”
  - Top 22.4% in “Pharmacology & pharmacy”

Original Articles

Original Articles

- Search for relevant articles
  - Ovid Medline or PubMed
- Retrieve target articles
  - Randomized control trials?
  - Cohort studies? Or Case-Control studies?
  - Case series or case report
- Literature evaluation
  - Quality
  - Applicability

PRACTICE

Data to Collect

- Incidence, risk factors
- Clinical manifestation
  - Symptoms, outcome
  - Time course: onset / duration
  - Dose relation
- Mechanism
- Management
  - Treatment, monitoring parameter
- Strength of evidence

Phenytoin induced Stevens-Johnson Syndrome

- 醫師打電話來說有一位44歲男性病人發生皮膚問題，他懷疑是Phenytoin induced Stevens-Johnson Syndrome (SJS)。
  - 據描述，病人使用Phenytoin後40天發生皮膚疹 (長的很像標靶)，第45天發現嘴巴黏膜有潰爛，，eosinophil升高，皮膚科醫師會診過，診斷為SJS, 已經做了支持療法
  - 因為時間點，不知是否該停用Phenytoin，詢問您的意見
  - 請問，此不良反應可能與Phenytoin有關嗎？根據相關文獻，您認為醫師該不該停用Phenytoin?

General Drug Safety of Etanercept

- 你在輪值藥物資訊櫃檯時，病人拿了一樣針劑過來問你，它是不是有什麼副作用。
  - 你看了藥名是Etanercept
  - 病人說他是因為類風濕性關節炎，醫師新開了這個藥品，但是他之前都是吃口服的藥品，第一次要打針，他很擔心副作用，想知道用這個藥有沒有什麼需要注意的地方

Amiodarone Induced Pulmonary Fibrosis

- 你在進行藥事照顧的時候發現一個病人肺功能在近三個月間持續下降
  - 痰液一直無法培養出任何相關病原，白血球計數也很正常，病人沒有發燒的症狀，胸腔X光檢查發現肺浸潤與纖維化，醫師也無法確定到底病人為何展現肺炎樣的表現。
  - 病人過去沒有下呼吸道感染的病史，只有四個月前，病人因為心室心律不整嚴重，藥物從原本的Beta-blocker加上Amiodarone.
  - Amiodarone可能與病人的反應有關嗎？
  - 該如何處理這個反應？

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Thank You!