การพัฒนาเกณฑ์การประเมินความสัมพันธ์ของความผิดปกติของเม็ดเลือด ที่มีสาเหตุจากยา ณ โรงพยาบาลจุฬาลงกรณ์

นาย สฤษดิ์ นามวงศ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

สาขาวิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรม

คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ปีการศึกษา 2545

ISBN 974-17-1911-6

DEVELOPMENT OF CAUSALITY ASSESSMENT CRITERIA IN DRUG-INDUCED BLOOD DYSCRASIA AT KING CHULALONGKORN MEMORIAL HOSPITAL

Mr. Sarit Namwong

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy in Clinical Pharmacy
Department of Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic 2002

ISBN 974-17-1911-6

Thesis Title	DEVELOPMENT OF CAUSALITY ASSESSMENT CRITERIA IN DRUG-INDUCED BLOOD DYSCRASIA AT KING CHULALONGKORN MEMORIAL HOSPITAL.
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สฤษดิ์ นามวงศ์ : การพัฒนาเกณฑ์การประเมินความสัมพันธ์ของความผิดปกติของเม็ดเลือดที่มีสาเหตุจากยา ณ โรงพยาบาลจุฬาลงกรณ์ (DEVELOPMENT OF CAUSALITY ASSESSMENT CRITERIA IN DRUG-INDUCED BLOOD DYSCRASIA AT KING CHULALONGKORN MEMORIAL HOSPITAL). อาจารย์ที่ปรึกษา: ผศ. นารัต เกษตรทัต, อาจารย์ที่ปรึกษาร่วม: ผศ. พญ. ปราณี สุจริตจันทร์ และ ผศ. นพ. พลภัทร โรจน์นครินทร์: 120 หน้า. ISBN 974-17-1911-6

วัตถุประสงค์: เพื่อพัฒนาเกณฑ์การประเมินความสัมพันธ์ของความผิดปกติของเม็ดเลือดที่มีสาเหตุมาจากยาให้มีความเหมาะสมสำหรับนำมาใช้ในประเทศไทย, เพื่อทดสอบความตรง ความเที่ยงและคุณสมบัติการวินิจฉัยของเกณฑ์ที่พัฒนาขึ้น นอกจากนี้เพื่อเปรียบเทียบเกณฑ์ประเมินที่พัฒนาขึ้นกับเกณฑ์ประเมินของ Naranjo เมื่อนำมาใช้ประเมินผู้ป่วยที่สงสัยว่าเกิดความผิดปกติของเม็ดเลือดที่มีสาเหตุจากยา

วิธีวิจัย: เกณฑ์ประเมินที่พัฒนาขึ้นประกอบด้วยส่วนต่างๆ ทั้งหมด 6 ส่วน ได้แก่ ความสัมพันธ์ระหว่างเวลา, สาเหตุอื่นๆ ที่เกี่ยวข้องกับการเกิดอาการ, ยาชนิดอื่นๆ ที่ผู้ป่วยได้รับร่วม, อาการแสดงทางคลินิกของผู้ป่วย, การได้รับยาที่สงสัยซ้ำ และข้อมูลจากการรายงานในวารสารทางการแพทย์ต่างๆ ซึ่งในแต่ละส่วนจะมีความสำคัญและถูกให้ค่าน้ำหนักคะแนนที่แตกต่างกันออกไป สำหรับเกณฑ์ประเมินนี้จะแบ่งระดับความน่าจะเป็นของการเกิดอาการอันไม่พึงประสงค์ออกเป็น 4 ระดับได้แก่ ไม่น่าใช่ อาจจะใช่ น่าจะใช่และใช่แน่ ซึ่งแต่ละระดับจะถูกแสดงโดยอาศัยผลรวมของคะแนนทั้งหมด การศึกษาในครั้งนี้กำหนดให้การประเมินจากแพทย์ผู้เชี่ยวชาญซึ่งเป็นโลหิตแพทย์จำนวน 2 ท่าน เป็นมาตรฐานสำหรับทดสอบค่าความตรงของเครื่องมือ ส่วนความเที่ยงของเครื่องมือจะถูกทดสอบโดยการประเมินจากเภสัชกร 2 ท่าน นอกจากนี้ความตรง ความเที่ยงและคุณสมบัติการวินิจฉัยของเกณฑ์การประเมินชนิดใหม่ยังถูกเปรียบเทียบกับเกณฑ์การประเมินของ Naranjo ทั้งนี้เพื่อศึกษาความแตกต่างของเครื่องมือทั้งสองชนิด สำหรับสถิติที่ใช้ในการวิเคราะห์หาค่าความสอดคล้องกันระหว่างแพทย์ผู้เชี่ยวชาญทั้ง 2 ท่านได้แก่ Intraclass correlation coefficient (ρ_I) ส่วนความตรงและความเที่ยงของเครื่องมือจะถูกวิเคราะห์โดย Weighted kappa coefficient (κ_w) นอกจากนี้การศึกษาคุณสมบัติการวินิจฉัยของเครื่องมือจะถูกพิจารณาจากค่า Cut-off point ความไว ความจำเพาะ ความแม่นยำ Predictive value และ likelihood ratio สำหรับกลุ่มตัวอย่างที่ใช้ในการศึกษานำมาจากผู้ป่วยที่เข้ารับการรักษา ณ หอผู้ป่วยอายุรกรรม โรงพยาบาลจุฬาลงกรณ์ และสงสัยว่าเกิดความผิดปกติของเม็ดเลือดที่มีสาเหตุจากยา

ผลการวิจัย: ในช่วงระหว่างวันที่ 1 มกราคม พ.ศ. 2544 ถึง 30 พฤศจิกายน พ.ศ. 2545 มีผู้ป่วยที่ถูกสงสัยว่าเกิดความผิดปกติของเม็ดเลือดที่มีสาเหตุมาจากยา จำนวนทั้งสิ้น 41 ราย ในจำนวนนี้พบอาการอันไม่พึงประสงค์จากยา 58 เหตุการณ์ จากผลการศึกษาพบว่า ความคิดเห็นของแพทย์ผู้เชี่ยวชาญทั้ง 2 ท่านเมื่อประเมินกลุ่มผู้ป่วยเดียวกันมีความสอดคล้องกันสูง (ρ_I 0.685; 95%CI 0.515-0.802) ส่วนความตรงของเกณฑ์การประเมินที่พัฒนาขึ้นก็มีค่าอยู่ในระดับสูงเช่นกันเมื่อเทียบกับมาตรฐาน (κ_w 0.712; 95%CI 0.520-0.904 และ κ_w 0.683; 95% CI 0.495-0.871 สำหรับเภสัชกรคนที่ 1 และ 2 ตามลำดับ) ในขณะที่ความเที่ยงของเครื่องมือระหว่างเภสัชกรทั้งสองก็อยู่ในเกณฑ์ที่ดีมาก (κ_w 0.866; 95%CI 0.672-1.060) เมื่อพิจารณาจากกราฟ ROC ของเภสัชกรทั้งสองพบว่าค่า cut-off point ที่เหมาะสมสำหรับเกณฑ์ประเมินที่สร้างขึ้นนี้มีค่าเท่ากับ 2 ซึ่งจากค่าดังกล่าวแสดงให้เห็นว่าเกณฑ์ประเมินที่พัฒนาขึ้นสามารถวินิจฉัยผู้ป่วยที่สงสัยว่าเกิดความผิดปกติของเม็ดเลือดที่มีสาเหตุจากยาด้วยความไวที่สูง (92.3%) ซึ่งเป็นไปในแนวทางเดียวกับค่าความจำเพาะของเครื่องมือ (94.74% สำหรับเภสัชกรคนที่ 1 และ 84.21% สำหรับเภสัชกรคนที่ 2) เมื่อทำการเปรียบเทียบเกณฑ์ประเมินชนิดใหม่กับเกณฑ์ประเมินของ Naranjo พบว่าเกณฑ์ประเมินที่สร้างขึ้นใหม่มีค่าความตรงสูงกว่าของ Naranjo อย่างเห็นได้ชัด (κ_w 0.712; 95%CI 0.520-0.904 vs. κ_w 0.411; 95%CI 0.258-0.564 สำหรับเภสัชกรคนที่ 1 และ κ_w 0.683; 95%CI 0.495-0.871 vs. κ_w 0.330; 95%CI 0.171-0.489 สำหรับเภสัชกรคนที่ 2) ในขณะที่ค่าของความเที่ยงก็สูงกว่าเช่นกัน (κ_w 0.866; 95% CI 0.672-1.060 vs. κ_w 0.563; 95%CI 0.367-0.759) ส่วนคุณสมบัติการวินิจฉัยของเกณฑ์ประเมินชนิดนี้ก็มีแนวโน้มที่ดีกว่าของ Naranjo เช่นกัน

สรุปผลการวิจัย: การศึกษานี้แสดงให้เห็นว่าเกณฑ์ประเมินที่พัฒนาขึ้นมีความตรงและความเที่ยงอยู่ในระดับสูง ซึ่งเป็นเครื่องมือที่สามารถช่วยบุคลากรทางการแพทย์ในการประเมินผู้ป่วยที่สงสัยว่าเกิดความผิดปกติของเม็ดเลือดที่มีสาเหตุจากยาได้อย่างมีประสิทธิภาพ

ภาควิชา เภสัชกรรม.....ลายมือชื่อนิสิต.....

สาขาวิชา เภสัชกรรมคลินิก.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา 2545.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4376631033: MAJOR CLINICAL PHARMACY
KEY WORD: DRUG-INDUCED BLOOD DYSCRASIAS, CAUSALITY ASSESSMENT CRITERIA, CAUSALITY ASSESSMENT SCALE.

SARIT NAMWONG: THESIS TITLE: DEVELOPMENT OF CAUSALITY ASSESSMENT CRITERIA IN DRUG-INDUCED BLOOD DYSCRASIA AT KING CHULALONGKORN MEMORIAL HOSPITAL. THESIS ADVISOR: ASST. PROF. NARAT KASETTRATAT, M.Sc. in Pharm. THESIS CO-ADVISORS: ASST. PROF. PRANEE SUCHARITCHAN, M.D. AND ASST. PROF. PONLAPAT ROJNUCKARIN, M.D., Ph.D., 120 pp. ISBN 974-17-1911-6

Objectives: The purposes of this study were to develop a causality assessment scale of drug-induced blood abnormalities for Thai clinical settings, to determine the validity, reliability and diagnostic markers of this scale, and to compare this scale with Naranjo's algorithm in assessing the causality of drug-induced blood dyscrasia cases.

Methods: The new causality assessment scale comprised six axes of decision strategies such as chronological relationship, alternative causes, concomitant medications, clinical features, rechallenge, and previous reports in medical literatures. The relative importance of each axis was weighted and scoring. The risk probability (i.e., unlikely, possible, probable, and highly probable) of the assessment was expressed as a total score that was summed from each axis. Validity and reliability of the scale were studied by comparing the new clinical scale with experts' opinion. Opinions from two experts were used as a gold standard. The reliability test was performed to determine the agreement between two experts. The agreement was presented as intraclass correlation coefficient (ρ_I). Rating scale assessment from two pharmacists using the new scale was used to study the reliability that was analyzed by weighted kappa coefficients (κ_w). The diagnostic markers (cut-off point, sensitivity, specificity, accuracy, predictive value and likelihood ratio) of the new scale were also tested for the appropriateness to diagnose patients with drug-induced blood dyscrasia. Patients with suspected drug-induced blood dyscrasias who was admitted at medical wards at King Chulalongkorn Memorial Hospital were recruited and used as cases for assessing the adverse drug events.

Results: During January 1, 2001 to November 30, 2002, forty-one patients with a total of 58 events of suspected drug-induced blood dyscrasias were enrolled in this study. The agreement between two experts when evaluating the case series of drug-induced blood dyscrasias was good relationship (ρ_I 0.685; 95%CI 0.515-0.802). In addition, this new scale showed the high level of validity when comparing with a gold standard (For pharmacist 1: κ_w 0.712; 95%CI 0.520-0.904 and κ_w 0.683; 95%CI 0.495-0.871 for pharmacist 2). As for the inter-rater reliability of the new scale, it had also a very good agreement (κ_w 0.866; 95%CI 0.672-1.060). From the ROC curve of both pharmacists, the score of 2 was considered as an appropriate cut-off point. It was shown that our scale could identify the cases of drug-induced blood dyscrasia with the high sensitivity (92.3%), as well as a high level of specificity (94.74% for pharmacist 1 and 84.21% for pharmacist 2). When compared with the Naranjo's algorithm, the weighted kappa coefficients (κ_w) of the new scale validity were significantly higher than those of Naranjo's algorithm (κ_w 0.712; 95%CI 0.520-0.904 vs. κ_w 0.411; 95%CI 0.258-0.564 for pharmacist 1 and κ_w 0.683; 95%CI 0.495-0.871 vs. κ_w 0.330; 95%CI 0.171-0.489 for pharmacist 2). The reliability of the new scale was also higher than that of Naranjo's algorithm (κ_w 0.866; 95%CI 0.672-1.060 vs. κ_w 0.563; 95%CI 0.367-0.759). Moreover, the diagnostic markers of this new scale tended to have higher values than those of Naranjo's.

Conclusion: This study suggested that the new causality assessment scale had high level of validity and reliability. Clinicians may use this clinical scale as a tool to effectively assess patients who suspected of drug-induced blood dyscrasias.

Department……Pharmacy…… Student's signature……..

Field of study……Clinical Pharmacy……..Advisor's signature…….……..…..

Academic year……2002……Co-advisor's signature…..…...…….

Co-advisor's signature…….…...…….

ACKNOWLEDGMENT

First of all, I would like to express my sincere gratitude to my thesis advisor, Assistant Professor Narat Kasettratat, at Clinical Pharmacy Division, Department of Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, for her valuable advice, suggestions, keen interests, and encouragement throughout the course of the study.

To Assistant Professor Pranee Sucharitchan, M.D. and Assistant Professor Ponlapat Rojnuckarin, M.D, Ph.D. at Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, my thesis co-advisors, I am grateful for their expert opinions on the clinical scale for diagnosis of drug-induced blood dyscrasias. Moreover, I wish to express my deep appreciation for the time that they devoted for helpful discussion and exceptionally wise counsel for my thesis, as well.

I wish to heartily thank to Assistant Professor Somrat Lertmaharit, Assistant Profesor Winit Winit-Watjana, Ph.D. and Dr. Supakit Wongwiwattanonuk, PharmD., Ph.D. for encouraging criticism and sharing their usefully statistical expertise.

My honest thanks are extended to all patients who let me use their clinical details for my study.

I also wish to express my grateful appreciation to all teachers at Clinical Pharmacy Program, Department of Pharmacy who gave me a precious opportunity for studying this great program and taught me how to apply the clinical knowledge for approaching my patients, as well as for their invaluable comment and suggestion.

I am grateful to Ms. Worawan Kongvattanakul and Ms. Supparat Chanprasert for their participation in the inter-rater reliability assessment.

My thankfulness is also extended to all staff-wards at Medicine Wards and Division of Hematology, including physicians, pharmacists, nurses, medical students as well as all staffs at Statistical and Medical Department of King Chulalongkorn Memorial Hospital, who are too numerous to mention here, for their helpfulness, kindness and also kept the intensive atmosphere of cheerfulness.

To all of my friends in the class of clinical pharmacy program, thank you for your never ending kind and friendships which have meant more than words that can express.

Thanks are also due to Chulalongkorn University for granting partial financial support to fulfill this study.

Finally, to my parent, thank you for your understanding of the importance of this thesis to me, but mostly for your constant love, support and encouragement.

CONTENTS

Page

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF FIGURES

ABBREVIATIONS

ADR	Adverse drug reaction
AF	Atrial fibrillation
A fib	Atrial fibrillation
AIDS	Acquired imunodeficiency syndromes
AIHA	Autoimmune hemolytic anemia
Alb	Albumin
ALT	Alanine transaminase
AMI	Acute myocardial infarction
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ARF	Acute renal failure
ASA	Aspirin
AST	Aspartase transaminase (SGOT)
AVR	Aortic valve replacement
AZT	Zidovudine (azidothymidine)
Bm Bx	Bone marrow biopsy
BID	Twice daily
BM	Bone marrow
BMT	Bone marrow transplantation
Bili	Bilirubin
BP	Blood pressure
BPH	Benign prostatic hypertrophy
BPM	Beats per minute; breaths per minute
BUN	Blood urea nitrogen
Bx	Biopsy
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAPD	Chronic ambulatory peritoneal dialysis
C BC	Complete blood count
CC	Chief complaint
CHF	Congestive heart failure

ABBREVIATIONS (CONT.)

CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRF	Chronic renal failure
c/s	Culture and sensitivity
CXR	Chest x-ray
DDI	Didanosine
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DOE	Dyspnea on exertion
Dx	Diagnosis
ECG	Electrocardiogram
ECHO	Echocardiogram
EKG	Electrocardiogram
ESRD	End-stage renal disease
Fx	Fracture
gm+	Gram-positive
gm-	Gram-negative
Gm-CSF	Granulocyte macrophage colony stimulating factor
HbsAg	Hepatitis B surface antigen
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HR	Heart rate
HT	Hypertension
Hx	History
HZV	Herpes zoster virus
ITP	Idiopathic thrombocytopenic purpura
MI	Myocardial infarction
MTX	Metrotrexate
mu	Million unit

ABBREVIATIONS (CONT.)

MVR	Mitral valve replacement
NKDA	No known drug allergy
PCP	*Pneumocystis carinii* pneumonia
PE	Physical examination
PTCA	Percutaneous transluminal coronary angioplasty
PU	Peptic ulcer
q	Every
RA	Rheumatoid arthritis
RHD	Rheumatic heart disease
r/o	Rule out
S_1	First heart sound
S_2	Second heart sound
SLE	Systemic lupus erythematosus
s/p	Status post
Tx	Therapy
UA	Urinalysis
UTI	Urinary tract infection
VZV	Varicella zoster virus
WBC	White blood cell

CHAPTER I

INTRODUCTION

Blood dyscrasia, any abnormal condition of the formed elements of blood or the constituents required for blood clotting, has always been a risk of drug therapy. [1] Numerous drugs have been incriminated for the etiology of blood dyscrasias. The four major types of drug-induced blood dyscrasias are: 1) hemolytic anemia, 2) aplastic anemia, 3) agranulocytosis or neutropenia, and 4) thrombocytopenia. [2] The incidence of agranulocytosis is 3.0-7.2 per million patients per year and 1.5-9.0 per million patients for aplastic anemia. [3] The severity of drug-induced cytopenia can range from mild to life-threatening reaction with high mortality. The mortality rate of drug-induced aplastic anemia and agranulocytosis is 46% and 9 %, respectively. [3,4] Most of hematologic adverse drug reactions are acute onset. [5]

In these consequences, the early and precise assessment of drug-related blood injuries, including the identification of the offending drug, are of great importance. Early detection may prevent the progression of event to more severe and may help patient avoiding the recurrence of new episodes. Although, recently, there are immunologic and genetic markers to confirm the drug-associated blood dyscrasias, [3,6,7] they can be used only in individual patient and can not be a standard tool to identify the event. In addition, some of these methods may be hazard to patients or may require special laboratory methods which are expensive and may not be available in all clinical settings, [6,7] especially such hospitals in rural area. Most clinicians usually assess the causality of drug-induced disease base on circumstantial evidences and patient history, such as drug therapy history, the chronological relationship between time of drug intake and the onset of clinical signs and symptoms or laboratory results as well as the exclusion of non-drug causes. [8] Clinical improvement after dechallenge of the offending drug is another evidence that may indicate a drug-related cause. Rechallenge of drug is generally considered to be the most reliable evidence in the diagnosis of suspected patient with hematologic adverse drug reaction but it is clearly dangerous and must be avoided. Nowadays, there are several algorithms and other decision tools to evaluate drug-induced diseases. [9-14] In Thailand, Naranjo's algorithm [11] is the most-used algorithm

to help evaluating causality of drug-induced reaction. However, there are a number of problems when people use this algorithm for adverse drug reaction assessment, [15-18] especially in clinical practice. Moreover, it may not appropriate for systemic approach to the patient who is suspected of drug-induced specific disorder such as blood dyscrasia, because it was developed for evaluation of all organ systems of adverse drug reaction. [19]

To our knowledge, there is only one study by international consensus meeting that has proposed standardized definitions and chronological criteria in assessing the cause of drug-induced blood dyscrasias. [5] However, it should be noted that these criteria were published in 1991 and not all clinicians have adopted these criteria. [20] Moreover, they were not tested for its validity, reliability and diagnostic markers, and there is some quibble with the relevant risk factor criteria in this algorithm. [5] Therefore, an appropriate assessment tool should be developed for use in Thai clinical settings.

Objectives

The purposes of this study were:

1) To develop the new causality assessment scale in drug-induced blood dyscrasias for Thai clinical settings.
2) To determine the validity, reliability and diagnostic markers of this scale.
3) To determine the agreement between the scores obtained from Naranjo's algorithm and the new clinical scale in rating a series of cases of drug-induced blood dyscrasias.

Significance of the Study

1. This study will provide the new clinical scale to evaluate drug-induced blood dyscrasias in Thai clinical settings.
2. The new clinical scale will be beneficial for clinicians in monitoring drug-induced blood disorders. The clinicians may use this scale simply and conveniently for their clinical judgements with decreasing inconsistency of evaluation.
3. The new clinical scale will be helpful for clinicians to identify the culprit drug when their patients taking a number of suspected drugs.
4. The new clinical scale will help the clinicians in making appropriate clinical decision for managing the patient with suspected drug-induced blood dyscrasias.

Conceptual Framework

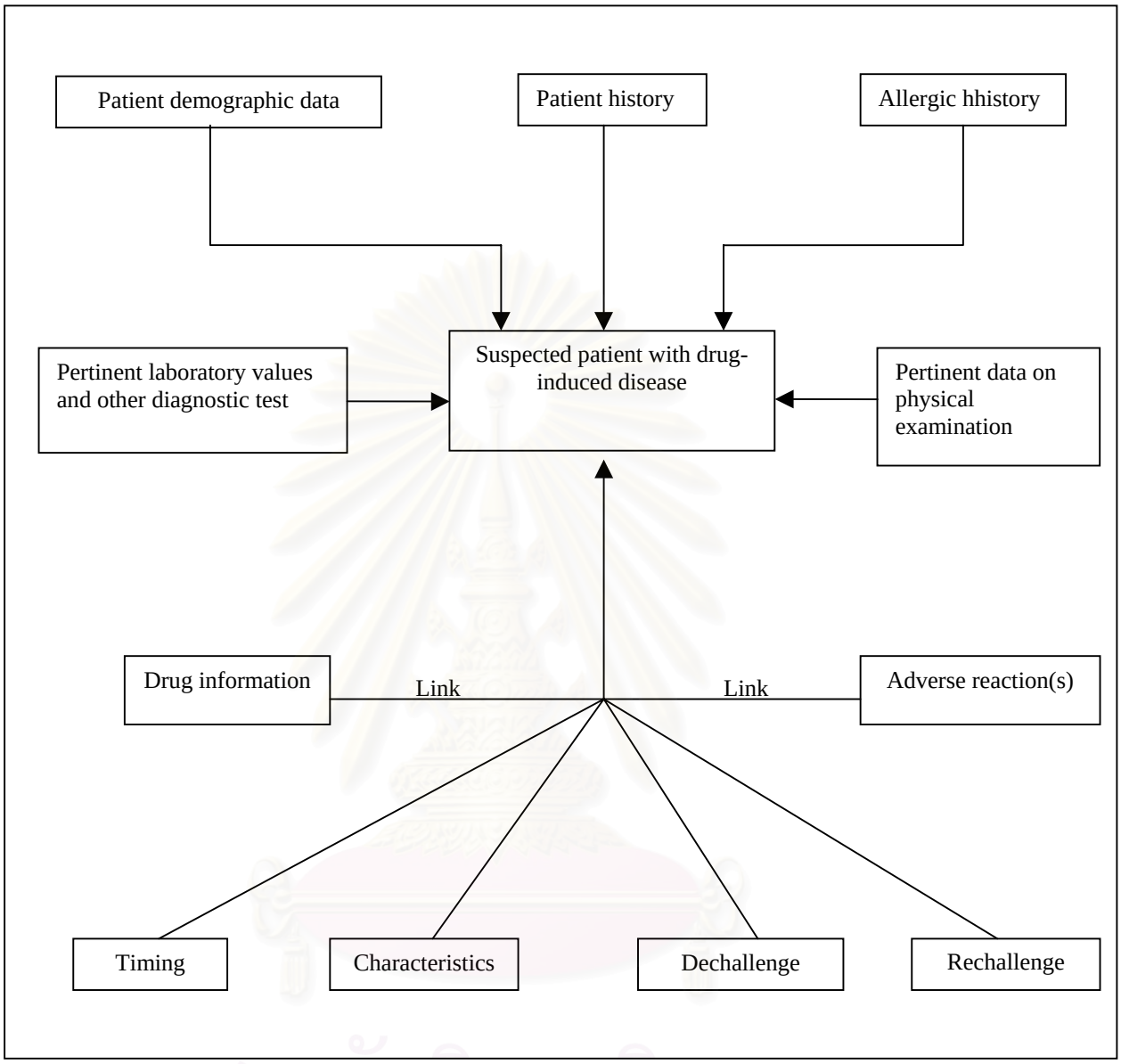


Figure 1.1 *The conceptual framework of evaluating patient with drug-induced disease*

In general, establishing a causality of a certain adverse hematologic drug reaction is challenge for many clinicians. The diagnosis of this reaction is a part of the differential diagnosis in a patient. To assess an adverse drug reaction existing in a patient, most clinicians practically consider all circumstantial evidences of the patient. They have to review and gather patient's data including history (i.e., the information of patient's previous illness or predisposing condition, present or concurrent illness, past medical illness, drug use history) , physical assessment, working diagnosis, laboratory results, other diagnostic tests as well as medication use. These evidences can help the clinicians to rule out the alternative

etiologies that may cause this event. In addition, the clinicians should link the information of either adverse reaction or suspected drug, such as 1) time relationship between drug and reaction 2) characteristics of this adverse reaction 3) alternative drug etiologies causing this reaction 4) dechallenge 5) rechallenge and finally, previous report of the suspected drug causing this event (Figure 1.1). The data as described above is essential for clinicians to evaluate the patient with drug-induced blood dycrasias.

CHAPTER II

CAUSALITY ASSESSMENT METHODS

In everyday clinical practice, adverse events associated with the use of medicine can lead to hospitalization, permanent disability and even death. Each year drug-induced diseases are the cause of significant morbidity and mortality. While most adverse events are predictable and can be anticipated, others are unpredictable, especially rare fatal idiosyncratic reaction.

The occurrences of adverse events report that between 3% and 11% of hospital admission. [21] The chance a patient will experience a drug-induced diseases during hospitalization ranges from 1% to 44%,[22,23] depend on the type of hospital, definition of an adverse event, and study methodology. [24] A substantial portion of drug-induced diseases are potential avoidable. [25,26]

When faced with a suspected adverse drug reaction, it is vitally important to try to find out whether the new clinical event in patient could be due to a medicine. The assessment of causality of drug-induced disease poses problems for clinician, including clinical pharmacists. The diagnosis of an adverse drug reaction is part of the broader diagnosis in a patient. If a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction. A complete drug history, including over-the-counter drugs, products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse), and long-term treatment that patient may forget (such as oral contraceptive), is critical to this process. [27] As the patient is taking several medicines, the problem is to distinguish which, if any, is causative. This problem is complex, because some of the patient's complaints might be due to other disease or to one or more of the drugs. In addition, defining the relationship between drug expose and the occurrence of an event is not easy, since drug-induced adverse effect may act through the same physiological and pathological pathway as normal disease. So they are difficult to distinguish and confirm a conclusion.

Generally, clinicians will not diagnose drug-induced diseases if there is inadequate evidence. [28] Correspondingly, if the evidence is clear, one should not hesitate to make the diagnosis confidently. Some clinicians [22,29] have suggested the step-wise process that to be helpful in assessing for a possible drug-related adverse event, as follows:

Step 1. Ensuring the drug ordered is the drug received;

Step 2. Ensuring the drug was actually taken;

Step 3. Verify that the onset of the event was after the drug was taken, not before;

Step 4. Determining the time interval between the beginning of drug treatment and the onset of the event;

Step 5. Dechallenge – stopping the drug and monitoring the patient's status, looking for improvement;

Step 6. Rechllenge – if appropriate, restarting the drug and monitoring for recurrence of any adverse events.

Step 7. Using personal experience as the clinical and relevant resources of drugs and adverse drug events (ADEs). The drug manufacturer can also be a resource of consultation. However, type B (unpredictable) reactions occur rarely which corroboration through clinical experience or the medical literature is difficult;

Step 8. Being aware of drug-drug, drug-food, and drug-device interactions, as a number of patients, especially in the hospitals, are taking multiple medications;

Step 9. Quantifying the drug levels if at all possible – some drugs will remain in the body for weeks after the drug is stopped.

In addition, the diagnosis of causality of drug-induced disease should consider the pattern recognition. [27] The pattern of the adverse effect may fit somehow the known pharmacology or allergy pattern of one of the suspected medicine or of chemical related or pharmacological related compounds. This information may be reported in the medical and pharmacotherapy literatures. However, it should not be used to rule out an association, particularly with a new medicine, since an adverse drug reaction may not be known, or even predictable, from the pharmacology. Next, one should consider the background frequency of the event and how often it is associated with the drug. For example, aplastic anemia has a low background incidence and is often associated with medicines; it is therefore more likely to be an adverse drug reaction. Besides, the clinicians should work out other relevant investigation [27] (such as plasma drug level, biopsies, or allergic tests) that can contribute to

the diagnosis, and also baseline parameters of organ functions (e.g., liver, kidney, or thyroid function) should be performed to anticipate an adverse drug reaction. Meanwhile, consequences to the patient after change in therapy should be prior considered and monitored. Nevertheless, such anticipation is of no help in some cases; for example, the white-cell count during carbimazole or methimazole therapy does not predict neutropenia, which can be diagnosis only when it occurs.

Several tests are performed to detect adverse drug events. Among them are unstructured open-ended questionnaires, using several physiologic measurements to fill out the questionnaires; structured questionnaires, which are symptom checklist with varied degrees of sophistication; and specialized tests, depending on the nature of the adverse event (e.g., liver biopsy and other tests). The systematic application of all these procedures generates an incredible amount of data, but there is still a need to determine whether there is a relationship between the administration of the drug and the occurrence of adverse reaction.

Causality assessment intends to systematically study the drug and the manifestations of adverse events to determine whether the particular association is causal or coincidental. The assessment of the causality of adverse events is usually accomplished through two procedures. The first, called global introspection, assesses the pattern of the drug-adverse event association. The second and more recent approach is the use of standardized causality assessment procedures of individual case report.

Global introspection has the following limitations: [30]

1) The ability of the human brain to make unaided assessments of uncertainly in complicated situations is poor.
2) Global introspection produces an answer that does not allow identification of the sources of disagreement.
3) Global introspection depends on implicit judgements for combining information about factors.
4) Global introspection depends on clinical judgement and experience.
5) Global introspection leads to frequent disagreements.
6) Global introspection cannot be accurately calibrated.

Because of the problems associated with this procedure, a number of standardized decisions aids for assessing adverse events have been proposed in recent years. Standardized decision aids are questionnaires or algorithms that try to systematically assess the factors needed for evaluating causality of adverse drug reactions. The first standardized method was developed by Karch and Lasagna in 1977. Table 2.1 shows a partial list of the standardized decision aids which are commonly used in clinical settings, researches, drug companies or regulatory agencies. These standardized decision aids vary from one that only has ten questions or less such as Karch and Lasagna [(9)] to ones that are fairly extensive and complicated such as proposed by Kramer et al. [(10)]

Standardized decision aids all share a common basic structure. They ask the user to answer a standard set of questions based on information about the case, combined with the background information according to his/her existing knowledge or obtain from a reference work. Although the authors of most methods intend that their questions have an objective or operational character, in fact that least some of the questions in all of the methods required considerable subjective judgement on the part of the assessor. In some methods, a score is assigned to each factor or axis on the basis of the user's responses to the appropriate questions, and these scores are merged, usually by simple addition. This final score is then interpreted as a probability category (e.g., "definite", "probable", "possible", or "unlikely"): the category describes the chance that the suspected drug caused the adverse event, within these methods, criteria are similar, but their gradation and weighting are different. When the same information is assessed by several methods, the conclusions are conflicting. These lead to the weakness and the nonreproducibility of most causality assessment methods.

Standardized decision aids have several advantages compared with global introspection. The advantages are standardized procedures facilitate the communication between those assessing adverse drug reactions, and several studies have conclusively shown that these procedures improve the reproducibility of assessments within and between raters. Moreover, standardized decision aids have helped to identify the relevant factors needed for performing causality assessment. It is important to emphasize that standardized decision aids currently available improve reproducibility because they control for the factors considered in each assessment, for the case information considered, and because they give a specific procedure for combining the evidence.

Nevertheless, none of them is completely satisfactory. Standardized decision aids have some problems and thus some of them have not been widely accepted. The main sources of disagreement come from what are called the judgmental questions. Moreover, some of them are too time-consuming, and therefore they may not be able to be applied to every single case of adverse event such as the Kramer's method.

Other major problems of causality assessment methods are: 1) they pretend to be applied to all adverse drug events, and 2) they propose levels for the various criteria but do not clearly define their limits. In order to try and resolve these issues, the Roussel Uclaf established an international consensus on causality assessment in 1989. A consensus reached on the definition of adverse reactions on the limits of the various chronological criteria and on the evaluation of the clinical context to reduce the individual interpretation and ensuring an excellent reproducibility. Moreover, a first international consensus on drug-induced liver disorders has also been established.

Table 2.1 *The characteristic of the algorithms*

Type	Characteristic description
Karch and Lasagna, 1977 [9]	This algorithm consists of a set of three-decision tables, namely 1) Identification of potential drug-related event 2) Assessment of link between agent and event 3) Cause if agent-related event These tables were designed to be applicable to wide variety of clinical circumstances. Karch and Lasagna stated that these tables were only the first step to the development if an objective system for assessing ADRs and not to achieve 100% accuracy. However it provided a framework for systematic evaluation of potential ADRs and it could reduced the ambiguity in the assessment of ADRs.
Kramer, 1979 [10]	This algorithm comprises six major axes of decision strategy, with a scoring system incorporated into each axis. The six decision strategies consist of: 1) Previous general experience with drug 2) Alternative etiology 3) Timing of adverse event 4) Drug levels and evidence of drug overdose 5) Dechallenge 6) Rechallenge Each axe comprises a complex detailed series of 'yes' or 'no' questions. After applied in each axis, the score of each axis is summed as total score. This

Type	Characteristic description
	total score is assigned as a probability category according to the following ordinal partition: +6 to +7 = Definite +4 to +5 = Probable 0 to +3 = Possible < 0 = Unlikely
Naranjo, 1981 [11]	This algorithm involves 10 questions concerning the following area: 1) Reported incidence of ADR 2) Timing of ADR 3) Dechalleng 4) Rechallenge 5) Alternative etiologies 6) Placebo rechallenge 7) Drug concentration 8) The severity of ADR when the drug dose was increased or decreased 9) The similarity of ADR when taking the same drug 10) Objective measurement of ADR The answers in this algorithm correspond with weighted numerical values that are summed to give a total score. ADR is assigned to a probability category from the total score such as follows: >8 = Definite 5–8 = Probable 1-4 = Possible <1 =Doubtful
Jones, 1982 [12]	This algorithm is more simplified algorithm, which includes area of ADR timing, dechallenge, rechallenge and alternative clinical condition. It is used by US FDA's Division of Drug Experience to determine the causality of ADRs. The response to any of the first three questions will result in following categories: remote, possible, probable or highly probable.
RUCAM, 1993 [13]	The content of this algorithm has been defined by experts in medical field and convened to organ-oriented ADR. The scale in each criterion is ranged from –3 to +3 which corresponding to the probability level of evidence. This algorithm consists of 7 axes, such as follows. 1) Time to onset: This criterion is attributed to the widest range (-3 to +3). The role of the drug must be ruled out by an incompatible time to onset. 2) Time of reaction course 3) The score of risk factor for the occurrence of adverse reactions does not exceed 2 point.

Type	Characteristic description
	4) Screening for non-drug causes. 5) Screening for concomitant drug causes. 6) Concerning previous knowledge of ADRs confirmation
Maria and Victorino, 1997 [14]	This algorithm was developed for evaluation patient with suspected drug-induced liver injury. It comprises several questions, namely: 1) Temporal relationship between drug intake and the onset of clinical event A: Time from drug intake until the onset of first clinical or laboratory manifestations B: Time from withdrawal of the drug until the onset of manifestations C: Time from withdrawal of the drug until normalization of laboratory values 2) Exclusion of alternative causes 3) Clinical manifestations 4) Intentional or accidental re-exposure to the drug 5) Previous report in the literature of cases

In each method, the basic key pieces of information required for such evaluation are:

1) The timing of the event in relation to drug administration: The time relationship between the use of the drug and the occurrence of the reaction should be assessed. And they plausibly linked? [27]
2) The response of the patient to removal of the drug.
3) The known potential of the drug to produce the event.
4) The available of alternative explanation for the event (concomitant medication or intercurrent illness).
5) The outcome of rechallenge if this occurred.

CHAPTER III

DRUG-INDUCED BLOOD DYSCRASIAS

Blood dyscrasias, any abnormality of the formed elements of blood or the clotting constituents, has always been a risk of drug therapy. These abnormalities can affect any blood cell line such as red blood cells, white blood cells and platelets.

Hematopoiesis

Blood is a suspension of cells in plasma, which is a solution of protein and salts. The hematopoietic system consists of three primary cell components: red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes). [31,32]

- Red blood cells (RBCs) are anuclear cells containing hemoglobins that carry oxygen from lung to body tissue and transfer CO_2 from tissues to the lung. RBCs have a life span of 120 days. At the end of their life, they are removed from circulation to the spleen, liver and bone marrow by phargocytes.
- White blood cells (WBCs) contain two major types: 1) Granulocytes (neutrophils, eosiniphils and basophils) and 2) agranulocytes (lymphocytes and monocytes). Their functions are to fight infection, defend the body from foreign organisms and produce anti-bodies.
- Platelets are necessary for clotting formation. They form plugs with coagulation proteins in the plasma to stop leaks from the blood vessels.

Hematopoiesis [33] is defined as the formation and maturation of blood cells and their derivatives. In human, blood cells originate in the bone marrow and are derived from the hematopoietic stem cells which give rise to hematopoietic progenitor cells (i.e., lymphoid and myeloid progenitor cells). The lymphoid progenitor cells differentiate further into T-cells and B-cells, whereas the myeloid progenitor cells are activated by colony stimulating factors (CSFs). These triggers are the synthesis of red blood cells, white blood cells and platelets (Fig 3.1).

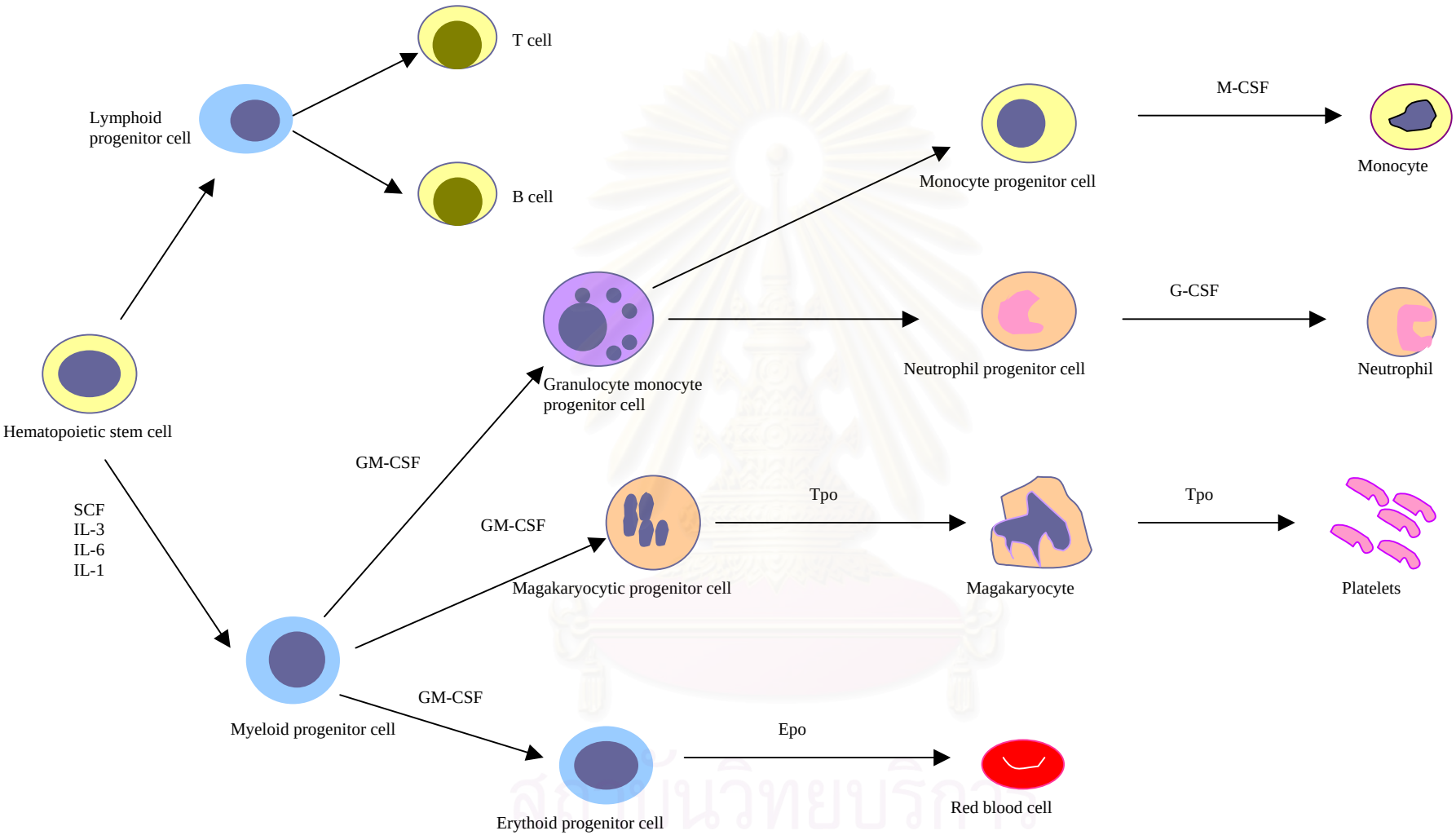


Fig. 3.1 *Hematopoiesis and hematopoietic growth fractors*

Drug-induced Blood Dyscrasias

Blood dyscrasias have always been associated to drug therapy. Any cell line can be affected in drug-induced hematologic disorders [34], including red blood cells, white blood cells and platelets (Figure 3.2). Hematologic abnormalities that affect the red blood cells result in anemia. Abnormalities that affect the white blood cells are referred to an agranulocytosis or granulocytopenia, and leukopenia. When the platelets are specifically affected, the term used is thrombocytopenia. Blood dyscrasias that affect all three cell lines can be classified as pancytopenia and aplastic anemia. There are many drugs causing predictable events, such as anti-neoplastic agents, as a result of their major pharmacologic effect. The others are idiosyncratic reactions not directly related to the drug's pharmacology. The most common drug-induced blood dyscrasias to be presented [20] are hemolytic anemia, aplastic anemia, neutropenia or agranulocytosis and thrombocytopenia. Their definitions are shown in Table 3.1.

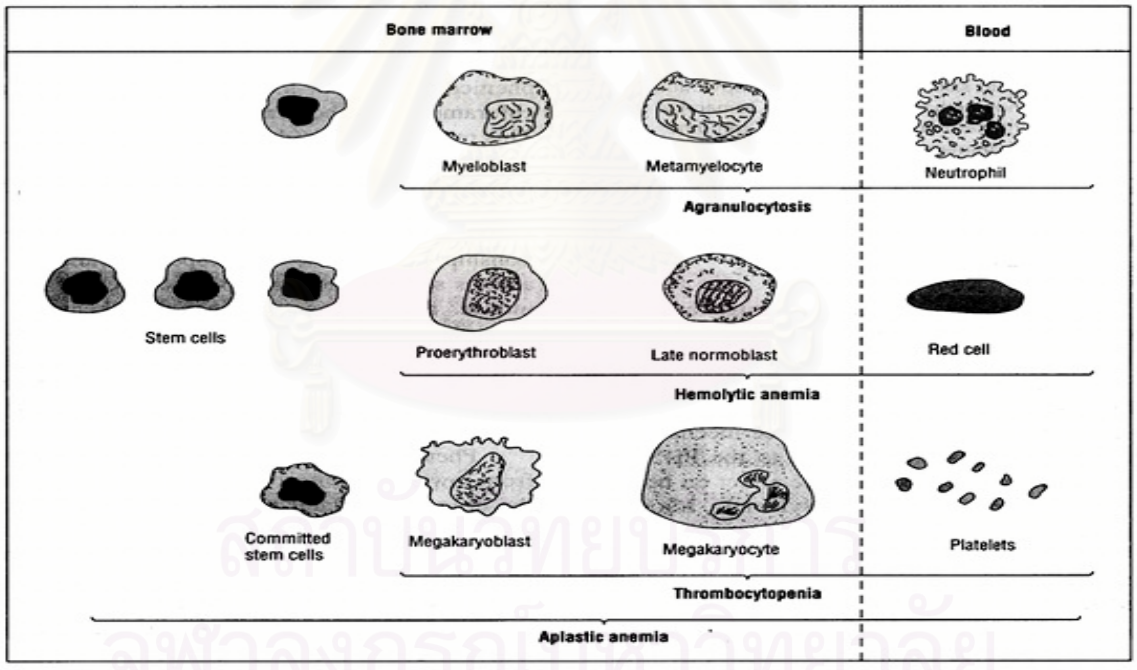


Figure 3.2 *Differentiation of stem cell to committed cell lines, illustrating the origins of various drug-induced hematologic disorders*

Table 3.1 *Definitions of blood dyscrasias* [5,35,36]

Type of dyscrasia		Definition
Anemia	:	A reduction in number of red blood cells per mm^3 or decrease in hemoglobin concentration below that necessary for tissue oxygenation
Hemolytic anemia	:	Hemoglobin ≤ 10 g/dL, reticulocyte count > 150,000/mm^3 (reticulocytosis), hyperbilirubinemia with marked predominance of unconjugated (indirect) bilirubin, increased levels of serum LDH, increased levels of serum iron, clinical: fever, back pain, chills, headache, vomiting, shock.
Aplastic anemia	:	Neutrophil (PMN) count ≤ 1500/mm^3(if not differential count, white blood count ≤ 3000/mm^3); Platelet count < 100,000/mm^3 ; Hemoglobin ≤ 10 g/dL; suggestive bone marrow biopsy (probable aplastic anemia if based only on bone marrow aspiration)
Pancytopenia	:	As for aplastic anemia, but no bone marrow biopsy performed
Bicytopenia	:	Two criteria of aplastic anemia
Leukopenia	:	White blood cells ≤ 3000/mm^3 (if not differential count)
Neutropenia	:	Neutrophil (segmented polymorphonucleocytes and band form) count ≤ 1500/mm^3
Severe neutropenia	:	Neutrophil count ≤ 500/mm^3
Agranulocytosis	:	Neutrophil count ≤ 500/mm^3; clinical symptoms present, including high grade fever, severe asthenia, sore throat, buccopharyngeal and/or perianeal ulcers.
Granulocytopenia	:	Granulocytes (neutrophils, eosinophils and basophils) ≤ 1,500/mm^3
Thrombocytopenia	:	Platelet count < 100,000/mm^3

Limited number of epidemiologic [3,4,37-41] studies have shown that the incidence of drug-induced blood disorders, although in general rarely incidence, they are important because they can be irreversible and/or life-threatening reactions which are associated with significantly high morbidity and mortality.

These reactions are needed early detection to prevent evolution progress to more severe abnormalities and to avoid the recurrence of new episodes. (Table 2.2).

Table 3.2 *The incidence and mortality rate of drug-induced blood dyscrasias* [3,4]

Type of dyscrasia	**Incidence (case/million persons/year)**	**Mortality rate (%)**
Aplastic anemia	0.5	46-50
Agranulocytosis	3.1	9-32
Hemolytic anemia	1.6	4
Thrombocytopenia	2.7	3

Drug-induced Hemolytic Anemia

Definition

Drug-induced hemolytic anemia refers to an increased rate of red blood cell (RBC) destruction, which caused directly or indirectly by drugs. [2] The causes of drug-induced hemolytic anemia can be divided into two categories, immune or metabolic. Patients with drug-induced hemolytic anemia can present with signs of intravascular (RBC destruction can occur within blood vessels) or extravascular hemolysis (RBC destruction occurs outside blood vessels). [1,2,34]

Normal red blood cells have a life span of 120 days before phagocytic cells of the liver and spleen remove them. [1,32,42] Red blood cells can be prematurely destroyed via hemolysis; certain drugs can promote this reaction by causing abnormalities on the intravascular environment and/or defects of the red blood cell membrane. The greatest clinical concern occurs when the rate of RBC destruction exceeds that of erythropoiesis. The hemolysis process may occur chronically or acute episode. Generally, acute hemolysis is considered a more clinically threatening event. A number of drugs can induce hemolytic anemia. [2] Many of these drug-induced hemolytic reactions can involve the immune system. [43] Some drug-induced this reactions relate to genetic deficiencies.

Pathogenesis

Drug molecules are potentially antigenic, but generally are too small to elicit antibody production by themselves. Drug-induced immune hemolytic anemia can occur when certain drugs interact with the RBC membrane, causing the cell to become antigen (the body identifies the cell as being foreign). [1,2,34,44] Antibodies form against the RBCs and they are removed from the circulation or lysed via the complement cascade. This occurrence is idiosyncratic (i.e., patients cannot be identified). Most immune-mediated drug-induced RBC destruction occurs extravascularly. [44]

The three basic mechanisms [2,44] by which drugs are thought to cause immunologic hemolytic anemia are 1) an autoimmune reaction, 2) a high-affinity hapten-type reaction, and 3) a low-affinity hapten-type reaction or immune complex formation, also known as an “innocent bystander reaction”. (Table 3.3)

Table 3.3 *Mechanism of drug-induced hemolytic anemia* [2,34,44]

Drug induced hemolytic anemia [a,b]			
Mechanism	**Process**	**Common drug**	**Comment**
High-affinity hapten-type reaction	Drug binds tightly to RBC membrane surface; immunoglobulins then form against the drug-membrane complex	Cephalosporins, penicillin, tetracycline	Penicillin is the classic prototype of this dose-related reaction.
Low-affinity hapten-type reaction or immune complex formation (Ternary complex)	Drug binds to either a) low-affinity specific antigenic loci on the cell membrane or b) to circulating proteins to form an immune complex which adheres loosely to RBCs. Lysis via complement activation ensues.	Acetaminophen, ASA, chlorpromazine, chlorpropamide, hydrochlorothiazide, INH, PAS, probenacid, quinidine, quinine, rifampin, sulfonamides	Subsequent to hemolysis, the drug or immune complex dissociated from RBC fragments, adheres to another RBC, and repeats the process. Small doses can cause large scale hemolysis. Quinidine is the prototype drug.
Autoimmune reaction	Drug stimulates production of anti-RBC antibodies. Autoantibodies coat RBCs and extravascular lysis	Levodopa, mefenamic acid, methyldopa, procainamide	Methyldopa is the prototype drug for autoimmune hemolysis.
Nonimmunologic protein adsorption	Drug possibly alters RBC membrane. It binds strongly to RBC membrane. It may occur within a day or two after taking drug.	Cephalothin	Cephalothin is the prototype drug. Less than 5 percent of patients receiving cephalosporin develop this process.

[a] RBC = red blood cell; ASA = acetylsalicylic acid; INH = isoniazid; PAS = para-aminosalicylate sodium

[b] Drugs and metabolites generally too small to elicit antibody production except when combined with larger molecules (e.g., proteins).

Clinical Presentations

The symptoms in hemolytic anemia [20] are related to the degree of anemia produced (in relation to baseline blood count) and the severity or rapidity of hemolysis. Immune complex-mediated hemolysis frequently results in more rapid RBC destruction and more acute symptoms. Since the hemolysis is largely intravascular, large amounts of free hemoglobin may be released, resulting in hemoglobinuria and even acute renal failure due to hemoglobin renal toxicity.

Causality Evaluation

Non-drug Etiology

Immune hemolysis due to drugs should be distinguished from: [44]

- Infusion of imcompatible blood
- Hemolytic disease of the newborn
- The warm-antibody types of idiopathic autoimmune hemolytic anemia
    a) Idiopathic
    b) "Secondary"
        (1) virus and mycoplasma infections
        (2) lymphosarcoma, chronic lymphocytic leukemia
        (3) other malignant diseases
        (4) immune-deficiency states
        (5) systemic lupus erythematosus and other "autoimmune" disorders
- The cold-antibody types of idiopathic autoimmune hemolytic anemia
    a) Cold hemagglutinin disease
        (1) idiopathic
        (2) secondary
    b) Paroxysmal cold hemoglobinuria
- Tramatic and microangiographic hemolytic anemias such as,
    a) Prosthetic valves and other cardiac abnormalities
    b) Hemolytic-uremic syndrome
    c) Thrombotic thrombocytopenic purpura
    d) Disseminated intravascular coagulation
    e) Associated with immunologic phenomena (graft rejection, immune complex, etc.)

- Infectious agent
    a) Protozoa: malaria, toxoplasmosis, leishmaniasis, trypanosomiasis, babesiosis
    b) Bacteria: bartonellosis, clostridal infection, cholera, typhoid fever, and other
- Thermal injury
- Hypophosphatemia
- Paroxymal nocturnal hemoglobinuria
- Spur-cell anemia in liver disease
- Vitamin E deficiency in newborns
- Chemicals and venoms
- Drug-mediated hemolysis due to disorders of red cell metabolism, such as glucose-6-phosphate dehydrogenase deficiency
- Congenital hemolytic anemias such as hereditary sherocytosis

Drug-induced Etiology

Drug History and Review

The importance of a thorough review of the patient's drug history cannot be overlooked. In current drug profile, agents commonly associated with immune hemolytic anemia should be sought first; then a more extensive review for associations may be conducted. A temporal relationship between time from drug intake and the onset of disorder must be established. This step is of great beneficial to rule out unrelated drugs and prevent misdiagnosis of such condition.

Temporal Relationship [5,35]

	Highly suggestive	**Suggestive**	**Compatible**	**Inconclusive**	**Incompatible**
Time to onset of the reaction					
-initial treatment			From start of drug administration > 15 days		With regard to start of drug administration, reaction occurred before the 15th day unless antidrug antibodies are present in the serum
- subsequent treatment(s)	From start of drug adminis-tration ≤ 1 days				From end of drug administration, first symptoms after 1 day.
Course of the reaction					
- if the drug is continued		Aggravation of clinical signs or laboratory abnormalities		Persistence of laboratory abnormalities or no information on the course.	Improvement of laboratory abnormalities
- If the drug has been stopped		Regression of the laboratory abnormalities within 15 days		No information on the course	No change or aggravation of laboratory abnormalities after 15 days.

Drug Associated with Hemolytic Anemia

There are many drugs that can cause hemolytic anemia. Drugs frequently associated are listed in table 3.4.

Table 3.4 *Drug associated with hemolytic anemia* [34,43,44]

Drug	**Drug**
Hapten or drug adsorption mechanism	
Penicillins	Tetracycline
Cephalosporins	
Low-affinity hapten-type reaction or immune complex formation (Ternary complex mechnism)	
Amphotericin B	Quinidine
Cephalosporins	Quinine
Chlorpropamide	Rifampicin
Diclofenac	Thiopental
Doxepin	Tolmetin
Probenecid	
Autoimmune reaction	
Cephalosporins	Latamoxef
Tolmetin	Procainamide
Methyldopa	Diclofenac
Mefenemic acid	Fludarabine
Non-immunologic protein adsorption	
Cephalosporins	Cisplatin
Uncertain mechanism of immune injury	

Drug	Drug
Insecticides	Ibuprofen
Chlopromazine	Triamterene
Melphalan	Erythromycin
Isoniazid	5-fluorouracil
p-aminosalicylic acid	Nalidixic acid
Acetaminophen	Sulindac
Thiazides	Omeprazole
Streptomycin	Carboplatin

Treatment [1,34,43,44]

- Discontinuation of the causative drug may alleviate the symptoms.
- Treatment with prednisolone is the first drug therapy that may be tried.
- Possible blood transfusions with carefully typed RBCs may be useful for some symptoms.

Drug–induced Neutropenia

Definition

There are several terms that are used to refer to abnormally low numbers of white blood cells (WBCs) or leukocytes. The range for a normal white blood count is 4,500 to 11,000 cells/mm^3. [45] Leukopenia [2,5,26,41] simply describes a total WBC count of $\leq$ 3,000 /mm^3, while neutropenia refers to a neutrophil count of $\leq$ 1500 /mm^3. Agranulocytosis [2,5,20,34] is charaterized by marked reduction in the number of neutrophils ($\leq$ 500 /mm^3). It is the most severe form of neutropenia with clinical sign, [2,5,20,345] including high-grade fever, sore throat, malaise, weakness, chill and buccopharyngeal and/or perianeal ulcers. Mortality rate of agranulocytosis is about 16% [34] (higher if bacteremia or renal failure). In addition, agranulocytosis occurs more frequently in females than male, [34] with unknown reason.

Pathogenesis

There are two basic mechanisms [34] that can produce drug-induced neutropenia (Table 3.5). First reaction is immunologically mediated, either through peripheral destruction of circulating neutrophils or immune suppression of bone marrow precursors. The other mechanism is through a direct, toxic on the bone marrow precursors.

Table 3.5 *The description of drug-induced neutropenia* [20]

Definition	Mechanism (Drug)	Comment
Absolute neutrophil (i.e., granulocyte) count $\leq$ 500-1500 /mm^3	1) Immunological suppression or destruction of marrow precursors (nafcillin) 2) Direct toxicity of marrow precursors (chlorpromazine)	> 100 implicated drugs but case reports do not provide enough data to establish mechanism

Clinical Presentations

The manifestation [34,41,45] can appear rapidly, within 7 to 14 days after starting of the offending agent. The signs and symptoms include 1) signs of infection (i.e., fever, chills, sore throat, headache, 2) oropharyngeal lesion, 3) low number of neutrophil count.

Causality Evaluation

Non-drug Etiology

Information or investigations to rule out other causes of neutropenia: [5,46]

- Recent Epstein-Barr virus (EBV) infection, viral hepatitis: Viral infections are a common cause of neutropenia, due either to bone marrow suppression or to peripheral destruction. The agents commonly implicated include Epstein-Barr virus, cytomegalovirus, hepatitis A and B viruses, parvovirus, *Influenzavirus* species, and measles. [47,48]
- Human immunodeficiency virus (HIV) infection: Infection with HIV is also associated with neutropenia and approximately 70% of patients infected with HIV are neutropenic during their illness. [49] The HIV virus may not only suppress hematopoiesis but also increases the risk of acquiring other infections. Furthermore, therapy with antiretoviral agents may dramatically decrease neutrophil counts. [46]
- Any bacterial infection can cause neutropenia, but it is most commonly seen in salmonellosis, brucellosis, pertussis, and rickettsial infections. Disseminated tuberculosis is also known to cause neutropenia. It is, however, unusual in fungal infections unless the bone marrow is extensively involved, as occasionally seen with disseminated histoplasmosis. [46,50]
- Antinuclear and anti-DNA antibodies or other evidence of autoimmune diseases: Nuetropenia may be a prominent feature of collagen vascular diseases. About 50% of patients with systemic lupus erythematosis have white blood cell counts of less than 4,500 /mm^3, but severe neutropenia is unusual and should prompt a search for other causes. [46] Splenomegaly and neutropenia (Felty's syndrome) may develop in patients with rheumatoid arthritis. [46,51,52] These patients may have an absolute neutrophil count of less than 100/ mm^3 and recurrent major and minor infections. Other collagen vascular disease such as Sjögren's syndrome, polymyalgia rheumatica, and mixed connective tissue disease have been known to cause autoimmune neutropenia. [46,53,54] The specific mechanism of the neutropenia associated with collagen vascular diseases is not known; however, circulating immune complexes and antineutrophil antibodies directed against specific neutrophil antigen have been identified in these patients. [55,56]
- Any previous concomitant diseases of the blood of bone marrow: Both benign and malignant hematopoietic diseases may cause neutropenia. For example,

vitamin B_{12} and folate deficiencies cause not only neutropenia but also anemia and thrombocytopenia. [52,55,56] Megaloblastic features are essentially always present in the circulating cells and in the marrow precursors. Leukemia, multiple myeloma, and myelodysplasia may all cause neutropenia by suppressing normal myelopoiesis. [46,57,58] A marrow aspiration should be carried out to rule out malignancy and to evaluate the likelihood of an infectious cause. The finding of hilar adenopathy, hepatospleenomegaly, and a pattern of apical pulmonary infiltrates suggested the diagnosis of sarcoid. These fingings are not specific, however, and may be associated with fungal and mycobacterial infections, toxoplasmosis, viral disease, systmic lupus erythematosis, and Wegener's granulomatosis. [59] The diagnosis of sarcoidosis is one of exclusion- ruling out infectious and immune causes for the clinical findings and for the tissue granulomas. [46,60]

Drug-induced Etiology

Drug History and Review

The importance of a thorough review of the patient's drug history cannot be overlooked. In current drug profile, agents commonly associated with neutropenia or agranulocytosis should be sought first; then a more extensive review for associations may be conducted. A temporal relationship between the start of agent and onset of the disorder must be established. This step can greatly assist in ruling out many drugs and prevent misdiagnosis of such condition. Neutropenia that is drug-induced often resolves within days to weeks after discontinuation of medicine. [46]

The information should be collected in a patient with an isolated leukopenia or neutropenia to permit the most accurate assessment of causality such as; [5]

- Sex, age, ethnic group, weight, height
- Other underlying diseases of conditions, and concurrent illness
- Disease(s) for which the patient has been treated with the suspected drug(s)
- All drug treatment within the previous four weeks and all previous long- term treatment.
- Occupational and toxic exposures (e.g., radioactive source, chemotherapy, benzene, other chemicals, etc.)
- Renal and hepatic function
- Chronic consumption of alcohol

Temporal Relationship [5,35]

	Highly suggestive	**Suggestive**	**Compatible**	**Inconclusive**	**Incompatible**
Time to onset of the reaction					
-Initial treatment			During treatment	Occurrence within 30 days or discovery after 30 days from end of drug administration	Drug taken after discovery of the reaction or occurrence after 30 days from end of drug administration.
-Subsequent treatment(s)		≤ 7 days	> 7 days		
Course of the reaction					
- If the drug is continued				Return of the WBC or neutrophil count to normal range.	
- If the drug has been stopped		Increase of neutrophil count return to normal range within 1 month.	Continuing decrease in neutrophil count	Persistence of neutrophil count of less than 1500 for more than one month.	

A drug-related etiology is more probable when: [35]

- The decrease of white blood cells develops recently.
- The bone marrow examination shows: hypocellular or regenerating granulocytic series, normal morphology of the different precursors, and absence of abnormal infiltration by hematopoietic of extrahematopoietic cells.
- The drug is known to have caused neutropenia.

Drug Associated with Neutropenia/Agranulocytosis

There are many drugs that can cause agranulocytosis. Drugs frequently associated are listed in table 3.6.

Table 3.6 *Drugs associated with agranulocytosis* [24]

Drugs Associated with Agranulocytosis		
Acetaminophen	Flucytosine	Penicillamine
Acetazolamide	Fosphenytoin	Pentazocine
Allopurinal	Furosemide	phenothiazines
p-Aminosalicylic acid	Ganciclovir	Phenytoin
Benzodiazepines	Gentamicin	Primidone
β-Lactam antibiotics	Gold salts	Procainamide
Brompheniramine	Griseofuvin	Propanolol
Captopril	Hydralazine	Propylthiouracil
Carbamazepine	Hydroxychloroquine	Pyrimethamine
Chloramphenicol	Imipenem-cilastatin	Quinine
Chlopropamide	Imipramine	Rifampin

Drugs Associated with Agranulocytosis		
Cimetidine	Isoniazid	Streptomycin
Clindamycin	Levodopa	Sulfonamides
Clomipramine	Lincomycin	Sulfonylureas
Clozapine	Meprobamate	Thiazide diuratics
Colchicine	Methazolamide	Ticlopidine
Dapsone	Methimazole	Tocainide
Desipramine	Methyldopa	Vancomycin
Doxycycline	Metronidazole	Zidovidine
Ethacrynic acid	Nitrofuratoin	
Ethosuximide	NSAIDS	

Treatment [1,2,3,5,20,34,35]

- Removal of the offending drug. After discontinuation of the drug, most cases of neutropenia will resolve over time. The time to recovery of the granulocyte count range from 3-15 days.
- Symptomatic treatment, such as antimicrobial agents for infection, may be necessary.
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF, may be used to decrease the time period of neutropenia.

Drug-induced Thrombocytopenia

Definition

Cases of suspected drug-induced thrombocytopenia are frequently reported to spontaneous adverse drug reaction reporting system. [38,61,62] Thrombocytopenia is defined as decrease in platelet count to $\leq$ 100,000/ mm^3 (normal value 150,000 to 450,000/mm^3) or a decline on platelets > 50 % from baseline [1,5,35], which may lead to bleeding disorder.

Pathogenesis

There are two mechanisms of drug-induced thrombocytopenia: [1,20]

1. Immune mediated reaction

In immune-mediated drug-induced thrombocytopenia, there is an increase number of megakaryocytes in the bone marrow as a result of increase destruction of peripheral platelets by antiplatelet antibodies. Development of antiplatelet antibodies most commonly involves IgG but IgA and IgM have also been implicated. Symptoms and degree of thrombocytopenia are very severe (< 10,000/mm^3) with a rapid onset (6-12 hours after re-exposure). The implicated drugs such as NSAIDs, heparin, carbamazepine, phenytoin, methyldopa, quinidine, quinine, valpoic acid have been reported.

2. Direct toxicity reaction

Direct bone marrow suppression can decrease production of platelets. It is mainly associated with antineoplastic drugs resulting from a dose-dependent effect, but other agents (i.e., orally administered furosemide and thiazide diuretics) have been associated with this mechanism. The thrombopoiesis suppression, seen with a direct toxicity mechanism, can be confirmed with a decrease of megakaryocytes within the bone marrow finding.

Clinical Presentations

The manifest presentation [1,2,3,5,20,,34,35,63] is symmatric petechiae (small red macules) and purpura (dark red-purple discoloration of the skin) on extremities and trunk, mild to moderate bleeding of mucosal surfaces (includes oropharynx, nose, GIT, pulmonary system and genitourinary system) as well as easy or spontaneous bleeding. Symptom and degree of severity depend on the number of platelet counts, such as 1) mild with few symptoms

(platelet counts < 100,000 and ≥50,000/mm^3), 2) moderate with some bleeding potential (platelet counts < 50,000 and ≥ 2,000/mm^3), 3) severe spontaneous fatal bleeding (platelet counts 10-20,000/mm^3). Wazny and Ariano [64] suggest the algorithm for identifying mechanism of drug-induced thrombocytopenia, as shown in figure 3.3.

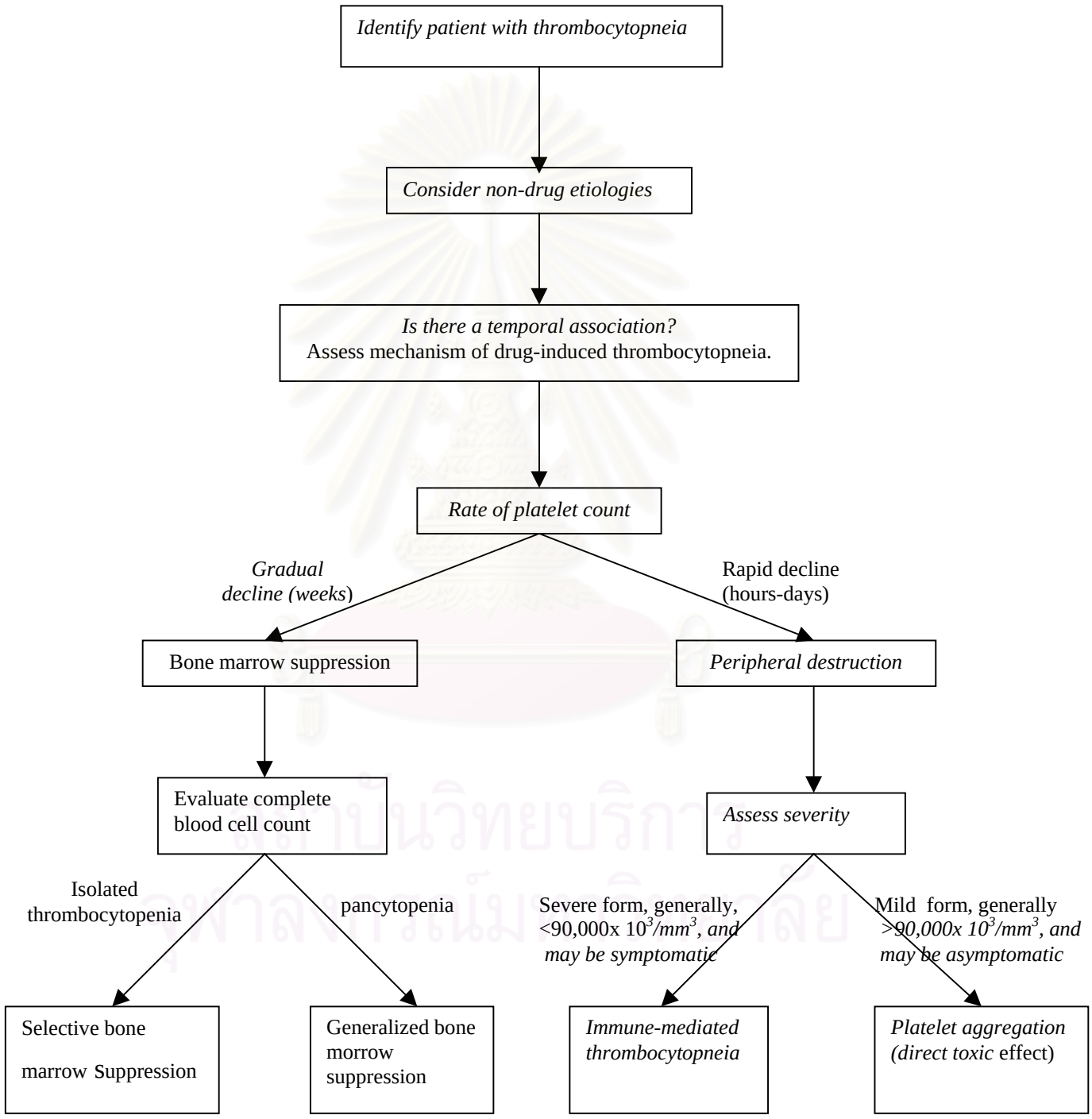


Figure 3.3 *Algorithm for identifying mechanism of drug-induced thrombocytopenia* [64]

Causality Evaluation

Non-drug Etiology

In establishing the diagnosis of drug-induced thrombocytopenia, nondrug etiologies must be considered first. After a thorough and careful review of the following non-drug etiologies [64], the clinician will obtain appropriate be better data for approaching the patient.

- History of drinking alcoholic beverages or chronic alcoholism: Selective bone marrow suppression secondary to alcohol.
- Human immunodeficiency viral (HIV) status: thrombocytopenia may occur at any stage of immunodefiency; 11 % of HIV positive patient and 24-45 % of individuals with the acquired immunodeficiency syndrome have platelet counts below $100x10^3/mm^3$; thrombocytopenia is often asymptomatic, but bleeding abnormalities may be presented.
- Splenomegaly: platelets are shifted into the spleen, and the platelet count appears low despite normal or increased total numbers; may occur in portal hypertension, sarcoidosis, lymphomas, Gaucher's disease, and Felty's syndrome.
- Increased prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrin split products (FSP), and decreased fibrinogen: suggests a DIC profile.
- Presence of prosthetic heart valves, artificial vascular grafts, Swan-Ganz catheters, or artificial heart implantation: platelet damage by abnormal vascular surface; thrombocytopenia is rare, as increased platelet production occurs to offset removal of damaged platelet destrution by a nonimmunologic mechanism.
- Blood transfusion within past week: rarely, purpura may develop within 1 week of tranfusion; it usually occurs in patients with a history of tranfusion or in women who have pregnancy.
- Massive blood transfusions: thrombocytopenia may develop due to infusion of nonviable platelets in stored blood; administering 1 unit of fresh blood for every 5 units stored blood may prevent this.
- Postdecompression sickness in divers: intravascular platelet aggregation.
- Systemic lupus erythematosus: patients may develop thrombocytopenia in months or years before other symptoms appear; autoimmune hemolytic anemia is often present.

- Viral infections (infectious mononucleosis, vericella, rubella): thrombocytopenia is usually subclinical, but severe thrombocytopenia and bleeding may develop in rare circumstances; high levels of IgG may be present.
- Acute hepatitis: high levels of IgG may be present.
- Hyperthyroidism: thrombocytopenia due to enhanced reticuloendothelial phagocytosis.
- Chronic lymphocytic leukemia, Hodgkin's disease, other lymphomas: abnormalities in white blood cells; platelet antibodies are uncommon.
- Sepsis: thrombocytopenia is commonly associated with both gram-negative and gram-positive sepsis.
- Surgical procedures requiring extracorporeal circulation pumps: thrombocytopenia results from platelet injury during passage through the pump; platelet counts are usually 50-100x10^3 /mm^3; rarely associated with severe bleeding; treat with blood or platelet transfusions.
- Microangiopathic processes [thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS)]: blood smear reveals nucleated red cells with schistocytes and microspherocytes; decreased haptoglobin levels; slight elevations in FSP and thrombin time; severe renal failure and hypertension are common with HUS.
- Concomitant anemia: red blood cell fragments on peripheral blood smear suggest a microangiopathic process (e.g., TTP, HUS) or may be due to folate or vitamin B_{12} deficiency.
- Aplastic anemia: thrombocytopenia may be an initial sign of anemia and granulocytopenia.
- Hypothermia: temperatures below 25 °C used in certain surgical procedures may produce a mild, reversible thrombocytopenia; in some patients the disorder may persist.
- Uremia: thrombocytopenia has been documented in 50% of uremic patients, may be a major cause of bleeding in addition to the inherent platelet dysfunction associated with uremia.
- Family history of hemorrhagic problems: genetic casuse such as Wiskott-Aldrich syndrome; Alport, Epstein, Fechtner, and related syndromes; Fanconi

syndrome; “gray” platelet syndrome; Chediak-steinbrink-Higashi anomaly, among other.

Drug-induced Etiology

Drug History and Review

The importance of a thorough review of the patient’s drug history cannot be overlooked. In current drug profile, agents commonly associated with thrombocytopenia should be sought first; then a more extensive review for associations may be conducted. A temporal relationship between the start of agent and onset of the disorder must be established. This step can greatly assist in ruling out many drugs and prevent misdiagnosis of such condition.

The information is collected in a patient with an isolated thrombocytopenia to permit the most accurate assessment of causality such as; [5]

- Sex, age, ethnic group, weight, height
- Other underlying diseases of conditions, and concurrent illness
- Disease(s) for which the patient has been treated with the suspected drug(s)
- All drug treatment within the previous four weeks and all previous long term treatment.
- Occupational and toxic exposures (e.g., radioactive source, chemotherapy)
- Renal and hepatic function
- Chronic consumption of alcohol

A review of recent antineoplastic exposure should be performed as these agents commonly are associated with delayed thrombocytopenia through bone marrow suppression. This form of thrombocytopenia is often overlooked, as the drug may not appear on the patient’s medication profile.

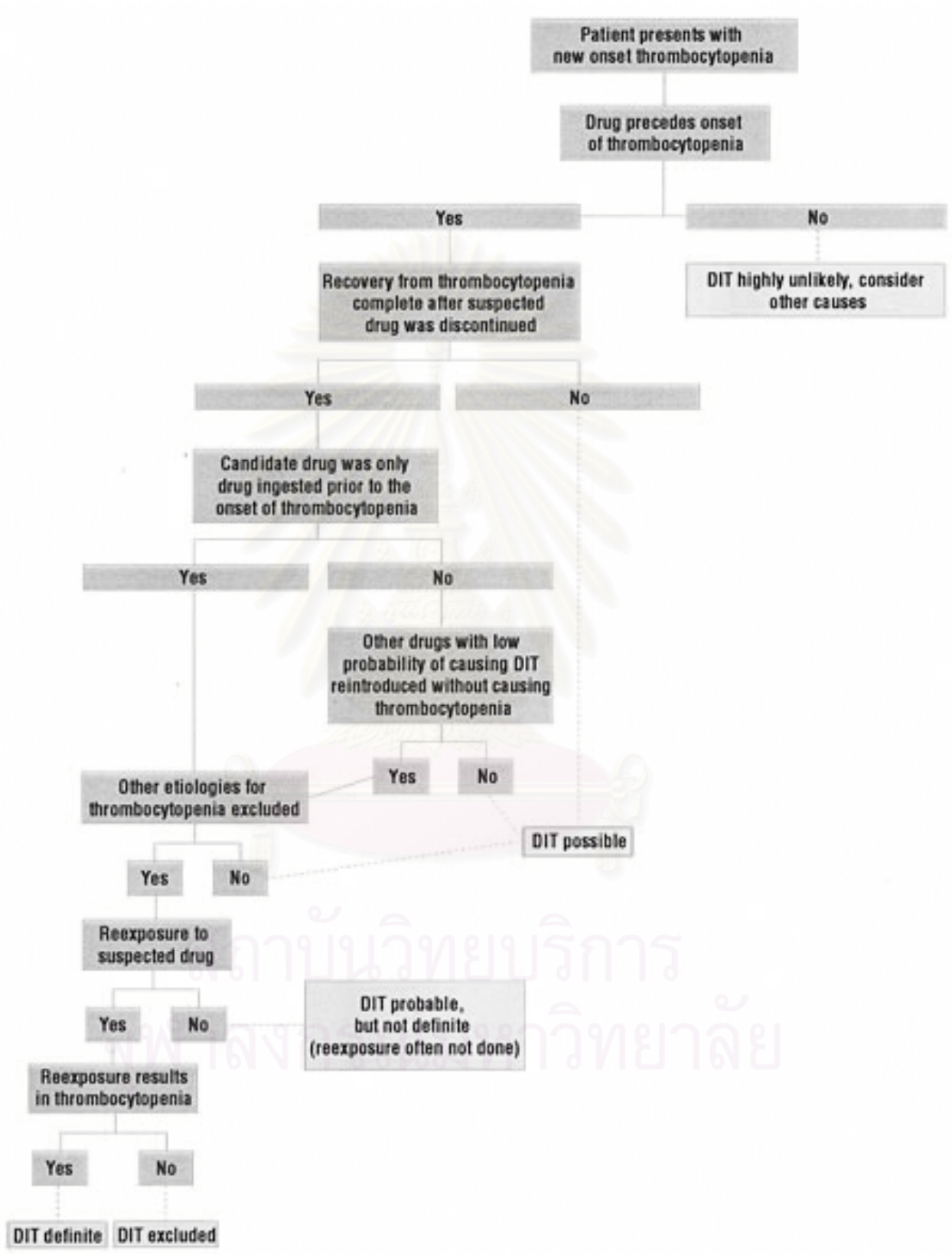


Figure 3.4 Flow diagram to evaluate drug-induced thrombocytopenia [63]

Temporal relationship [5,35]

	Highly suggestive	Suggestive	Compatible	Inconclusive	Incompatible
Time to onset of the reaction					
-initial treatment		≤1 month	>1 month	Discovery within 1 month after stopping the exposure: or discovery more than 1 month after stopping exposure if there is no information on platelet counts in the interim.	Discovery of thrombocytopenia before the beginning of the drug exposure or occurrence of thrombocytopenia more than one month after causation of exposure - i.e. platelet count was normal at least 1 month after stopping the drug.
- subsequent treatment(s)	≤ 7 days	8 days-1month			
Course of the reaction					
- if the drug is continued			Continuing decrease in platelet counts	No recovery of thrombocytopenia	
- If the drug has been stopped			Recovery within 3 weeks with or without treatment (steroid).	Recovery after three weeks with or without treatment (steroid).	Any relapse of thrombocytopenia more than 3 weeks after stopping the drug unless there has been subsequent re-expore.

A drug-related etiology is more probable when: [35]

- The bone marrow is normal and rich in megakaryocytes.
- Thrombocytopenia develops in the month that follows institution of initial treatment with a drug or in the week after subsequent treatment with the drug.
- Thrombocytopenia resolves fully and definitively within 6 week of withdrawal of the medication in the absence of symptomatic treatment (steroids).
- The drug(s) is (are) known to produce thrombocytopenia.

Drugs Related to Thrombocytopenia

There are many drugs that related to thrombocytopenia as shown in table 3.7.

Table 3.7 *Critical care agents associated with thrombocytopenia* [64]

Drug Name	No. of case reports	Mechanism
Abcixicab	7	IM
Acetaminophen	10	IM
Acetazolamide	3	IM?
Allopurinal	3	IM?
Amiodarone	2	IM?
Amphotericin B	3	BM?
Ampicillin	4	IM
Amrinone	3	PA
Antineoplastics	Well documented	BMG
Aspirin	3	IM?
Captopril	5	IM?
Carbamazepine	16	IM?
Cefotetan	2	IM
Ceftazidime	4	IM
Ceftriaxone	1	IM
Cefuroxime	1	IM
Chlorothiazide	15	BMS, IM?
Cimetidine	23	IM,BM?
Ciprofloxacin	1	IM?
Clarithromycin	1	IM?
Cocaine	12	IM?
Cyclosporine	2	IM?
Diazepam	3	IM?
Diazoxide	2	IM?
Digoxin	6	IM
Diltiazem	4	IM?
Enalapril	1	IM?
Ethambutol	2	IM?
Ethanol	Well documented	BMS
Famotidine	4	IM?
Fluconazole	3	Unknown
Furosemide	1	IM?
Ganciclovir	1	BM

Drug Name	No. of case reports	Mechanism
Gentamicin	1	IM?
Haloperidol	3	IM
Heparin	Well documented	PA, IM
Heparin, low molecular-weight	< 1 % frequency	PA, IM
Hydralazine	1	IM?
Hydrochlorothiazide	6	IM?
Interferon-α	9	BMS
Locetamic acid (contrast agent)	2	IM?
Iopanoic acid (contrast agent)	3	IM?
Isoniazid	1	IM?
Itraconazole	1	Unknown
Lidocaine	1	IM?
Methyldopa	8	IM?
Milrinone	0.4% frequency	PA
Minoxidil	1	IM?
Morphine	1	IM
Nifedipine	1	IM
Nitroglycerin	1	IM?
Nitroprusside	2	IM?
Octreotide	1	IM?
Ondansetron	6	IM?
Penicillin	2	IM
Phenobarbitol	1	IM?
Phenytoin	25	IM?
Piperacillin	2	IM
Prednisolone	8	IM?
Procainamide	12	IM
Prochlorperazine	1	IM?
Protamine	1	PA
Pyrazinamide	2	IM?
Quinidine	71	IM
Ranitidine	9	IM?
Rifampin	17	IM
Ticlopidine	2	Unknown
Tobramycin	1	IM?
Trimethoprim-sulfamethoxazole	24	BMS?, IM
Valproic acid	3	IM?

Drug Name	No. of case reports	Mechanism
Vancomycin	7	IM?

IM = immune-mediated; PA = platelet aggregation; BM + bone marrow suppression, type not specified; BMS = bone marrow suppression, megakaryocyte selective; BMG = bone marrow suppression, generalized.

For the immune-mediated (IM?) mechanism, definite evidence for antibodies is not available for the agents listed; however, clinical features suggest an immune-mediated reaction.

Treatment [1,2,3,5,20,,34,35,64]

- Discontinue the offending drug if possible, especially if immune-mediated.
- Prophylactic platelet transfusions once plate counts fall to 10,000-20,000/mm^3
- Use of corticosteroids (shorten the recovery period)
- Supportive treatment
- Tailor chemotherapy regimen to avoid simultaneous administration of drug that induced thrombocytopenia (must weigh benefits and risk)

Drug-induce Aplastic Anemia

Definition

Aplastic anemia is defined [2] as bicytopenia or pancytopenia with bone marrow biopsy showing evidence of decreased cellularity and absence of infiltration, and significant fibrosis that is unrelated to malignancy or myeloproliferative disease. It develops when hematopoiesis is interrupted due to deficient or defective stem cells. Pancytopenia[5,35] is characterized by the presence of anemia (Hb < 10 g/dL), neutropenia and thrombocytopenia. Whereas, bicytopenia is the presence of any two of these three abnormalities. Diagnostic criteria also exist for cases of bicytopenia or pancytopenia with less definitive bone marrow finding.

Although drug-induced aplastic anemia is a rare, high mortality. The incidence is 0.5-5 cases in one million and it is higher in patients taking NSAIDs. [1,39]

Pathogenesis

Mechanisms of drug-induced aplastic anemia are such as follows: (Table 3.8):

1) Idiosyncratic effect
   - Unexpected at normal does not dose dependent
   - Due to individual variation in the pharmacokinetic of the suspected drug or hypersensitivity of the stem cells to the drug
2) Dose-dependent toxic effects of hematopoiesis (e.g., antineoplastic agents or large dose of chloramphenical). These drug can suppress one or more lines and the suppression is usually reversible when remove the offending drug. The degree of suppression and cell line involved depends on the nature of the drug.

Table 3.8 *Mechanism of drug-induced aplastic anemia* [2,20]

Definition	Mechanism	Comment
Severs marrow aplastic anemia and pancytopenia (↓ or absent RBCs, WBCs, and platelets)	1) Idiosyncratic effect ▪ Unexpected at normal doses ▪ Due to individual variation in the pharmacokinetic 2) Direct toxicity to the pluripotential stem cell before process of differentiation to committed stem cells	Rarest, least understood, most serious (50 % mortality) of blood dyscrasias

Clinical Presentations

The onset of drug-induced aplastic anemia is variable. Manifestations usually appear 6 weeks after the initiation of the offending drug. The patients may present with fatigue, weakness, easy bruising, frank bleeding, stomatitis (inflamation of the mouth) and infections. These signs and symptoms are associated with anemia, thrombocytopenia and neutropenia. The diagnostic tests usually are peripheral blood counts and bone marrow biopsy which performed to exclude other causes.

Causality evaluation

Non-drug etiology

Information or investigations for ruling out other causes of pancytopenia or aplastic anemia are as follows: [65]

- Human immunodeficiency virus (HIV) infection is frequently associated with vary degree of cytopenia. The marrow is often cellular, but occasional causes of aplastic anemia have been noted. In these patients, marrow hypoplasia may result both from viral suppression and from the many drugs used to control viral replication in this disorder.
- Recent Epstein-Barr virus (EBV) infection has been implicated in the pathogenesis of aplastic anemia. The onset usually occurs within 4 to 6 weeks of infection. In some cases infectious mononucleosis is subclinical, with a finding of atypical lymphocytes in the blood film and serological results consistent with a recent infection. EBV has been detected in marrow cells but it is uncertain whether aplastic results from a direct effect or from an immunologic response by the host. Some patients have recovered following therapy with antithymocyte globulin.
- Viral hepatitis was improving or had resolved when the aplastic anemia was noted 4 to 12 weeks later. Approximately 10 percent of cases occurred more than 1 year after the initial diagnosis of hepatitis. Most patients were young (18 to 20 years), two-thirds were male, and their survival was short (10 weeks). Although hepatitis A and B have been implicated in aplastic anemia in a small number of cases, most cases are related to non-A, non-B hepatitis.
- Pregnancy: there are a number of reports of pregnancy-associated aplastic anemia. In some patients, preexisting aplastic anemia is exacerbated during pregnancy only and improve following termination of pregnancy. In other

cases, the aplasia develops during pregnancy with recurrence during subsequent pregnancies.

- Benzene was the first chemical substance which found to be linked to aplasic anemia, based on studies in factory workers before the twentieth century. The other chemical substances are such as DDT (chlorophenothene), lidane, chlordance, etc.
- Any previous concomitant disease of the blood of bone marrow
- Size of spleen
- Antinuclear and anti-DNA antibodies or other evidence of auto-immune disease: rheumatoid arthritis is not ordinarily associated with severe aplastic anemia but an epidemilogic atudy in France revealed a seven folds increasing in the incidence of aplastic anemia in patients with this disorder. It is uncertain whether the aplastic anemia is related directly to rheumatoid arthritis due to the various drugs used to treat the condition (gold salts, D-penicillamine, and nonsteroidal agents). Occasional cases of aplastic anemia are seen in conjunction with systemic lupus erythematosus. In vitro studies have suggested the presence of an antibody or suppressor cell directed againt hematopoietic progenitor cells directly against hematopoietic progenitor cells. Patients have recovered after plasma phoresis, glucocorticosteroids, or cyclophosphamide therapy, suggesting a possible immune etiology.
- Folate or vitamin B12 deficiency
- Pregnancy
- Cytogenetic test to detect malignant clonal marrow disease
- Congenital anomalies and chromosome fragility (especially in children) such as Fanconi anemia, Dyskeratosis congenita, Schwachman syndrome.
- Paroxysmal nocturnal hemoglobinuria

Drug-induced Etiology

Drug History and Review

The importance of a thorough review of the patient's drug history cannot be overlooked. In current drug profile, agents commonly associated with aplastic anemia should be sought first by; then a more extensive review for associations may be conducted. A temporal relationship between the time from drug intake and the onset of disorder must be

established. This step is of great beneficial for ruling out unrelated drugs and prevent misdiagnosis of such condition.

Temporal Relationship [5,35]

	Highly suggestive	Suggestive	Compatible	Inconclusive	Incompatible
Time to onset of the reaction					
-Initial treatment			Discovery of pancytopenia or bicytopenia more than 4 days after the onset of exposure.		Discovery of pancytopenia or bicytopenia before the beginning of drug of within four days.
-Subsequent treatment(s)			All time interval		
Time to onset from the end of the drug administration					
			≤ 120 days		> 120 days
Course of the reaction					
- If the drug is continued				No change or aggrevation	Inprovement in pancytopenia or bicytopenia
- If the drug has been stopped			Spontaneous recovery within 6 months: neutrophil > 1500 and platelets > 100,000.	No change or aggrevation or improvement with supportive therapy.	

Drug associatred with Aplastic Anemia

There are many drugs associated with aplastic anemia. The prototype of drug-induced aplastic anemia is chloramphenicol which exhibits both dose dependent and idiosyncratic mechanism. Other drugs that can cause aplastic anemia are listd in table 3.9.

Table 3.9 *Drug associated with aplastic anemia* [66]

Category	High risk	Moderate risk	Low risk
Analgesic			*Aspirin*
Antiarrhythmic			*Quinidine, tocainamide*
Antiarthritics		*Gold salt*	*Colchicine*
Anticonvulsant		*Carbamazepine,*	

Category	High risk	Moderate risk	Low risk
		hydrntoin, felbamate	
Antihistamine			*Chlorpheniramine*
Antihypertensive			*Captopril, methyldopa*
Anti-inflammatory		*Penicillamine, phenylbutazone,*	*Diclofenac, ibuprofen, indomethacin, naproxen, sulindac*
Antimicrobial			
Antibacterial		*Chloramphenicol*	*Dapsone, methicillin, penicillin, streptomycin, β-lactam antibiotics*
Antifungal			*Amphotericin, flucytosine*
Antiprotozoal		*Quinacrine*	*Chloroquine, pyrimethamine*
Antineoplastic drugs			
Alkylating agents	*Busulfan, cyclophosphamide, melphalan, nitrogen mustard*		
Antimetabolites	*Fluorouracil, mercaptopurine, methotrexate*		
Cytotoxic antibiotics	*Daunorubicine, doxorubicin, mitoxantrone*		
Antiplatelet			*Ticlopidine*
Antithyroid			*Carbimazole, methimazole, methylthiouracil, potassium perchlorate, propylthiouracil, sodium thiocyanate*
Sedative and tranquilizer			*Chlordiazepoxide, chlorpromazine (and other phenothiazines),lithium, meprobamate*
Sulfonamides and derivative Antibacterial Diuretic Hypoglycemic		*Acetazolamide*	*Numerous sulfonamides* *Chlorothiazide, furosemide* *Chlorpropamide*
Miscellaneous			*Allopurinal, interferon, pentoxifylline*

Note: Drugs that invariably cause marrow aplasia with high doses are termed high risk; drugs with 30 or more reported cases are listed as moderate risk; others are less often associated with aplastic anemia (low risk).

The information is collected in a patient with an aplastic anemia to permit the most accurate assessment of causality such as; [5]

- Sex, age, ethnic group, weight, height
- Other underlying diseases of conditions, and concurrent illness
- Disease(s) for which the patient has been treated with the suspected drug(s)
- All drug treatment within the previous four weeks and all previous long term treatment.
- Occupational and toxic exposures (e.g., radioactive source, chemotherapy)

- Renal and hepatic function
- Chronic consumption of alcohol

Treatment

Management of patients with drug-induced aplastic anemia includes removal of the causative agents. Symptomatic treatment, including starting antibiotics for infection and blood tranfusion of blood products, is usually necessary. In cases who are irreversible, immunosuppressants (antithymocyte; ATG, antilymphocyte globulin; ALG, corticosteroid, cyclosporin) and colony-stumulating factors have all been used as treatment options in appropriated cases such as the older patients or the patients without an HLA-matched marrow donor. Bone marrow transplant is treatment of choice for severe aplastic anemia.

CHAPTER IV

METHODS

Research Design

This study was a descriptive (historical retrospective) study.

Research Setting

King Chulalongkorn Memorial Hospital which is a teaching hospital.

Population

Target Population

Thai patients who were suspected of blood dyscrasias related to drug therapy including hemolytic anemia, neutropenia/agranulocytosis, thrombocytopenia and aplastic anemia.

Sampled Population

The patients suspected of drug-induced blood dyscrasias who were admitted at medical wards in King Chulalongkorn Memorial Hospital during January 1, 2001 to November 30, 2002.

Number of Subjects

The acceptable number of subjects (n) of this study was calculated by the following equation; [67]

$$n \geq 3(g)^2$$

Where: g is the number of causality measurement or judgement category. In this study, there are 4 categories of the new clinical scale, so g = 4 is applied in this equation.

So; $n \geq 3(4)^2$

$\geq 3(16)$

≥ 48

Therefore, the number of subjects for this study would be at least 48 subjects.

Eligible Criteria

Inclusion criteria

1. Inpatient whose aged > 18 years old.
2. Patients who were suspected of drug-induced blood dyscrasias (i.e., hemolytic anemia, neutropenia/agranulocytosis, thrombocytopenia or aplastic anemia,).
3. Patients who had an appropriate temporal sequence of drug administration and the onset of the adverse event, and the clinical course of patients were not consistent with the known effects of any concurrent illness or non-drug therapy.

Exclusion criteria

1. Insufficient clinical data to evaluate the relationship between drug administration and blood dyscrasias.
2. Patients who received chemotherapeutic agent(s) for treating cancer or malignant disease.
3. Pregnant patients.

Definitions of Operative Procedure

1. Adverse Drug Reaction (ADR) [27] :	WHO's definition of is a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.
2. Blood dyscrasia [2] :	The abnormality of red blood cells and/or white blood cells and/or platelets.
3. Neutropenia [2,35,36] :	Neutrophil (segmented polymorphonucleocytes and band form) count ≤ 1500/mm^3 (if not differential count, white blood count ≤ 3000/mm^3); no significant alternation of platelets, hemoglobin or hematrocrit when compare with baseline values except explained by other condition.
4. Agranulocytosis [2,35,36] :	Neutrophil count ≤ 500/mm^3; no significant alternation of hemoglobin, hematrocrit or platelets except explained by other condition; clinical symptoms present, including

	high grade fever, severe asthenia, sore throat, buccopharyngeal and/or perianeal ulcers.
5. Thrombocytopenia [2,35,36] :	Platelet count < 100,000/mm^3; no significant alternation of white blood cells, hemoglobin or hematrocrit except explained by other condition.
6. Hemolytic anemia [2,35,36] :	Hemoglobin ≤ 10 g/dl. Presence of two of these three criteria: - Clinical: fever, back pain, chills, headache, vomiting, shock - Hemoglobinuria - Reticulocytosis (reticulocyte count > 150,000/mm^3) or hyperbilirubinemia with marked predominance of unconjugated (indirect) bilirubin or increased levels of serum LDH or increased levels of serum iron or reduced serum haptoglobin level.
7. Aplastic anemia [2,35,36] :	Neutrophil (PMN) count ≤ 1500/mm^3(if not differential count, white blood count ≤ 3000/mm^3); Platelet count < 100,000/mm^3 ; Hemoglobin ≤ 10 g/dl; suggestive bone marrow biopsy (probable aplastic anemia if based only on bone marrow aspiration)
8. Pancytopenia [2,35,36] :	As for aplastic anemia, but no bone marrow biopsy performed
9. Bicytopenia [2,35,36] :	Two criteria of aplastic anemia
10. Mild Disagreement [67] :	One-level category disagreement, e.g. unlikely vs. possible
11. Moderate Disagreement [67] :	Two-level category disagreement, e.g. highly probable vs. possible.
12. Complete Disagreement[67] :	Three-level category disagreement, e.g. unlikely vs. highly probable

Methods

1. Patient recruitment and data collection

Patients who were suspected of drug-induced blood dyscrasias (i.e., hemolytic anemia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia/pancytopenia/ bicytopenia) and were admitted in Medicine Wards, Department of Internal medicine at King Chulalongkorn Memorial Hospital since January 1, 2001 to October 1, 2002 were recruited into this study. The clinical profile of each patient in medical chart and OPD card were obtained and systematically reviewed for following information: demographic data, medical history including the time of drug-induced blood dyscrasia, medication used and social history, previous and present investigations performed. This data was completely recorded in the Adverse Drug Reaction Form. (Appendix C)

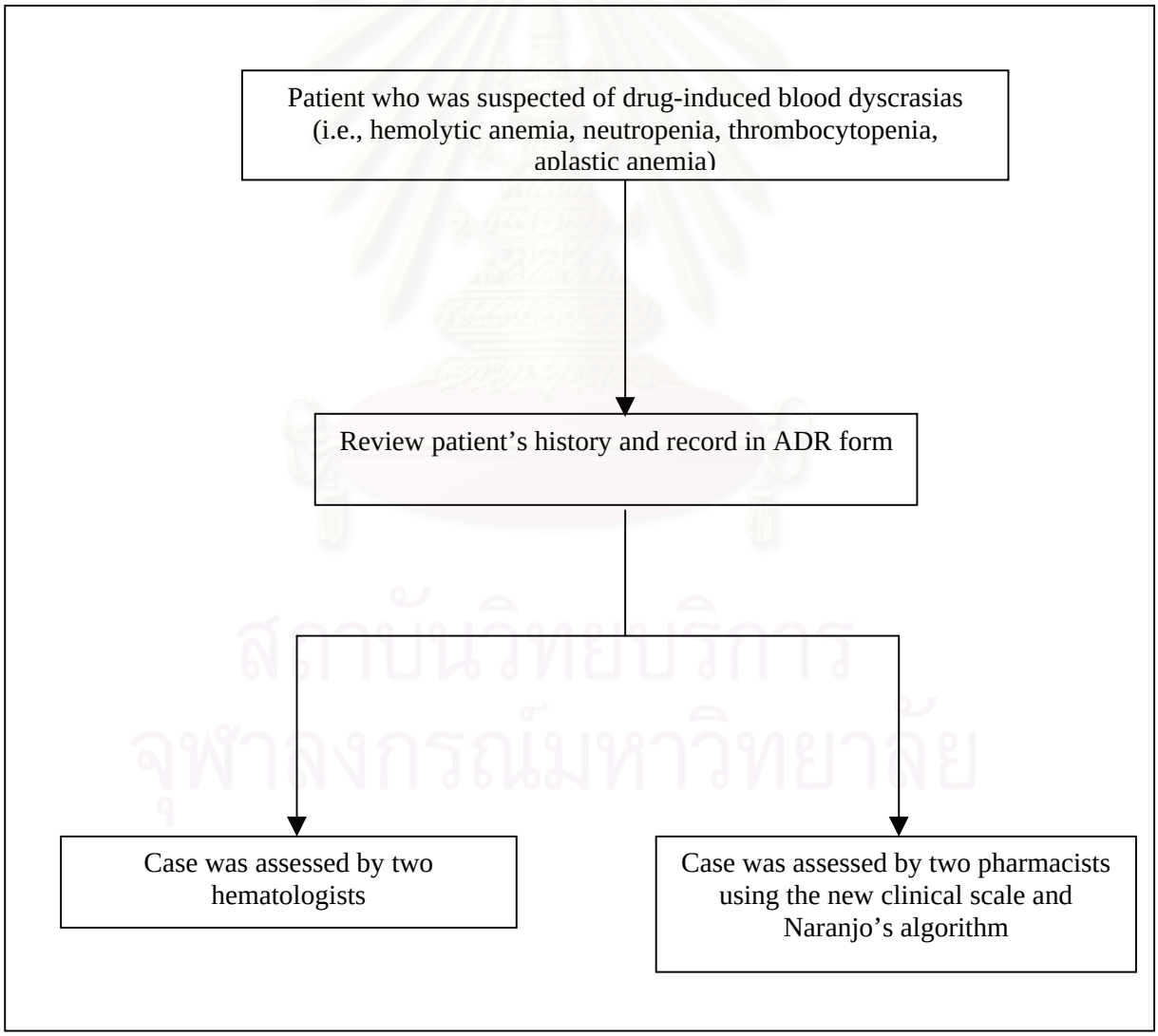


Figure 4.1 *Method of evaluating the patient with drug-induced blood dyscrasias.*

2. Establishment of gold standard

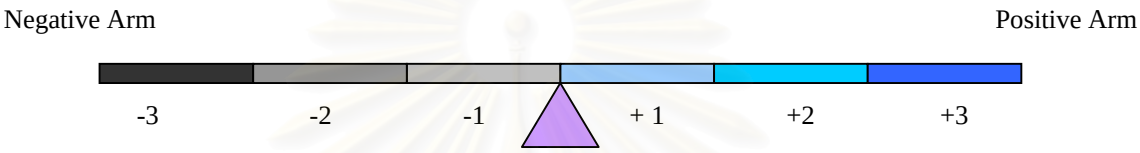
All cases were submitted to two experts who are experienced hematologists for defining the probability of ADR diagnosis according to their own opinion. The essential elements of each case including a clinical patient history, nature of adverse event, the result of laboratory tests and all relevant investigated procedures such as bone marrow biopsy, pharmacological data and patient's outcome, were presented to two hematologists. Each hematologist marked a point on the line of a visual analogue scale to rate the probability of drug-induced blood dyscrasia, as illustrated in Appendix D. This analogue visual scale was adapted from Shear's visual scale. [68] The point marked by each expert was then measured as length. The length obtained from two experts was calculated to average length. This average length was translated to be a probability rating score (i.e. unlikely, possible, probable, highly probable) by using Shear's standard rating as shown in Appendix E. This rating score was considered as an gold standard for this study.

3. Development of the new clinical scale

The new causality assessment scale was developed by utilizing several features of two previous tools, namely Roussel Uclaf Causality Assessment method (RUCAM) [13] and Maria&Victorino [14] clinical scale for which drug-induced hepatotoxicity (Appendix F and G, respectively). This clinical scale for evaluating drug-induced blood dyscrasia were developed to 4 forms, each for one certain hematologic disorder which were: immune hemolytic anemia, leukopenia/neutropenia/agranulocytosis, thrombocytopenia, and aplastic anemia/related disorders. Each form comprised the six axes of decision strategies, including 1) chronological relationship 2) exclusion of non-drug related causes 3) concomitant medications 4) clinical features 5) intentional or accidental rechallenge and 6) previous reports.

Each axis consisted of pertinent question that the clinician should try to answer it to approach the patient with drug-induced blood abnormalities. The question(s) was developed pertaining to the etiologies and characteristics of the event, which based on the medical and pharmacotherapy literatures. In addition, each axis was weighted the individual score by using a beam balance model as shown below. A score of +3, +2, +1, 0, -1, -2, -3 was used to assign for weight of evidence in each axis. The right (positive) arm had three zone (i.e., +1,+2,+3) and the opposite arm was scored –1, -2 and –3. The center point was zero score. Like playing the puzzle game, when starting the consideration of scoring system, you were

standing at the zero point and could walk three steps to the right (positive) or left (negative) side. The positive or negative score depended on whether the evidence clearly favored or opposed the identification of causative agent that could cause drug-induced blood dyscrasias. If the evidence of the patient was a strong level for ruling in the drug-induced blood dyscrasia, you could walk three steps in the right side. For example, if your patient had reexposed the suspected drug, after that he/she developed the same feature of drug-induced blood dyscrasia, therefore, this evidence was a strong level to rule in the drug-induced blood dyscrasia in this patient, the weighted score was +3.



Where;	+3	=	a strong evidence to rule in the drug-induced blood dyscrasia.
	+2	=	a intermediate evidence to rule in the drug-induced blood dyscrasia.
	+1	=	a weak evidence to rule in the drug-induced blood dyscrasia.
	0	=	a evidence is insufficient, equivocal, controversial or contradictory.
	-1	=	a weak evidence to rule out the drug-induced blood dyscrasia.
	-2	=	a intermediate evidence to rule out the drug-induced blood dyscrasia.
	-3	=	a strong evidence to rule out the drug-induced blood dyscrasia.

The development of the component details of each axis were described such as follows:

Axis 1: The chronological (temporal) relationship

We developed the content of this axis based on the consensus meeting of hematologists in 1990. [3] This axis consisted of three criteria, namely 1) criterion concerning an unrelated adverse reaction, 2) criterion concerning the onset of adverse reaction after taking the offending drug, 3) criterion concerning the characteristic course of hematologic adverse reaction after stopping the offending drug. We believed that this axis was very important because most of the adverse drug reactions had specific characteristics and could also be distinguished from non-drug reactions by time-relationship. Hence, we considered this axis as the first step to identify the causality. If you found that the time-relationship was incompatible (criterion 1), this suspected adverse event was unrelated to the culprit drug. The first criterion was like as an entrance. If you were unable to open it, you would not go ahead. So, if you considered that the blood dyscrasia was not related to the suspected drug, you did

not need to answer the next questions in other axes. We believed that this point could help the assessor to rule out the other drug and non-drug causes.

For the scoring system of the criterion 2 and 3, the levels of compatibility of the causal role of the suspected drug was based on the criteria which were proposed in the consensus meeting of hematologists. The compatibility level ranged from the highly suggestive to the incompatible level, as shown below.

Is the timing of the event related to administration of suspected drug?			Score
Time to onset of the reaction: Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
	Highly suggestive	Highly suggestive	+3
	Suggestive	Suggestive	+2
	Compatible	Compatible	+1
	Inconclusion	Inconclusion	0
	Incompatible	Incompatible	-1 to -3

Does the problem improve when discontinue the offending drug?			Score
Course of the reaction: Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
	Highly suggestive	Highly suggestive	+3
	Suggestive	Suggestive	+2
	Compatible	Compatible	+1
	Inconclusion	Inconclusion	0
	Incompatible	Incompatible	-1 to -3

Axis 2: Exclusion of non-drug related cause(s)

Each type of drug-induced blood dyscrasias had different alternative causes that should be ruled out before confirming of drug-related event. In this criterion, we listed the most common causes that should be excluded. [3,39] However, it did not mean that the blood abnormality in the patient who had these common causes was exactly occurred from these causes, it might be caused by the drug(s) that the patient received. So, the clinician should consider the positive and negative evidences of individual patient before ruling out or ruling in the alternative cause(s).

In giving score to each item, we adapted it from Maria&Victorino Clinical Scale. Some items were added or omitted as well, the features of this axis were shown as below.

We weighted the score of item 1 was equal to +3 and of item 2 was equal to +1. If there had no investigated evidences, the score of 0 was assigned. For ruling out the drug-induced blood dyscrasia, the weighted score was based on the level of evidence.

Are there any common alternative causes?	Score
Completely excluded	+3
Partially excluded with no evidences that rule in another causes	+1
Not investigated	0
Possible another cause detected	-1
Probable another cause detected	-2
Highly probable another cause detected	-3

Axis 3: Concomitant medication(s)

Apart from suspected drug, the clinician should consider other medication(s) that can cause this abnormality. To consider this criterion, the clinician should use epidemiologic knowledge concerning the incidence of blood abnormality on each drug. The drug that has a high risk may be the more causative drug than the others.

This axis was developed from the content of RUCAM and Maria&Victorino Clinical Scale. However, there had some difference points. We weighted the score of item 1 (no concomitant drug(s) or yes, if the onset is incompatible) was equal to +1 because we believed that it was only a weak evidence to identify the drug under suspicion. Moreover, we believed that the distinction between drug marketed for up to 5 years and those marketed for more than 5 years was important for weighting the probability of that drug being involved in blood dyscrasia. So, we determined the 5 years to be the cut-off time for evaluating the probability of drug-induced blood dyscrasia.

Does the patient receive another drug that may be cause this event?	Score
No concomitant drug(s) or Yes, if the onset is incompatible	+1
No documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.	0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.	-1
Yes, if the onset is compatible with known reaction.	-2
Yes, if the onset is compatible with evidence for this event.	-3

Axis 4: Clinical presentation

The clinical presentation was not the specific evidence to identify the drug-induced blood dyscrasia. So, we provided the importance of this axis less than other axis. Although our patient no have the clinical features, it did not mean our patient no have drug-induced blood dyscrasia. Therefore, the weighted score of this point was not much different (+1 vs. 0). In addition, the clinician should ask himself or herself with the following questions, " Does the patient have any classical clinical feature(s) which indicate(s) this adverse reaction?" In this axis, we list the clinical feature(s) in each type of drug-induced blood dyscrasias. Moreover, the clinical manifestation in each patient can also be the severity indicator.

Does the patient have any clinical features?	Score
Yes	+1
None	0

Axis 5: Intentional or accidental readministration

Rechallenge was frequently considered to be the most reliable test in the diagnosis of suspected cause of drug-induced disease, but it is clearly harmful and should be avoided, [21] especially in the patient with drug-induced blood dyscrasias. We believed that the word, intentional or accidental readministration, was appropriated for use in this axis. We considered that this axis was very important for identifying the drug-induced blood dyscrasia (+3 vs.-3).

Does the problem recur with intentional or accidental reexposure to suspected drug?	Score
Yes, positive rechallenge	+3
Not done or No documented	0
Yes, negative rechallenge	-3

Axis 6: Previous report

After the suspected drug had been launched into the market for 5 years, it could be believed that this drug was enough information to confirm or deny the adverse drug complication. [69] If the suspected drug had been marketed for more than 5 years with no reports of such drug-induced blood dyscrasia, the score of -2 was attributed. It meant that the probability of that drug being involved in cytopenia was reduced. In contrast, if the drug-marketed time was less than 5 years, with no previous reports concerning this abnormality, it was attributed score of 0, due to liking as unknown documentation.

Has this type of adverse event previously been reported?	Score
Yes	+2
No: drug marketed ≤ 5 years	0
No: drug marketed > 5 years	-2

Note:

The new clinical scale was applied to a blood dyscrasia that occurred after administration of a single suspected drug. If several drugs could have caused the blood dyscrasia, each drug should be assessed separately and the drug with the highest score was considered on the most likely involved in blood dyscrasia.

4. Development of the risk probability score

After a score had been given to each of the six axes, the individual score from each axis was added to get a total score which corresponding to a risk probability. Risk probability scores of the new clinical scale was developed by using the scoring system of two methods, RUCAM and Maria&Victorino clinical scale, which are methods for evaluating the patient with drug-induced hepatotoxicity. The average score in each causality category of these two methods was determined to be our probability score (Appendix J). In these consequences, we assigned the scores as the following:

Score ≥ 9 = highly probable

Score 6-8 = probable

Score 3-5 = possible

Score ≤ 2 = unlikely

Table 4.1 *Drug-induced hemolytic anemia clinical scale: Description of the component elements and attributed scores*

Drug-induced Hemolytic Anemia			
Approach Questions			**Scores**
I. Chronological criterion:* *Is the timing of the event related to administration of suspected drug? And, does the problem improve when discontinue the offending drug?*			
- Discovery before taken the drug or within 4 days for initial therapy or > 120 days after stop the drug			Unrelated
-Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
		≤ 1 day	+3
	Within 7-15 days		+2
	> 15 days	> 1 day	+1
	Reaction occurred before starting of drug intake		Unrelated
- Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
	Aggravation of clinical signs or laboratory abnormalities	Regression of the laboratory abnormalities within 15 days	+1
	Persistence of laboratory abnormalities or No information	No information	0
	Improvement of laboratory abnormalities	No change or Aggravation of laboratory abnormalities after 15 days	-3
II. Alternative Cause(s): *Are there any common alternative causes (e.g., blood disorder; connective tissue disease; infection; immunodeficiency state; malignancy, etc) that could explain this event?*			
Completely excluded			+3
Partially excluded with no evidences that rule in another causes			+1
Not investigated			0
Possible another cause detected			-1
Probable another cause detected			-2
Highly probable another cause detected			-3
III. Concomitant Drug(s): *Does the patient receive another drug that may be caused this event?*			
No concomitant drug or Yes , if the onset is incompatible			+1
Not documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.			0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.			-1
Yes, if the onset is compatible with known reaction.			-2
Yes, if the onset is compatible with evidence for this event.			-3
IV. Clinical Feature(s): *Does the patient have any clinical features (e.g., lambar pain, abdominal pain, bone pain, headache, splenomegaly, fever, shock/collapsus, jaundice, dark urine, anuria, etc.)?*			
Yes			+1
None			0
V. *Rechallenge:* *Did the problem recur with intentional or accidental re-exposure to suspected drug?*			
Yes, positive rechallenge			+3
Not done or Not documented			0
Yes, negative rechallenge			-3
VI. Previous Report: *Has this type of adverse event previously been reported?*			
Yes			+2
No: drug marketed ≤ 5 years			0
No: drug marketed > 5 years			-2
		Total score	
≥ 9 Highly probable	6-8 Probable	3-5 Possible	≤ 2 Unlikely

* adapted from: Adverse drug reactions. Apractical guide to diagnosis and management. Edited by C. Bénichou. © 1994 john Wiley & Sons Ltd.

Table 4.2 *Drug-induced neutropenia clinical scale: Description of the component elements and attributed scores*

Drug-induced Neutropenia/ Related disorder			
Approach Questions			**Scores**
I. **Chronological criterion: *** *Is the timing of the event related to administration of suspected drug? And, does the problem improve when discontinue the offending drug?*			
- Drug taken after onset of event or Occurrence after 30 days from end of drug administration.			Unrelated
-Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
		≤ 7 days	+2
	Any time	> 7 days	+1
	within 30 days after stopping		0
- Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
		↑ neutrophils > 1500 within 1 month.	+2
	Continuing ↓ in neutrophil counts.		+1
	Return to normal range	Persistence neutrophil counts < 1500 for more than 1 month	0
II. **Alternative Cause(s):** *Are there any common alternative causes (e.g., bacterial and viral infection; systemic disease; blood disorders; autoimmune neutropenia; toxic agents) that could explain this event?*			
Completely excluded			+3
Partially excluded with no evidences that rule in another causes			+1
Not investigated			0
Possible another cause detected			-1
Probable another cause detected			-2
Highly probable another cause detected			-3
III. **Concomitant Drug(s):** *Does the patient receive another drug that may be caused this event?*			
No concomitant drug or Yes, if the onset is incompatible			+1
Not documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.			0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.			-1
Yes, if the onset is compatible with known reaction.			-2
Yes, if the onset is compatible with evidence for this event.			-3
IV. **Clinical Feature(s):** *Does the patient have any clinical features (e.g., high graded fever, severe asthenia, sore throat, buccopharyngeal and/ or perianeal ulcers)?*			
Yes			+1
None			0
V. **Rechallenge:** *Does the problem recur with intentional or accidental re-exposure to suspected drug?*			
Yes, positive rechallenge			+3
Not done or Not documented			0
Yes, negative rechallenge			-3
VI. ***Previous Report:*** Has this type of adverse event previously been reported?			
Yes			+2
No: drug marketed ≤ 5 years			0
No: drug marketed > 5 years			-2
		Total score	

≥ 9 Highly probable	6-8 Probable	3-5 Possible	≤ 2 Unlikely

* adapted from: Standardization of definitions and criteria of assessment of drug-induced cytopenia (Int J Clin Pharmacol Toxicol 1990; 29: 75-81.)

Table 4.3 *Drug-induced thrombocytopenia clinical scale: Description of the component elements and attributed scores*

Drug-induced Thrombocytopenia			
Approach Questions			**Scores**
I. Chronological criterion:* *Is the timing of the event related to administration of suspected drug? And, does the problem improve when discontinue the offending drug?*			
- Discovery of event before take the suspected drug or more than 1 month after stop the drug			Unrelated
-Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
		≤ 7 days	+3
	≤ 1 month	8-30 days	+2
	> 1 month	> 1 month	+1
	Within 1 month after stopping		0
- Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
	Continuing ↓ in platelet	Recovery within 3 weeks with or without treatment	+1
	Disappearance of thrombocytopenia	Recovery after 3 weeks with or without treatment	0
		Relapse after 3 weeks.	-3
II. Alternative Cause: *Are there any common alternative causes (e.g., aplasia, blood disorder; liver disease with or without alcoholism; bacterial or viral infection; Idiopathic thromcytopenic purpur: ITP, etc.) that could explain this event?*			
Completely excluded			+3
Partially excluded with no evidences that rule in another causes			+1
Not investigated			0
Possible another cause detected			-1
Probable another cause detected			-2
Highly probable another cause detected			-3
III. Concomitant Drug: *Does the patient receive another drug that may be cause this event?*			
No concomitant drug or Yes, if the onset is incompatible			+1
No documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.			0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.			-1
Yes, if the onset is compatible with known reaction.			-2
Yes, if the onset is compatible with evidence for this event.			-3
IV. Clinical Feature: *Does the patient have any clinical features (e.g.,petechia, ecchymoses, epistaxis, hemorrhagic bullae inside the mouth, gingival bleeding, conjuntival or retinal bleeding, GI bleeding, hypermenorrhea, etc.)?*			
Yes			+1
None			0
V. Rechallenge: *Did the problem recur with intentional or accidental re-exposure to suspected drug?*			
Yes, positive rechallenge			+3
Not done or No documented			0
Yes, negative rechallenge			-3
VI. Previous Report: *Has this type of adverse event previously been reported?*			
Yes			+2
No: drug marketed ≤ 5 years			0
No: drug marketed > 5 years			-2
		Total score	

≥ 9 Highly probable	6-8 Probable	3-5 Possible	≤ 2 Unlikely

* adapted from: Standardization of definitions and criteria of assessment of drug-induced cytopenia (Int J Clin Pharmacol Toxicol 1990; 29: 75-81.)

Table 4.4 *Drug-induced aplastic anemia clinical scale: Description of the component elements and attributed scores*

Drug-induced Aplastic Anemia/Related Disorder			
Approach Question			**Scores**
***I. Chronological criterion:** * Is the timing of the event related to administration of suspected drug? And, does the problem improve when discontinue the offending drug?*			
- Discovery before taken the drug or within 4 days for initial therapy or > 120 days after stop the drug			Unrelated
-Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
	> 4 days	After beginning	+1 or +1
	Within 4 month after stop the drug		
- Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
	No change or Aggravation	Spontaneous ↑ in PMN count up to 1500 and platelet count up to 100000 within 6 months	-2
	Improvement with supportive therapy	No change or Aggravation or Improvement with supportive therapy	0 -3
	Improvement of event without therapy	Re-occurrence of event	
***II. Alternative Cause(s):** Are there any common alternative causes (such as, malignancy; blood disorder; myelofibrosis; infection; pregnancy; radiation; toxins/ chemical agents) that could explain this event?*			
Completely excluded			+3
Partially excluded with no evidences that rule in another causes			+1
Not investigated			0
Possible another cause detected			-1
Probable another cause detected			-2
Highly probable another cause detected			-3
***III. Concomitant Drug(s):** Does the patient receive another drug that may be caused this event?*			
No concomitant drug or Yes, if the onset is incompatible			+1
Not documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.			0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.			-1
Yes, if the onset is compatible with known reaction.			-2
Yes, if the onset is compatible with evidence for this event.			-3
***IV. Clinical Feature(s):** Does the patient have any clinical features (such as, fever, fatigue, dyspnea, bleeding)?*			
Yes			+1
None			0
***V. Rechallenge:** Does the problem recur with intentional or accidental re-exposure to suspected drug?*			
Yes, positive rechallenge			+3
Not done or Not documented			0
Yes, negative rechallenge			-3
***VI. Previous Report:** Has this type of adverse event previously been reported?*			
Yes			+1
No: drug marketed ≤ 5 years			0
No: drug marketed > 5 years			-1
Total score			

≥ 9 Highly probable	6-8 Probable	3-5 Possible	≤ 2 Unlikely

* adapted from: Standardization of definitions and criteria of assessment of drug-induced cytopenia (Int J Clin Pharmacol Toxicol 1990; 29: 75-81.)

5. Reliability test of the expert opinions

The agreement of opinion between the two experts (hematologists) for each event was studied to determine the inter-rater reliability by using intraclass correlation coefficient analysis as shown in figure 4.2.

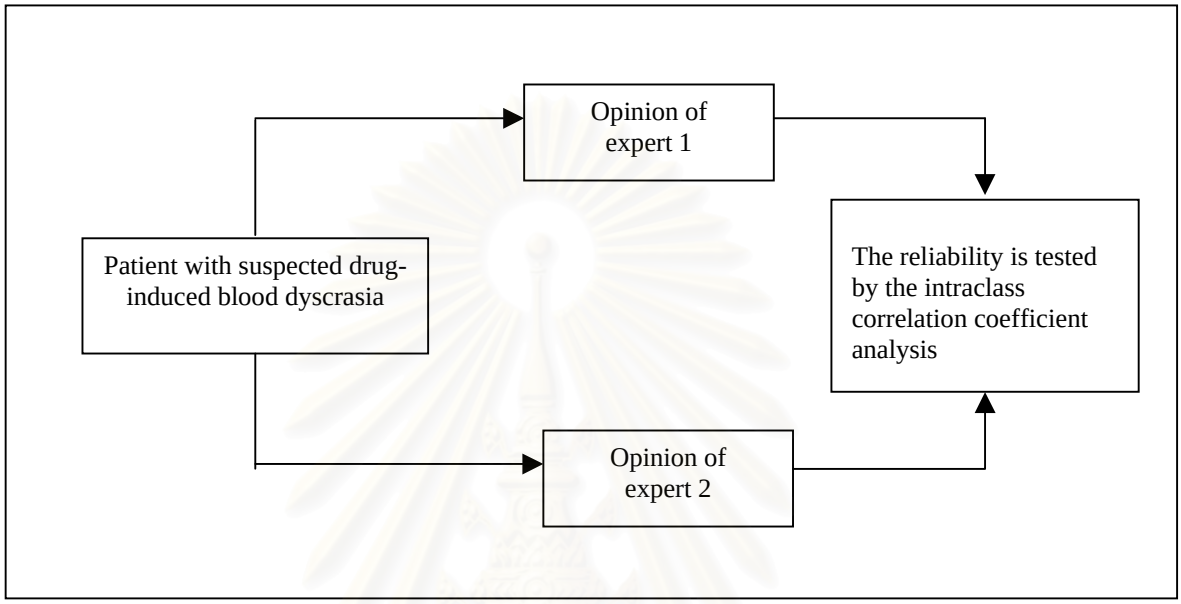


Figure 4.2 *The process of reliability test of two expert opinions.*

6. Validity and reliability test of the new clinical scale and Naranjo's algorithm

The suspected cases with drug-induced blood dyscrasias were consecutively submitted to two clinical pharmacists who have experience in providing pharmaceutical care for internal medicine patients in order to assess the causality of the adverse drug events by using the new developed criteria and Naranjo's algorithm (Appendix H). Before using the new clinical scale, they were explained on concepts and assessment process.

6.1 Validity test

The results of new clinical scale obtained from the two pharmacists were compared with the results of the experts' opinion in order to test the validity of the new criteria as illustrated in Figure 4.3. The weighted agreement and weighted kappa (κ_w) were calculated. Meanwhile, the disagreement between the two groups was categorized as mild, moderate or complete disagreement.

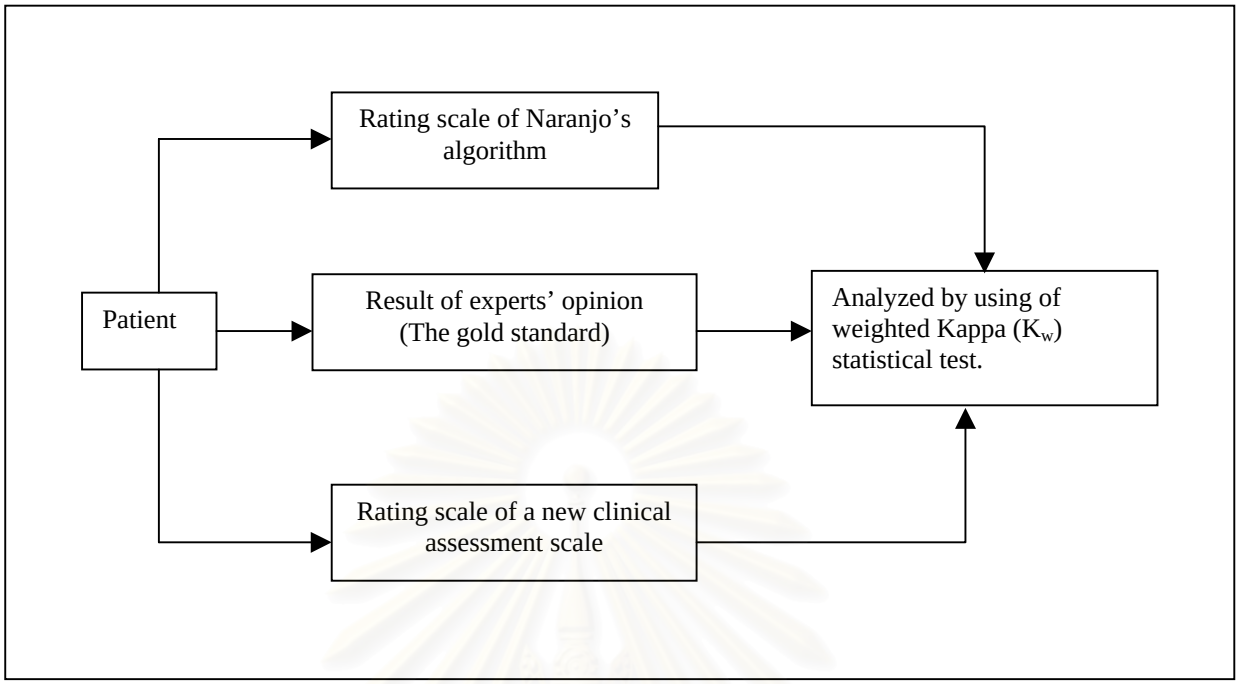


Figure 4.3. *The scheme of validity test.*

6.2 Reliability Test

The agreement of assessment between the two pharmacists for each event was studied to determine the inter-rater reliability using weighted Kappa analysis as shown in Figure 4.4. Also, the disagreement of assessment between the two pharmacists was categorized.

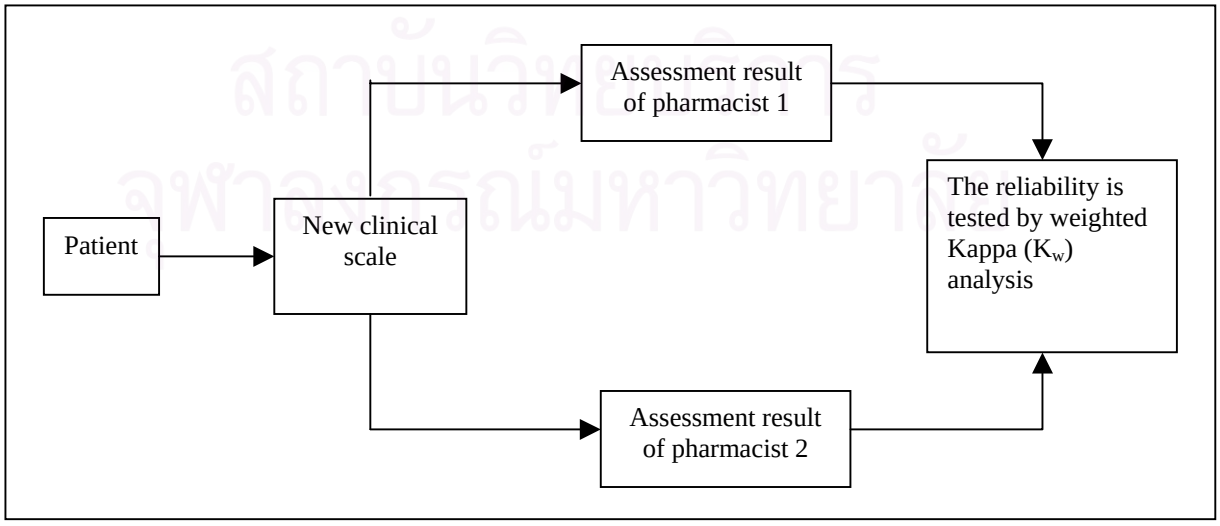


Figure 4.4 *The process of reliability test.*

7. Diagnostic marker test

Diagnosis is an essential part of clinical practice, the new clinical scale was developed to improved a diagnosis of drug-induced blood dyscrasias. It should to know whether the probability of the test was giving the correct diagnosis, so the diagnostic markers (i.e., cut off point, sensitivity, specificity, predictive value, likelihood ratio) were calculated to use for making a diagnosis (Figure 4.5).

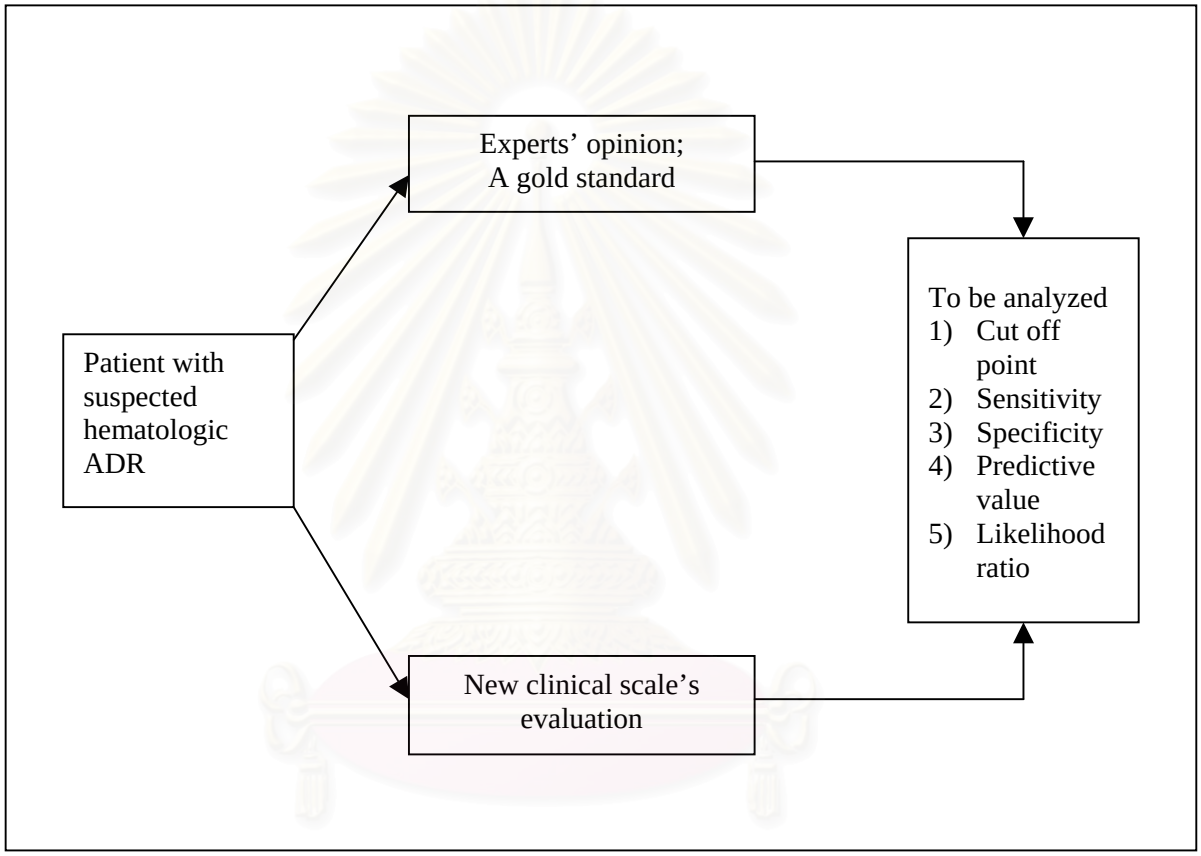


Figure 4.5 *The scheme of diagnostic test.*

Statistical Analysis

Reliability test of opinions of two experts

In this study, the length of Shear's visual scale that obtained from each expert was used to measure the expert opinion. This method was used for translating the subjective data (expert's opinion), to be the objective data (measurable data). Because the length of Shear's scale was continuous data, the appropriate statistics for testing the reliability between two expert opinions was the intraclass correlation coefficient (ρ_I),[67] which combined a measure of correlation with test in the difference means. In this study, the intraclass correlation coefficient was determined by using the SPSS program version 10.0 for window. The intraclass correlation coefficient could vary between –1 (perfect disagreement) to +1 (perfect agreement). The interpretation of value of intraclass correlation coefficient was shown in Table 4.5. [70]

Table 4.5 *The interpretation of value of Interclass Correlation Coefficient (ρ_I).* [70]

Value of Intraclass Correlation Coefficient (ρ_I)	Strength of agreement
$\rho_I < 0.40$	Poor agreement
$0.40 \leq \rho_I < 0.75$	Fair to good agreement
$\rho_I \geq 0.75$	Very good agreement

Validity and inter-rater reliability test

Because the data in this study was the ordinal scale, the appropriate statistics test for analysis of the data was the weighted kappa (K_w) test [69,71,72] which was used for measuring the agreement between the clinical scale and a gold standard, and between two raters (inter-rater reliability). The weighted kappa was derived from kappa (κ) with assigned weights based on the magnitudes of observed disagreements. The weighted corresponding to varying degrees of disagreement were usually assigned as shown in Table 4.6: 0 = perfect agreement (e.g. both A and B report unlikely rating), 1 = one-category disagreement (e.g. unlikely vs. possible rating), 2 = two-category disagreement (e.g. unlikely vs. probable rating), and so on up to a maximum weight of g-1, where g was the number of categories in the ordinal scale. The K_w was defined in manner similar to unweighted kappa (κ), but was easier to calculate when based on q (the proportion of disagreements) rather than p (the proportion of agreement). Since p = 1-q,

$$\kappa_w = 1 - \frac{q_{o'}}{q_{c'}}$$

where $q_{o'}$ = observed proportion of weighted disagreements and $q_{c'}$ = chance-expected proportion of weighted disagreements.

Table 4.6 *ADR agreement matrix containing observed classification (O_{ij}) and assigned weighted (w) for disagreement.*

Method A	***Method B***				***Total***
	1	2	3	4	
1 (Unlikely)	O_{11} (0)	O_{12} (1)	O_{13} (2)	O_{14} (3)	r_1
2 (Possible)	O_{21} (1)	O_{22} (0)	O_{23} (1)	O_{24} (2)	r_2
3 (Probable)	O_{31} (2)	O_{32} (1)	O_{33} (0)	O_{34} (1)	r_3
4 (Highly Probable)	O_{41} (3)	O_{42} (2)	O_{43} (1)	O_{44} (0)	r_4
Total	C_1	C_2	C_3	C_4	N

Decision of a quantitative level of significance for the value of K_w was somewhat arbitrary. Landis and Koch had suggested the following guidelines (Table 4.7). The K_w values ranged from –1 (absolute disagreement) to +1 (absolute agreement), with 0 representing chance-expected weighted agreement. Although the degree of acceptable agreement must depend on circumstances, any value of much below 0.5, in practice, would indicate poor agreement. The example of calculation of K_w value was shown in Appendix L.

Table 4.7 *Quantitative level of significance for the value of weighted kappa (K_w).*[67]

Value of K_w	**Strength of agreement**
< 0	Poor
0-0.20	Slight
0.21-0.40	Fair
0.41-.060	Moderate
0.61-0.80	Good
0.81-1.00	Very good

Note: $K_w = 1$ Agreement is perfect $K_w = 0$ No agreement is better than chance

$K_w < 0$ Worse than chance agreement (Poor) $K_w = -1$ Absolute disagreement

Diagnostic marker test

In clinical practice, the new clinical scale could help the clinicians to diagnose the drug-induced blood dyscrasias. A best cut-off point was determined by using a receiver operating characteristic curve (ROC curve), which was a graphical approach that was to plot the sensitivity versus 1-specificity for each cut-off, and to join the points. Then the diagnostic markers of the clinical scale must to be calculated to determine the diagnostic marker test. [73,74] The calculation of these values was as shown below (Table 4.8). The whole markers of a diagnostic test were used to show diagnostic power of the clinical scale.

Table 4.8 *The relationship between a result of the new criteria and the occurrence of drug-blood dyscrasia.*

Result of the new clinical scale	Drug-induced blood dyscrasia		Total
	+ ve disease	- ve disease	
+ ve result	a	b	a+b
- ve result	c	d	c+d
Total	a+c	b+d	a+b+c+d

- Sensitivity was the proportion of positive disease that were correctly identified by the test: a/(a+c)
- Specificity was the proportion of negative disease that were correctly identified by the test: d/(b+d)
- Accuracy was the proportion of correctly result identified by the test: (a+d)/ (a+b+c+d)
- Positive predictive value was the proportion of patients with positive test results who had disease: a/(a+b)
- Negative predictive value was the proportion of patients with negative test results who did not had disease: d/(c+d)
- Posttest likelihood if test negative was the proportion of patient with negative test result, but they had disease: c/(c+d)
- Likelihood ratios are the two likelihood of obtaining a particular test result :

$$= \frac{\text{Likelihood of test result in patients with disease}}{\text{Likelihood of test result in patients without disease}}$$

$$= \frac{a/\ a+c}{b/\ b+d}$$

The value of the likelihood ratio could between zero (0) to infinity (∝) as shown in Table 4.9.

Table 4.9 *The likelihood ratios and their effects on the probability of a disease.* [(75)]

Likelihood ratio	Effect on probability of the disease
Zero (0)	Test result rules out the disease.
Very small (e.g., 0.01)	Test result greatly decreases the probability of the disease.
<1 (e.g., 0.5)	Test result decreases the probability of the disease.
One (1)	Test result has no effect on the probability of the disease.
>1 (e.g., 2)	Test result increases the probability of the disease.
Very big (e.g., 50)	Test result greatly increases the probability of the disease.
Infinite (∝)	Test result rules in the disease.

CHAPTER V

RESULTS

The complex process of drug-induced blood dyscrasia diagnosis required an experienced clinician. The translation of such experience and subjective clinical judgment into quantitative measurement to define the probability of an adverse drug event was major importance. The complexity of the clinical diagnosis had led to attempt to improve *in vitro* diagnostic tests to detect toxic drug metabolites or drug hypersensitivity. [6] In spite of significant improvement in the understanding of the metabolic and immunologic basic of drug-induced blood dyscrasia, the diagnosis still was dependent predominantly on clinical criteria. [3,6,7] In this study, we developed the new clinical scale which comprised six criteria to identify drug-induced blood dyscrasias and tested its validity, reliability and diagnostic markers.

To study the validity, reliability and diagnostic markers of the new developed clinical scale, we had to implement this clinical scale to the patients with suspected drug-induced disorders who were collected at Internal Medical Wards at King Chulalongkorn Memorial Hospital, during January 1, 2001 to November 30, 2002. A total of 41 patients were enrolled in this study. There were 23 cases (56.1%) of thrombocytopenia, 11 cases (26.8%) of leukopenia/related disease, 3 cases (7.3%) of bicytopenia, 1 case (2.44%) of pancytopenia, and 3 (7.3%) cases of immune hemolytic anemia. The mean age of these patients was 53.8 years (ranged from 24 to 83 years), 24 patients (58.5 %) were male, and 11 patients (26.3%) with HIV sero-positive (table 5.1). The other clinical details of individual patient were shown in Appendix A.

Table 5.1 *Baseline characteristic of patients with suspected drug-induced cytopenia*

	Frequency (Cases)	Percent (%)
Sex		
Female	17	41.5
Male	24	58.5
Age average (Min.-Max.)	53.8 years	(24-83 years)
Type of cytopenia		
Thrombocytopenia	23	56.1
Leukopenia/ neutropenia/ agranulocytosis	11	26.8
Immune hemolytic anemia	3	7.3
Aplastic anemia/ bicytopenia/ pancytopenia	4	9.8
Underlying disease		
HIV patient	11	26.3
Non-HIV patient	30	73.17

5.1 Experts' opinion

In these 41 patients, 58 events were generated because more than one drug were suspected in some patients. All 58 events were evaluated by two experts (hematologists) to be used as our external standard (an adopted gold standard). The Shear's visual analogue scale was placed a mark "X" on the probability line by each expert, which corresponded to the opinion of each one. Table 5.2 showed the intraclass correlation coefficient of two expert opinions that was 0.6845 (95%CI: 0.5152-0.8016) which represented a good agreement between two experts when evaluated the patient with suspected drug-induced blood dyscrasia.

Table 5.2 *Intraclass correlation coefficient of the two experts' opinion*

Reliability Analysis
Intraclass correlation coefficient = 0.6845
95% CI: Lower = 0.5152 Upper = 0.8016

According to the experts' opinion, these 58 events were classified as the followings: 19 events (32.8%) were unlikely, 12 events (20.7%) were possible, 21 events (36.2%) were probable and 6 events (10.3%) for highly probable scale, as displayed in Table 5.3. The other detail of probability scales of consensus expert opinion for each patient was shown in Appendix B.

Table 5.3 *The probability scale obtained from consensus expert opinion, the new clinical scale and Naranjo's algorithm*

	Unlikely	Possible	Probable	Highly probable
Consensus expert opinion	19 (32.8%)	12 (20.7%)	21 (36.2%)	6 (10.3%)
New clinical scale: Pharmacist 1	21 (36.2%)	14 (24.1%)	21 (36.2%)	2 (3.4%)
New clinical scale: Pharmacist 2	19 (32.8%)	16 (27.6%)	19 (32.8%)	4 (6.9%)
Naranjo's algorithm: Pharmacist 1	3 (5.2%)	21 (36.2%)	31 (53.4%)	3 (5.2%)
Naranjo's algorithm: Pharmacist 2	4 (6.9%)	27 (46.6%)	27 (46.9%)	0 (0%)

5.2 Test of Validity

For the validity test, the records of the 41 cases were consecutively assessed the causality of hematologic adverse drug events by two clinical pharmacists, the scores obtained from the pharmacist 1 and 2 using the new clinical scale were compared with the consensus expert opinion (external standard) as shown in Table 5.4 and 5.5, respectively. The agreement between our clinical scale and consensus expert opinion was 70.68% (41 events) for pharmacist 1 and 65.52% (38 events) for pharmacist 2. The weighted agreement in pharmacist 1 was 89.66% and κ_w of 0.712 (95%CI; 0.520-0.904), while a level of weighted agreement of pharmacist 2 was 88.50% and κ_w of 0.683 (95%CI; 0.495-0.871). There was only one event of moderate disagreement (e.g., highly probable *vs.* possible) in pharmacist 1 whereas none in pharmacist 2. The other was mild disagreement (e.g., unlikely *vs*. possible), which were 16 of 58 events (27.59%) in pharmacist 1 and 20 of 58 (34.48%) in pharmacist 2. There was no high disagreement (e.g., unlikely *vs.* highly probable) in this study.

Table 5.4 *Distribution of causality assessments between the gold standard and new clinical scale in pharmacist 1*

Consensus expert opinion (gold standard)	Pharmacist 1: New clinical scale				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	18	1			19
Possible	3	7	2		12
Probable		5	15	1	21
Highly probable		1	4	1	6
Total	21	14	21	2	58

Note: Weighted agreement = 89.66 % κ_w = 0.712 (95%CI; 0.520-0.904)

Table 5.5 *Distribution of causality assessments between the gold standard and new clinical scale in pharmacist 2*

Consensus expert opinion (gold standard)	Pharmacist 2: New clinical scale				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	16	3			19
Possible	3	7	2		12
Probable		6	13	2	21
Highly probable			4	2	6
Total	19	16	19	4	58

Note: Weighted agreement = 88.50 % κ_w = 0.683 (95%CI; 0.495-0.871)

5.3 Inter-rater reliability test

Table 5.6 shown the results of the inter-rater reliability test when the four defined categories were used. The inter-rater agreement was observed in 87.93% (51 of 58 events) with a weighted agreement of 95.4 % and κ_w of 0.866 (95%CI; 0.627-1.060). There was one of moderate disagreement, 6 events (10.3%) of mild disagreement but none of high disagreement.

Table 5.6 *Inter-rater Agreement: Classified by Category of causality assessment*

The new clinical scale: Pharmacist 1	The new clinical scale: Pharmacist 2				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	19	2			21
Possible		13		1	14
Probable		1	18	2	21
Highly probable			1	1	2
Total	19	16	19	4	58

Note: Weighted agreement = 95.4 % κ_w = 0.866 (95%CI; 0.672-1.060)

5.4 Diagnostic marker test of the new clinical scale

From the diagnostic marker test, our clinical scale score of > 2 was chosen as the critical value (cut-off point). This cut-off point was obtained from the Receiver Operating Charateristic (ROC) curve as illustrated in Figure 5.1, to determine the blood dyscrasia that was more likely caused by the suspected drug.

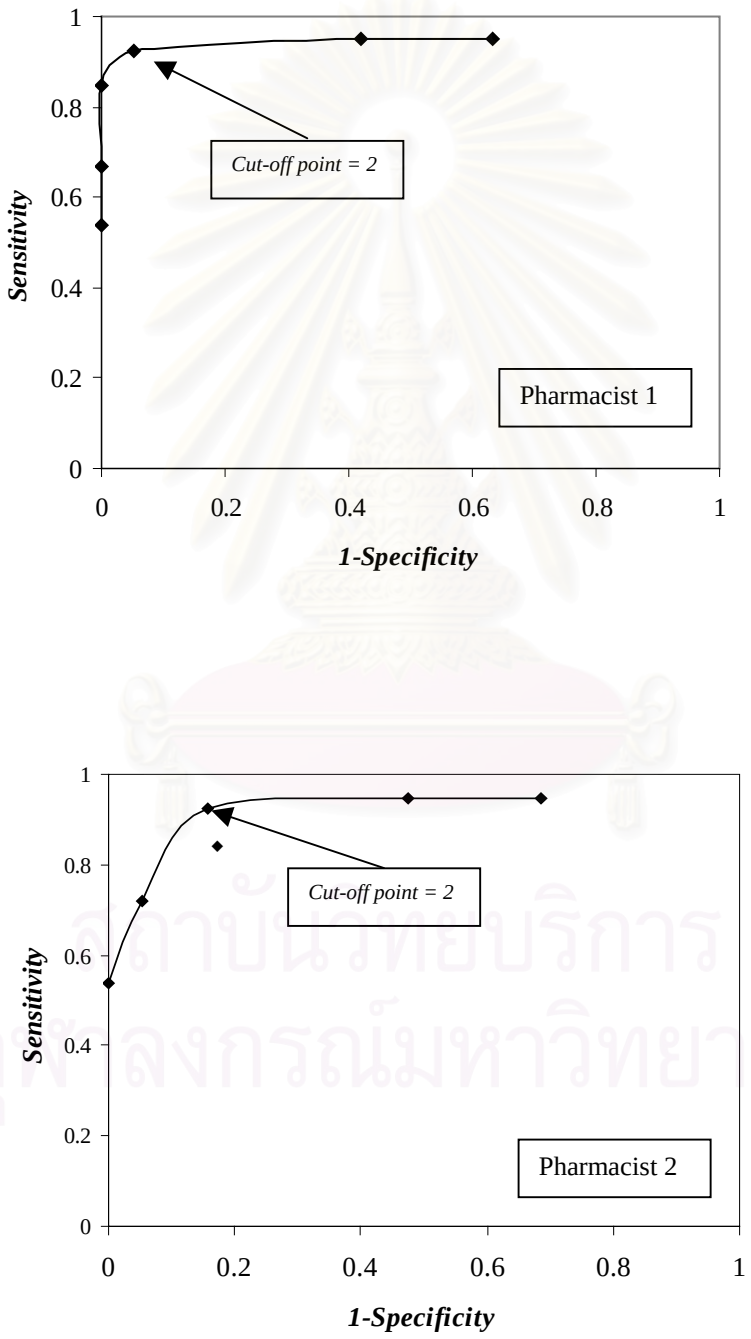


Fig. 5.1 *A receiver operator characteristic (ROC) curve of a diagnostic marker test for drug-induced blood dyscrasias*

Table 5.7 *The relationship between a result of the new clinical scale and the occurrence of drug-blood dyscrasia in pharmacist 1, when the cut-off point was 2*

Result of the new clinical scale : Pharmacist 1	Drug-induced blood dyscrasia: Experts' Opinion		Total
	+ ve	- ve	
+ ve	36	1	37
- ve	3	18	21
Total	39	19	58

Note: *sensitivity = 92.31 %* *specificity = 94.74 %*
accuracy = 93.10 % *positive predictive value = 97.30 %*
negative predictive value = 85.71 % *posttest likelihood if test negative = 17.25 %*
likelihood ratio = 17.54

Meanwhile, Table 5.7 and 5.8 showed diagnostic markers of the new clinical scale, which was derived from two pharmacists. As a clinical score of 2 was taken as a cut-off point, it could identify the events of drug-induced blood dyscrasia with 92.31 % sensitivity and 94.74 % specificity in pharmacist 1. For pharmacist 2, the sensitivity was the same as pharmacist 1 (92.31%), while the specificity was 84.21%, which was likely closed to pharmacist 1. The other diagnostic markers obtained from pharmacist 1 tended to similarity to those of pharmacist 2.

Table 5.8 *The relationship between a result of the new clinical scale and the occurrence of drug-blood dyscrasia in pharmacist 2, when the cut off point was 2*

Result of the new clinical scale : Pharmacist 2	Drug-induced blood dyscrasia: Experts' Opinion		Total
	+ ve	- ve	
+ ve	36	3	39
- ve	3	16	19
Total	39	19	58

Note: *sensitivity = 92.31 %* *specificity = 84.21 %*
accuracy = 89.66 % *positive predictive value = 95.3 %*
negative predictive value = 84.21 % *posttest likelihood if test negative = 15.79 %*
likelihood ratio = 5.85

5.5 Comparison of scores between the gold standard and Naranjo's algorithm.

Agreement between Naranjo's algorithm and our adopted gold standard (consensus expert diagnosis) when applied to cases of suspected blood dyscrasia was shown in Table 5.9 and 5.10. In pharmacist 1, high agreement between consensus expert opinion and Naranjo's algorithm was obtained in 26 cases (44.8%) for pharmacist 1 and 27 cases (37.9%) for pharmacist 2. In pharmacist 1 the weighted agreement was 80.46 % and 0.411 of κ_w (95%CI; 0.258-0.564), whereas a weighted agreement was 78.73% and κ_w was 0.312 (95%CI; 0.171-0.487) in pharmacist 2.

Table 5.9 *Distribution of scores between the gold standard and Naranjo's algorithm*: *in pharmacist 1*

Consensus expert opinion (gold standard)	Naranjo's algorithm: Pharmacisr 1				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	3	15	1		19
Possible		5	7		12
Probable			18	3	21
Highly probable		1	5	0	6
Total	3	21	31	3	58

Note: Weighted agreement = 80.46% κ_w = 0.411 (95%CI; 0.258-0.564)

Table 5.10 *Distribution of scores between the gold standard and Naranjo's algorithm in pharmacist 2*

Consensus expert opinion (gold standard)	Naranjo's algorithm: Pharmacist 2				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	3	15	1		19
Possible	1	5	6		12
Probable		7	14		21
Highly probable			6	0	6
Total	4	27	27	0	58

Note: Weighted agreement = 78.73% κ_w = 0.330 (95%CI; 0.171-0.489)

5.6 Inter-rater reliability of Naranjo's algorithm

Table 5.11 shows the distribution of the classification of inter-rater agreement, there was high agreement between two pharmacists in 41 cases (70.69%), corresponding to a weighted agreement of 90.2% and κ_w of 0.563 (95%CI; 0.367-0.759).

Table 5.11 *Inter-rater Agreement: Classified by Probability Category*

Naranjo's algorithm: Pharmacist 1	Naranjo's algorithm: Pharmacist 2				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	2	1			21
Possible	2	17	2		14
Probable		9	22		21
Highly probable			3	0	2
Total	4	27	27	0	58

Note: Weighted agreement = 90.2% κ_w = 0.563 (95%CI; 0.367-0.759)

5.7 Comparison of scores between the new clinical scale and Naranjo's algorithm

Table 5.12 and 5.13 present the agreement between the new clinical scale and Naranjo's algorithm when applied to cases of suspected drug-induced blood dyscrasia. There was agreement between the two tools in 22 of 58 events (32.7%) for pharmacist 1 and 27 rating (46.5%) for pharmacist 2. The weighted agreement for pharmacist 1 was 63.2% with 0.357 of κ_w coefficient (95%CI; 0.210-0.504), while the weighted agreement for pharmacist 2 was 82.18% with 0.415 of κ_w coefficient (95%CI; 0.254-0.576).

Table 5.12 *Agreement between the new clinical scale and Naranjo's algorithm in pharmacist1*

New Clinical Scale: Pharmacist 1	Naranjo's algorithm: Pharmacist 1				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	3	18	1		22
Possible		2	11		13
Probable		1	17	3	21
Highly probable			2	0	2
Total	3	21	31	3	58

Note: Weighted agreement = 63.2 % κ_w = 0.357 (95%CI; 0.210-0.504)

Table 5.13 *Agreement between the new clinical scale and Naranjo's algorithm in pharmacist2*

New Clinical Scale: Pharmacist 2	Naranjo's algorithm: Pharmacist 2				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	3	16			19
Possible	1	8	7		16
Probable		3	16		19
Highly probable			4	0	4
Total	4	27	27	0	58

Note: Weighted agreement = 82.18% κ_w = 0.420 (95%CI; 0.254-0.576)

5.8 Comparison of validity and reliability between two tools (new clinical scale vs. Naranjo's algorithm)

Table 5.14 and 5.15 depict the value of weighted % agreement and κ_w coefficient of validity and reliability when compared the new clinical scale with Naranjo's algorithm. For validity test, it was found that the new clinical scale had higher value of weighted % agreement and κ_w than Naranjo's algorithm. In addition, weighted % agreement and κ_w of the new clinical scale in reliability test were also higher than those of Naranjo's algorithm.

Table 5.14 *Comparing the value of % weighted agreement and 95% CI* κ_w *of validity test*

Validity test	Pharmacist 1		Pharmacist 2	
	% weighted agreement	κ_w (95%CI)	% weighted agreement	κ_w (95%CI)
New clinical scale vs. External standard	89.66	0.712 (0.520-0.904)	88.50	0.683 (0.495-0.871)
Naranjo's algorithm vs. External standard	80.46	0.411 (0.258-0.564)	78.73	0.312 (0.171-0.489)

Table 5.15 *Comparing the value of* % weighted *agreement and 95%CI* κ_w *of inter-rater reliability test*

Inter-rater reliability	% weighted agreement	κ_w (95%CI)
New clinical scale	95.4	0.866 (0.672-1.060)
Naranjo's algorithm	90.2	0.563 (0.367-0.759)

5.9 Comparison of diagnostic markers between the new clinical scale and Naranjo's algorithm

To compare the diagnostic markers, Naranjo score of > 0 was chosen as a critical value (cut-off point) to determine the drug-induced blood dyscrasia which was the score used to separate between unlikely and possible probability. Meanwhile, we considered the score of >2 as a cut-off point for the new clinical scale using ROC curve. It was also found that the diagnostic marker values of the new clinical scale tended to higher than those of Naranjo's algorithm, as shown in Table 5.16

Table 5.16 *Diagnostic marker test of the new clinical scale and Naranjo's algorithm*

Diagnostic Marker	Pharmacist 1		Pharmacist 2	
	New clinical scale	Naranjo's algorithm	New clinical scale	Naranjo's algorithm
Sensitivity	92.31%	100%	92.31%	97.44%
Specificity	94.74%	15.79%	84.21%	15.79%
Accuracy	93.10%	72.41%	89.66%	70.69%
Positive Predictive Value	97.30%	70.91%	92.3%	70.37%
Negative Predictive Value	85.71%	100%	84.21%	75.0%
Post-test likelihood if test negative	14.28%	0%	15.79%	25%
Likelihood ratio	17.54	1.19	5.85	1.16

CHAPTER VI

DISCUSSIONS

The objectives of this study were to develop the clinical scale in drug-induced blood dyscrasias that would be appropriate for Thai clinical settings, to determine the validity, reliability and diagnostic test of the new clinical scale, and to compare the result of the new clinical scale and the classical algorithm (Naranjo's) [11] when using for assessing the hematologic adverse events.

Development of the new clinical scale

The complex process to identify the drug-induced blood dyscrasia usually requires an experienced clinician who is deeply aware of the critical components to be weighed for an accurate identification, including a good knowledge of the published literature. The translation of such experience and subjective clinical judgement into a quantitative (objective) measurement to define the probability of an adverse drug event is of great importance. Our clinical scale is developed to resolve this problem.

The criterion details of our clinical scale are considered by using Bayes' theory [76] which consists of timing, dechallenge and rechallenge, alternative etiological candidates, and previous experience with the drug. In addition, we also use the appropriate criteria of definition and causality assessment of ADRs, which are suggested by Benichou and Danan [77] in consensus meeting in 1990. From our clinical scale, it is worthily noted that our clinical scale was considered similarity with the one that produced by RUCAM and by Maria et al., which considered the inclusion of many evaluated criterions, such as the chronological relationship (both time of onset and withdrawal response), the exclusion of alternative cause, the re-exposure to the drugs, and previous reporting in the medical and pharmacotherapeutical literatures. Each axis consists of pertinent question(s) that the clinician should try to answer it to approach the patient with drug-induced blood abnormalities. The criterion of each axis has considered all possible situations, which allow the assessor to flexibly use all the factors that affect a causality assessment appropriately. Thus, we believed that our clinical scale is well designed for causality assessment of evaluating drug-induced blood dyscrasias. However, when there are more than one drug

under suspicion, scores are computed to each drug, and the drug with the highest score is considered as the most likely involved in blood dyscrasia.

Reliability test of the expert opinions

In this study, we describe an assessment instrument for evaluating the drug-induced blood dyscrasia in Thai patients. In present day, there are no an established gold standard for confirming the drug-induced blood dyscrasia. It is the problem for validating our new clinical scale. However, we believed that the opinion of a panel of experts may solve this problem.

For test of reliability of two expert opinions, it was found that the agreement between two experts has a high level (Intraclass Correlation Coefficient = 0.6845, 95% CI: 0.5152-0.8016). So, we believed that the expert's opinion is appropriate to be used as a gold standard for identifying the patient with suspected drug-induced blood dyscrasia in this study.

Validity, reliability and diagnostic markers of the new clinical scale

In general, drug-induced blood dyscrasias has usually low incidence, thus the clinicians may require several years of post-marketing surveillance to identify a particular drug that can be a causative agent of blood injury. Although previous study [5] attempted to express the likelihood of the diagnosis as a probability by means of measurement instruments, detailed validation studies have not been published.

When comparing the clinical scale with the opinion of an expert panel (a gold standard), the assessment of agreement reveals a κ_w value of 0.712 (95% CI; 0.820-0.904) in pharmacist 1 and that of 0.683 (95%CI; 0.495-0.871) in pharmacist 2. It is noted that the κ_w value of pharmacist 1 is slightly higher than value of pharmacist 2, but both values reveal high level of consistency which can be considered as good concordance (seen in Table 4.7). In addition, it is also worthily noted that a disagreement higher than one level is observed in only 1 of 58 events in pharmacist 1, whereas none in pharmacist 2. Therefore, an overall risk probability score of our clinical scale correlates well with the classification of consensus expert opinion.

In relation to reliability, a κ_w coefficient of 0.866 (95% CI; 0.672-1.060) represents a very high level of agreement. There are 7 events, which are disagreement, only 1 event for moderate disagreement and the other are mild. It is noted that there is no high disagreement in our reliability test. The agreement observed in our clinical scale may be related to the exclusion of alternative cause(s) of blood dyscrasia, which is complexity and has variety situations for considering the probability of adverse drug reaction. Although the inter-rater reliability observed in this study can be considered excellent, we believed that this particular point of the scale can be improved by better specifying clinical conditions and details that can help the clinician excluding the alternative cause(s), and revising the alternative cause axis to obtain more details. In addition, the clinician should mainly use the clinical condition details of each individual patient to evaluate the drug-induced blood dyscrasias.

For this study, we considered the panel of expert (hematologist) opinions as the gold standard for diagnostic marker test of the new clinical scale. When considering the ROC curve, the appropriate score for use as a critical value or cut-off point to confirm the drug-induced blood dyscrasia is >2. The sensitivity of our scale is more than 90%, while the specificity is more than 80 %. It is shown that by using the new clinical scale, we can identify the true case of drug-induced blood abnormality with more than 90% and the true absence of drug-induced cytopenia of more than 80%. Furthermore, our clinical scale also has high level of accuracy, positive and negative predictive value (> 80%). Whereas, the posttest likelihood if test negative is less than 18%. For example, if the result of clinical diagnostic scale is negative, the patient may have a chance to present the drug-induced blood dyscrasia less than 18%. Therefore, we believe that the score of 2, in our clinical scale, is an appropriate cut off point for clinician to decision making in clinical practice. If the score obtained from our scale is more than 2 points, the clinician should be aware that the suspected drug might be related to the patient disease and he/she should plan for further management.

Comparison between the new clinical scale and Naranjo's algorithm

When comparing our clinical scale with Naranjo's algorithm, we found that our clinical scale have higher degree of concordance than Naranjo's algorithm when use it in specific field, such as hematologic adverse drug reaction. Moreover, its diagnostic markers are also better than Naranjo's. These results may be from the reason that our clinical scale is

developed base on specific drug-induced disease (blood dyscrasia) whereas Naranjo's algorithm is developed for general type of adverse drug reaction. Thus, our scale is more appropriate for evaluation of drug-induced blood dyscrasia than Naranjo's algorithm.

Recommendation of using the new clinical scale

In clinical practice, the causality assessment of drug-induced disease is not a pure science, [71] but it is a combination between science and art, it is neither black nor white color but it is like gray color. It likes hardened criminal that is trying to convict a drug as a crime of causing blood dyscrasias. A suspected drug may be capable of causing an adverse reaction, however this does not mean that it did. Like as rule of law, the clinical scale is based on medical precedent, but will never be definitive. Clinical scale simply allows us to utilize standard guidelines in a systematic approach way. Ultimately, all such judgments are arbitrary and subject to dispute. Assessments of the past do not lead to a precise validation (real life outcome). But, at least with a clinical scale, the data collection (e.g., patient history, subjective and objective data in support of a problem, etc.) should be more consistent, because assessment of patients requires the gathering of specific information.

The technique that we use for evaluating our patient with drug-induced blood dyscrasias is utilizing a graph paper (see in Appendix K). Time sequence of event is drawn on a graph paper. The assessors can easily gather the patient data and come in view of adverse event before identifying the causative drug(s). We believe that our diagnostic scale is an appropriate guideline to help clinician for evaluating drug-induced blood dyscrasia. However, the application of this scale does not cover in all situations of drug-induced blood dyscrasias, especially in atypical case (e.g., patient who has adverse event after withdrawn the offending drug). In situation that patient has been exposed to more than one drug, the clinician should assess each drug separately. If the score of each suspected drug is equal, the clinician should use this clinical scale with the knowledge of drug-specific characteristics of adverse event, which is crucial in clinical evaluation of suspected case. Most of these characteristics may get from case reports in the medical journals. This combination can establish the assessment more accurately than using the scale alone.

In addition, when faced with a suspected adverse drug reaction in everyday clinical practice, the clinicians should ask themselves with these questions, [42] such as follows:

What clinically significant adverse effects of drug therapy could possibly occur?

What would be the nature of this possible adversity and what would be its significance in this particular patient?

What is the probability that an adversity may occur and with what frequency is it encountered in the general population of patients?

What parameters will you inspect during treatment as an indication of adversity?

Moreover, we think that clinical experience is required to identify the offending drug that may be the causality of this hematological adverse reaction.

Limitation of our study

1. Due to limitation of budget and time, this study was designed in only one specific study area (Medical wards at King Chulalongkorn Memorial Hospital).
2. This study is a historical retrospective study. All data was collected from patient chart and OPD card. Therefore, some relevant data associated with the drug-induced blood dyscrasia could not be collected because it was not recorded in the charts or OPD card. Moreover, some data was incomplete record, especially in cases who lost of follow up or died. These incomplete data may affect the evaluation of drug-induced blood dyscrasia.
3. In the fact that the incidence of drug-induced blood dyscrasia is rare, especially drug-induced immune hemolytic anemia and aplastic anemia. In this study, there were only 3 and 4 cases of immune hemolytic anemia and aplastic anemia, respectively. So, we can not study each type of drug-induced blood dyscrasia separately.

CHAPTER VII

CONCLUSIONS

Conclusion

Because many pharmacists spend much of their working day reviewing medicines prescribed for patient, they commonly encounter to potential or actual adverse reactions, including drug-induced blood dyscrasias. In clinical practice, evaluation of the suspicious event is not followed through in a logical and systemic manner. [78] Although there are a number of algorithms available to assist pharmacists for evaluating adverse drug reaction, there have no one that is specific to drug-induced blood dyscrasias. Therefore, we developed the appropriated clinical scale to help pharmacist to evaluated hematologic adverse drug reaction, and tested its validity, reliability and diagnostic markers.

The new developed causality assessment scale consisted of six operational axes, namely chronological relationship, exclusion of non-drug causes, concomitant medications, clinical features, rechallenges, and previous reports in medical literatures. The final total of the sum of the individual scores for the six axes provided a measure of the risk probability that a suspicious event was drug-related.

Forty-one patients with 58 reactions of suspected drug-induced blood dyscrasias were assessed by three methods (experts' opinion, the new clinical scale and Naranjo's algorithm). It was found that the new clinical scale showed a high level of validity when compared with our adopted gold standard. As for its the inter-rater reliability, it was considered as very good agreement. From the ROC curve, the optimal cut-off point of the new scale was established as 2. When chose this cut point, it was shown that the new scale could identify the cases of drug-induced blood dyscrasias with high sensitivity as well as a high level of specificity. When comparing the new scale with Naranjo's algorithm, it was shown that the weighted Kappa coefficients (κ_w) of validity and reliability of the new clinical scale were high than those of Naranjo's. In addition, the diagnostic markers of the new scale tended to have a higher value than those of Naranjo's.

In conclusion, this clinical assessment scale correlates well with the gold standard and is a high level of inter-rater reliability. It also appears to have a good discriminatory capacity between different levels of probability. In addition, this scale is easily and correctly when apply in clinical practice and it may help clinicians to overcome the difficulties in the process of causality assessment in drug-induced blood dyscrasias.

Consideration of further study

1. Due to limitation of budget and time, our study can not study each type of drug-induced blood dyscrasia separately. Therefore, the further study should determine the validity, reliability and diagnostic test of the clinical scale in each type of drug-induced blood dyscrasia separately.
2. Although our sampled population is the patient whose aged > 18 year old, we believe that our clinical scale can also use in patient whose aged ≤ 18 year old. Therefore, the further study in pediatric patients may need to confirm our hypothesis.
3. Because of limitation of time and budget, we can study the reliability of only two clinical pharmacists at King Chulalongkorn Memorial Hospital, so the further study which more raters in another clinical settings may need.
4. In the fact that the HIV-seropositive patients usually have blood abnormality, evaluating the patients is difficult to separate between non-drug cause and drug related cause. Therefore, the investigator should address using of this clinical scale in these patients.

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APPENDICES

APPENDIX A

Clinical details of 41 patients with suspected drug-induced blood dyscrasias

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
1.	M/81	Agranulocytosis	Cefepime	6	5	Improvement	1.Hypertension	1. Prolong fever
			Omeprazole	17	16	Improvement	2. DM type 2	2. Liver abcess
							3. Right basal ganglion	3. GI bleeding
							hemorrhage	4. ARF
								5.Anemia: r/o UGIB
								6. Thrombocytopenia:
								r/o from sepsis
2.	M/25	Neutropenia	Cloxacillin	23	26	Improvement	1. Hemophilia A	1. left patella fracture
								2. hemathroses of both
								knee
								3. septic arthritis
								4. maculopapular rash
3.	F/55	Thrombocytopenia	Cyclosporin A	Without	≈ 9 months	Improvement	1. Hypertension	1. PTT prolong
				stopped			2. ESRD with	
							proteinuria	
							3. s/p kidney transplant	

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
4.	M/33	Thrombocytopenia	Co-trimoxazole	≈ 14	≈ 14	Improvement	1. HIV + ve	1. cryptomeningitis
							2. Herpes zoster	
							3. Fungal infection	
5.	M/79	Thrombocytopenia	Ranitidine	18	8	Improvement	1. COPD	1. UGIB
			Sulperazone	8	4	Improvement	2. Left hemiparesis	2. Pneumonia
							3. Bed ridden	3. AF with RVR
								4. COPD with acute
								exacerbation
6.	M/38	Thrombocytopenia	Rifmpicin	11	11	Improvement	1. Symptomatic HIV	1. Pulmonary TB
							2. PCP	
							3. MAC	
7.	F/56	Thrombocytopenia	Furosemide	2	4	Improvement	1. HCV +ve	1. TIPS
							2. Cirrhosis with ascites	2. post OLT
							3. UGIB	
							4. hydrothorax	
8.	M/83	Immune hemolytic	Cefepime	4	2	No change	1. 2° adrenal insuff.	1. Fever
		anemia						2. Myalgia
								3. N/V

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
9.	M/68	Thrombocytopenia	Doxazosin	≈ 1 year	≈ 1 year	Aggravation	1. CAD with s/p PTCA	1.Anemia
							2. Hyperlipidemia	
							3. BPH	
10.	F/64	Thrombocytopenia	Cefpirom	9	10	Improvement	1. CHF	1. Liver abscess
								2. r/o SLE
11.	M/57	Thrombocytopenia	Ceftriaxone	12	24	Improvement	None	1. Acute pyelonephritis
			Ciprofloxacin	14	12	Improvement		2. Right basal ganglion
								hemorrhage
								3.Essential hypertension
12.	M/31	Thrombocytopenia	Perphenazine	≈ 5 months	≈ 5 months	Improvement	1. HIV +ve	1. Chronic diarrhea
			Artance	≈ 5 months	≈ 5 months	Improvement		2. Fatigue
								3. Psychosis
13.	F/31	Thrombocytopenia	Amphotericin B	No stopping	24	Aggravation	1. ANLL-M_4	1. ANLL-M_4
14.	F/55	Thrombocytopenia	Phynetoin	2	2	Improvement	1. Addison's disease	1. Alteration of conscious
			Cefotaxime	4	3	Improvement		2. Pneumonia
								3. Respiratory alkalosis
15.	M/24	Hemolytic Anemia	Paracetamol	4-5	6	Improvement	None	1. High grade fever

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
								2. Acute hepatitis A
								3.. r/o G-6-PD deficiency
16.	F/30	Agranulocytosis	Ganciclovir	27	20	Aggravation	1. HIV +ve	1. TB infection
								2. CMV retinitis
17.	F/67	Thrombocytopenia	Aspirin	≈ 8 months	≈ 8 months	Aggravation	1. Hypertension	1. Acute febrile illness:
							2. Chronic thrombocyto-	r/o UTI
							penia	
18.	F/40	Bicytopenia	Cotrimoxazole	≈ 5 months	≈ 4 months	Improvement	1. Sympatomatic HIV	1. Cyptomeningitis
								2. Fever
19.	M/70	Thrombocytopenia	Thiazide	15	12	No change	1. DM type 2	1. Chest pain
			Clopedogrel	No stopping	≈ 12 months	No change	2. Old CVA	2. Anemia
							3. Left facial pulsey	
							4. TVD s/p PTCA	
							5. s/p craniectomy	
20.	F/37	AIHA	Amophotericin B	14	6	Improvement	1. HIV +ve	1. Cerebral cryptococosis
			Cotrimoxazole	24	7	Improvement	2. Herpes zoster	2. PCP
21.	M/59	Neutropenia	Cefotaxime	2	3	No change	1.Alcoholic cirrhosis	1. UGIB

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
			Omeprazole	9	3	No change		2. Ascites
								3. thrombocytopenia
22.	M/51	Pancytopenia	AZT	≈ 17 months	≈ 17 months	Improvement	1. HIV +ve	1. Near syncope
			DDI	≈ 17 months	≈ 17 months	Improvement		
23.	F/31	Thrombocytopenia	Cotrimoxazole	No stopping	1	Aggravation	1. HIV +ve	1. Prolong fever
							2. HZV	2. chronic cough
							3. PCP	3. Dyspnea
								4. Anemia
24.	F/68	Thrombocytopenia	Omeprazole	No stopping	7	Aggravation	1. HT	1. Aspiration pneumonia
			Cetazidime	No stopping	4	Aggravation	2. DM type 2	2. Mucomycoses
							3. s/p cholecystectomy	3. DM
								4. Renal insufficiency
								5. Diarrhea
								6. Anemia
25.	F/27	Agranulocytosis	Ganciclovir	No stopping	2	Aggravation	1. HIV +ve	1. Chronic diarrhea
			Ciprofloxacin	No stopping	5	Aggravation		2. Salmonella septicemia
			HAART regimen	No stopping	3	Aggravation		3. Disseminated CMV
								4. Pnemothrorax
								5. Pancytopenia
								6. Prolong fever

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
								7. Genital herpes simplex
								8. Oral candidiasis
26.	F/41	Leukopenia	Cyclophosphamide	1	7	Improvement	1. SLE	1. Lupus nephritis with
							2. Steroid-induced	recurrent proteinuria
							myopathy	
27.	M/75	Thrombocytopenia	Omeprazole	> 20	> 16	Improvement	1. HT	1. TVD s/p CABG
			Aspirin	20	16	Improvement	2. AF	2. Fever w/ pneumonia
							3. CHF	3. Hypernatremia
							4. Dyslipidemia	4. Alteration of conscious-
								ness
28.	M/32	Neutropenia	Cortimoxazole	41	41	No change	1. HIV +ve	1. Cryptococcal meningitis
			Amphotericin B	25	21	No change		
29.	M/39	Agranulocytosis	PGS	20	19	Improvement	1. RHD w/ AF	1. IE
							2. s/p AVR	2. ARF
								3. Anemia
								4. Thrombocytopenia
30.	M/63	Bicytopenia	Captopril	≈ 2 months	≈ 2 months	Improvement	1. Pentalogy of Fallot	1. CHF
							2. AML w/ mild AF	2. CO_2 narcosis
								3. r/o Bronchitis

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
31.	F/78	Thrombocytopenia	Carbamazepine	8	12	Improvement	1. Occipital numbness	1. Acute febrile illness
								2. Head injury
32.	M/69	Thrombocytopenia	Aspirin	≈ 7 years	≈ 7 years	uninterpretable	1. CVA	1. Hyperglycemia
			Phenytoin	≈ 2 years	≈ 2 years	uninterpretable	2. Epilepsy	2. Septic shock
							3. DM type 2	
							4. HT	
33.	F/70	Thrombocytopenia	Enoxaparin	2	1	Improvement	1. DM type 2	1. Bleeding tendency
							2. HT	2. Cord edema
							3. CRI	3. Non-ST elevation MI
							4. CAD	4. CRF
								5. HT
								6. Fever
34.	M/68	Leukopenia	Colchicin	≈ 1 years	≈ 1 years	Improvement	1. DM type	1. Ischemic stroke
			Cyclophosphamide	≈ 1 years	≈ 1 years	Improvement	2. Dyslipidemia	2. Hyponatremia
							3. Idiopathic pulmonary	3. UGIB
							fibrosis (IPF)	
							4. Ischemic stroke	
35.	M/64	Thrombocytopenia	Clindamycin	6	3	Improvement	1. HT	1. MI w/ arteriosclerosis
							2. Dyslipidemia	2. Pneumonia

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
							3. Gout	3. UGIB
							4. Old CVA	4. Sudden cardiac arrest
36.	F/65	Thrombocytopenia	Meloxicam	≈ 1 years	≈ 7-8 months	Improvement	1. Dyslipedimia	1. Low-grade fever
							2. OA	2. Petichael rash
37.	M/35	Neutropenia	Cotrimoxazole	≈ 6 months	≈ 6 months	Improvement	1. Symptomatic HIV	1. HIV infection
							2. Hbs Ag +ve	2. liver cirrhosis
							3. Cirrhosis	3. teeth root infection
							4. Hepatospleenomegaly	4. Portal hypertension
								5. Pancytop[enia
38.	M/78	Bicytopenia	Omeprazole	11	8	Uninterpretable	1. CRF	1.Pneumonia
			Cefdinir	10	6	Uninterpretable	2. Gouty arthritis	2. ARF
							3. Chronic AF	3. CHF
							4. BPH	4. Anemia
							5. COPD	5. Gouty arthritis
							6. Anemia	
							7. 2° adrenal insuff.	
39.	F/73	Thrombocytopenia	Heparin	6	3	Improvement	1. DM type 2	1. plan: CABG
							2. HT	
							3. Dyslipedimia	

Cont…

Case No.	Sex/Age (yr.)	Blood dyscrasia	Suspected Drug	Duration of therapy (days)	Time to onset (days)	Immediate result	Underlying Disease	Concurrent illness / Condition
40.	M/68	Thrombocytopenia	Cotrimoxazole	14	4	Uninterpretable	1. 1° CNS lymphoma	1. URI
								2. ARDS
								3. r/o primary bacteremia
								4. Pneumothorax
								5. Lung hemorrhage
41.	M/38	Leukopenia	Cloxacillin	12	9	Improvement	1. Hepatitis B infection	1. Hemolytic anemia
							2. G6PD deficiency	2. ATN
								3. UGIB
								4. Catheter related infection

Probability rating scale of consensus expert opinion and 2 raters

Case No.	Type of Blood dyscrasia	Suspected Drug(s)	Consensus expert scale (External standard)	Pharmacist 1		Pharmacist 2	
				New clinical scale [a,b]	Naranjo's algorithm [a,b]	New clinical scale [a,b]	Naranjo's algorithm [a,b]
1.	Agranulocytosis	Omeprazole	Probable	Possible	Probable	Possible	Possible
		Cefepime	Probable	Possible	Probable	Possible	Probable
2.	Neutropenia	Cloxacillin	Probable	Probable	Probable	Probable	Probable
3.	Thrombocytopenia	Cyclosporin A	Unlikely	Unlikely	Possible	Possible	Possible
4.	Thrombocytopenia	Co-trimoxazole	Probable	Probable	Probable	Probable	Probable
5.	Thrombocytopenia	Ranitidine	Probable	Probable	Probable	Probable	Probable
		Sulperazone	Unlikely	Unlikely	Possible	Unlikely	Possible
6.	Thrombocytopenia	Rifmpicin	Probable	Probable	Probable	Highly Probable	Probable
7.	Thrombocytopenia	Furosemide	Unlikely	Unlikely	Possible	Possible	Possible
8.	Immune hemolytic anemia	Cefepime	Unlikely	Unlikely	Possible	Unlikely	Possible
9.	Thrombocytopenia	Doxazosin	Unlikely	Unlikely	Possible	Unlikely	Possible
10.	Thrombocytopenia	Cefpirom	Probable	Probable	Probable	Possible	Probable
11.	Thrombocytopenia	Ceftriaxone	Probable	Probable	Probable	Probable	Possible
		Ciprofloxacin	Probable	Probable	Probable	Probable	Probable
12.	Thrombocytopenia	Perphenazine	Unlikely	Possible	Possible	Possible	Probable
		Artance	Unlikely	Unlikely	Possible	Unlikely	Possible
13.	Thrombocytopenia	Amphotericin B	Possible	Possible	Possible	Possible	Doubtful
14.	Thrombocytopenia	Phynetoin	Unlikely	Unlikely	Possible	Unlikely	Possible
		Cefotaxime	Unlikely	Unlikely	Possible	Unlikely	Possible
15.	Hemolytic Anemia	Paracetamol	Unlikely	Unlikely	Possible	Unlikely	Possible

Cont...

Case No.	Type of Blood dyscrasia	Suspected Drug(s)	Consensus expert scale (External standard)	Pharmacist 1		Pharmacist 2	
				New clinical scale [a,b]	Naranjo's algorithm [a,b]	New clinical scale [a,b]	Naranjo's algorithm [a,b]
16.	Agranulocytosis	Ganciclovir	Probable	Probable	Probable	Probable	Possible
17.	Thrombocytopenia	Aspirin	Unlikely	Unrelated	Doubtful	Unrelated	Possible
18.	Bicytopenia	Cotrimoxazole	Probable	Probable	Probable	Probable	Possible
19.	Thrombocytopenia	Thiazide	Unlikely	Unlikely	Possible	Unlikely	Doubtful
		Clopedogrel	Unlikely	Unlikely	Possible	Unlikely	Possible
20.	Immune hemolytic anemia	Amophotericin B	Possible	Possible	Probable	Possible	Probable
		Cotrimoxazole	Unlikely	Unlikely	Probable	Unlikely	Possible
21.	Neutropenia	Cefotaxime	Unlikely	Unlikely	Possible	Unlikely	Possible
		Omeprazole	Unlikely	Unlikely	Possible	Unlikely	Possible
22.	Pancytopenia	AZT	Highly Probable	Probable	Probable	Highly Probable	Probable
		DDI	Highly Probable	Possible	Probable	Highly Probable	Probable
23.	Thrombocytopenia	Cotrimoxazole	Probable	Probable	Probable	Probable	Probable
24.	Thrombocytopenia	Omeprazole	Possible	Probable	Probable	Probable	Probable
		Cetazidime	Possible	Probable	Probable	Probable	Probable
25.	Agranulocytosis	Ganciclovir	Probable	Probable	Definite	Probable	Probable
		Ciprofloxacin	Probable	Probable	Definite	Probable	Probable
		HAART regimen	Probable	Probable	Definite	Probable	Probable
26.	Leukopenia	Cyclophosphamide	Highly Probable	Probable	Possible	Probable	Probable
27.	Thrombocytopenia	Omeprazole	Possible	Unlikely	Possible	Unlikely	Possible
		Aspirin	Possible	Unlikely	Possible	Unlikely	Possible
28.	Neutropenia	Cortimoxazole	Probable	Possible	Probable	Possible	Possible
		Amphotericin B	Possible	Possible	Probable	Possible	Possible
29.	Agranulocytosis	PGS	Highly Probable	Highly Probable	Probable	Probable	Probable

Cont...

Case No.	Type of Blood dyscrasia	Suspected Drug(s)	Consensus expert scale (External standard)	Pharmacist 1		Pharmacist 2	
				New clinical scale [a,b]	Naranjo's algorithm [a,b]	New clinical scale [a,b]	Naranjo's algorithm [a,b]
30.	Bicytopenia	Captopril	Probable	Highly Probable	Probable	Highly Probable	Probable
31.	Thrombocytopenia	Carbamazepine	Probable	Probable	Probable	Probable	Probable
32.	Thrombocytopenia	Aspirin	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
		Phenytoin	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
33.	Thrombocytopenia	Enoxaparin	Possible	Possible	Probable	Possible	Probable
34.	Leukopenia	Colchicin	Probable	Possible	Probable	Possible	Possible
		Cyclophosphamide	Probable	Possible	Probable	Possible	Possible
35.	Thrombocytopenia	Clindamycin	Unlikely	Unlikely	Possible	Unlikely	Possible
36.	Thrombocytopenia	Meloxicam	Highly Probable	Probable	Probable	Probable	Probable
37.	Neutropenia	Cotrimoxazole	Possible	Possible	Possible	Possible	Possible
38.	Bicytopenia	Omeprazole	Possible	Possible	Probable	Possible	Probable
		Cefdinir	Possible	Possible	Probable	Possible	Probable
39.	Thrombocytopenia	Heparin	Probable	Probable	Probable	Probable	Probable
40.	Thrombocytopenia	Cotrimoxazole	Possible	Unlikely	Possible	Unlikely	Possible
41.	Leukopenia	Cloxacillin	Highly probable	Probable	Probable	Probable	Probable

[a] unlikely = unrelated = doubtful

[b] highly probable = definite

APPENDIX C

ADVERSE DRUG REACTION	Date.	HN. AN.

I. THE PATIENT

INITIALS (first, last): SEX: WEIGHT; OTHER;
OCCUPATION: AGE; HEIGHT;

PREVIOUS RELEVENT HISTORY

	No	Yes	Specify
HEREDITARY HEMOLYSIS;	☐	☐	
Patient ☐ Family ☐			
Hematological-Oncological	☐	☐	
Allergic disease	☐	☐	
Allergic reactions	☐	☐	
Smoking	☐	☐	

	No	Yes	Specify
Drug intolerance	☐	☐	
Alcohol	☐	☐	
Other:			

II. THE ADVERSE REACTION

DATE OF ONSET: NATURE OF FIRST SIGNS:

DESCRIPTION

	No	Yes	Date
Purpura	☐	☐	
Epistaxis	☐	☐	
Gingivorrhagia	☐	☐	
GI bleeding	☐	☐	
Genital bleeding	☐	☐	
Cerebro-meningeal Bleeding	☐	☐	
Retinal bleeding	☐	☐	
☐ Other bleeding: Specify			

	No	Yes	Date
Fever	☐	☐	
Headache	☐	☐	
Oropharyngeal ulceration	☐	☐	
Perineal ulceration	☐	☐	
Lumbar pain	☐	☐	
Abdominal pain	☐	☐	
Bone pain	☐	☐	
☐ Other:			

	No	Yes	Date
Jaundicce	☐	☐	
Splenomegaly	☐	☐	
Black/red urine	☐	☐	
Anuria	☐	☐	
Shock/collapsus	☐	☐	
Infection	☐	☐	
Localized			

LABORATORY DATA: Before/during/after treatment

Date										
Temp										
BP										
RR										
PR										
Date										
RBC (4.6-6.2 /4.2-5.4 x10^6)										
Hemoglobin (13-18/12-16)										
Hematocrit (40-54/37-47)										
MCV (80-100)										
MCH (27-34)										
MCHC (33-35)										
RDW										
WBC (4500-11000)										
PMN (40-75%)										
Lymphocytes (20-50 %)										
Monocytes (2-10 %)										
Baso (<1%)										
Eosinos (1-6 %)										
Platelets (15-450 000/mm^3)										
ESR										
Date										
Total bilirubin										
Direct bilirubin										
Bleeding time										
PTT (28-42 sec) (Pt/control)										
INR										
PT (11-15 sec)										
BUN/SCr										
Alb										
SGOT/SGPT										
LDH										

OTHER LAB DATA:				Not done	Neg.	Pos.	
C/S	Result	Date:	ANA	☐	☐	☐	Type:
			HIV serology	☐	☐	☐	Method:
			Other serologies	☐	☐	☐	Virus: Titre:
				☐	☐	☐	Virus: Titre:
				☐	☐	☐	Virus: Titre:
				☐	☐	☐	Virus: Titre:
			Serum freezing	☐ No	☐Yes	Date:	
			Other (specify)				

Bone Marrow Aspiration			
Cellularity	☐ Increase	☐ Normal	☐ Decrease
Megakaryocyted	☐ Increase	☐ Normal	☐ Decrease
Myelocytes	☐ Increase	☐ Normal	☐ Decrease

Bone Marrow Biopsy

☐ No

☐ Yes, If yes, attach the result

Coomb's test	☐ Not done	☐ Neg.	☐ Pos.	Date
Indirect Coomb's test	☐ Not done	☐ Neg.	☐ Pos.	Date
Cold aggutinin	☐ Not done	☐ Neg.	☐ Pos.	Date
Titre:				

If positive Coomb's test

Type:

Specificity:

TREATMENT OF THE HEMOLYSIS ANC/OR ITS COMPLICATIONS (specify doses and duration)		OUTCOME (Tick more than one if necessary)	
☐ Steroids	Other, specify	☐ No hospitalization	☐ Death Date:
☐ RBC transfusions, dates:		☐ Hospitalization necessary	Cause
☐ Platlet transfusion		☐ Prolonged hospitalization	Relationship b/w rxn and death
Date Type		☐ Complete recovery	☐ Not assessable
☐ Immunoglobulin		☐ Recovery with sequelae (specify):	☐ Unlikely ☐ Likely

III. SUSPECTED DRUG				
Name	ADMINISTRATION AFTER THE BEGINNIKG OF RXN	IMMEDIATEE RESULT	READMINISTRATION	PREVIOUS THERAPY w/ THE SAME DRUG
Indication		☐ Improvement	☐ No	☐ No
Daily dose	☐ Stop	☐ Aggravation	☐ Yes, and if yes	☐ Yes
Route	☐ Continued (same dose)	☐ No change	RECURRENCE OF THE REACTION	Safety issue:
Date beginning	☐ Reduced dose:	☐ Uninterpretable	☐ No	
Date end	Other:		☐ Yes	
Duration			☐ Uninterpretable	

Time Sequence

APPENDIX D

Expert's Opinion Form
Patient Name..... **HN**.....**AN**.....
Suspected Drug.....
Please mark "X" on the probability line

Impossible. No way	I cannot be sure. One way or the other	Absolutely. No doubt.

Expert Name.....

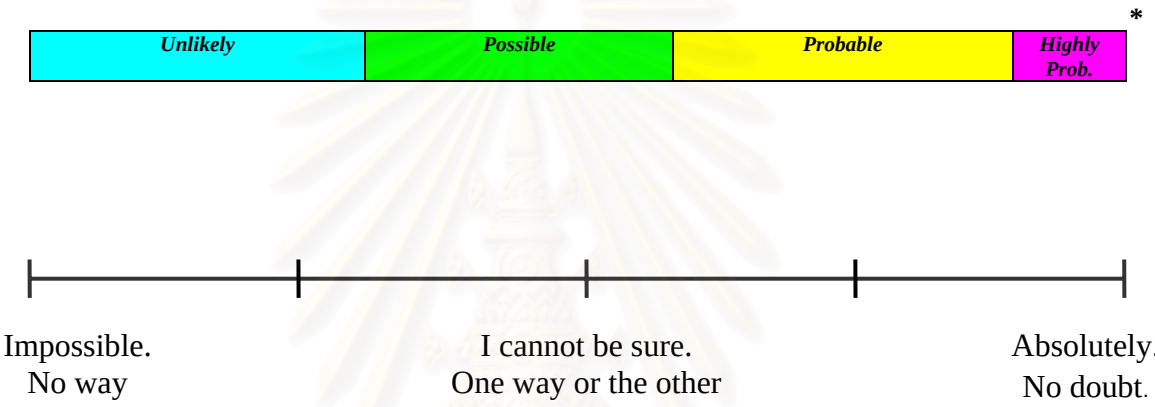
APPENDIX E

Expert's Opinion Form

Patient Name..... **HN**.....**AN**.....

Suspected Drug.....

Please mark "X" on the probability line



Expert Name.....

* adapted from Shear's visual analogue scale for which diagnosing cutaneous adverse drug reaction. [63]

APPENDIX F

Causality Assessment of a Drug in a Case of Acute Liver Injury [13]

	Heptocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to Onset					
Incompatible	Reaction occurred before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)		Reaction occurred 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 time to onset, then the cases is				Insuff. documented
- From the beginning of the drug					Score (Circle the results)
Suggestive	5 to 90 days	1 to 15 days	5 to 90 days	1 to 90 days	+2
Compatible	<5 or ≥ 90 days	> 15 days	<5 or ≥ 90 days	> 90 days	+1
- From cessation of the drug					
Compatible	≤ 15days	≤ 15days	≤ 30 days	≤ 30 days	+1
2. Course	Difference between the peak of ALT (SGOT) and upper limit of normal values		Difference between the peak of AP (or TB) and upper limit of normal values		
After cessation of the drug					
Highly suggestive	Decrease ≥ 50 % within 8 days		Not applicable		+3
Suggestive	Decrease ≥ 50 % within 30 days		Decrease ≥ 50 % within 180 days		+2
Compatible	Not applicable		Decrease ≥ 50 % within 180 days		+1
Inconclusive	No information		Persistence of increase or no information		0
Against the role of the drug	Decrease ≥ 50 %, after the 30th day, or Decrease < 50 %, after the 30th day,		No situation		-2
If the drug is continued	or recurrent increase		Not applicable		-2
Inconclusive	All situation		All situation		0
3. Risk factors	Ethanol		Ethanol or pregnancy		
Presence					+1
Absence					0
Age ≥ 55 years					+1
Age < 55 years					0
4. Concomitant drug(s)					
None or on information or concomitant drugs 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 (positive rechallenge or validated test)					-3
5. Search for nondrug causes					
Group (6 causes)= Recent viral infection with HAV (IgM anti-HAV antibody) or HBV (IgM anti-HBc antibody and circumstantial arguments for non A-non B hepatitis); Biliary obstruction (ultrasonography); Alcoholism (AST/ALT ≥ 2); Acute recent hypotension history (particularly if underlying heart disease) Group II= Complications of underlying disease(s); Clinical and/or biological context suggesting CMV, EBV or Herpes virus infection	All causes-groups I and II-reasonably ruled out				+2
	The 6 causes of group I ruled out				+1
	5 or 4 causes of group I ruled out				0
	Less than 4 causes of group I ruled out				-2
	Non drug cause highly probable				-3
6. Previous information of hepatotoxicity of the drug					
Reaction labelled in the product characteristic					+2
Reaction published but unlabelled					+1
Reaction unknown					0
7. Response to readministration					
Positive	Doubling of ALT with the drug alone		Doubling of AP (or TB) with the drug alone		+3
Compatible	Doubling of ALT with the drugs already given at the time of the 1st reaction		Doubling of AP (or TB) with the drugs already given at the time of the 1st reaction		+1
Negative	Increase of ALT but less than N in the same conditions as for the first administration		Increase of AP (or TB) but less than N in the same conditions as for the first administration		-2
Not done or not interpretable	Other situation		Other situation		0
				Total score	

APPENDIX G

Drug-induced Liver Injury (DILI) Diagnostic Scale [14]

I. Temporal Relationship Between Drug Intake and the Onset of Clinical Picture	
A. Time from drug intake until the onset of first clinical or laboratory manifestations	Score
4 days to 8 weeks (or less than 4 days in cases of reexposure).....	3
Less than 4 days or more than 8 weeks.....	1
B. Time from withdrawal of the drug until the onset of manifestations	Score
0 to 7 days.....	3
8 to 15 days.....	0
More than 15 days*.....	-3
C. Time from withdrawal of the drug until normalization of laboratory values†	Score
Less than 6 months (cholestatic or mixed patterns) or 2 months (hepatocellular)..	3
More than 6 months (cholestatic or mixed) or 2 months (hepatocellular).....	0
II. Exclusion of Alternative Causes‡	
Viral hepatitis (HAV, HBV, HCV, CMV, EBV) Alcoholic liver disease Biliary tree obstruction Preexisting liver disease Other (pregnancy, acute hypotension)	Score
Complete exclusion.....	3
Partial exclusion.....	0
Possible alternative cause detected.....	-1
Probable alternative cause detected.....	-3
III. Extrahapatic manifestrations	
Rash, fever, arthralgia, eosinophilia (>6%), cytopenia	Score
4 or more.....	3
2 or 3	2
1.....	1
None.....	0
IV. Interantional or Accedental Reexposure to the drug	
Positive rechallenge test.....	3
Negative or absent rechallenge test.....	0
V. Previous report in the Literature of Cases of DILI Associated with the Drug	
Yes.....	2
No (drugs marketed for up to five years).....	0
No (drugs marketed for more than five years).....	-3
Total score	

APPENDIX H

Naranjo's algorithm

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total Score			

The total score calculated from this table defines the category an adverse reaction belongs to. The categories are defined as follows:

Definite	(total score > 9)
Probable	(total score 5-8)
Possible	(total score 1-4)
Doubtful	(total score ≤ 0)

APPENDIX I

Estimation of Risk Probability Score

Maria and Victorino Scale

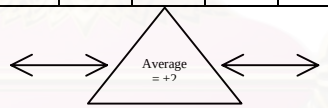
-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

RUCAM

-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14

New causality assessment criteria

-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14



Unlikely

Probable

Possible

Highly probable

APPENDIX J

Statistics of concordance for ADR agreement [61,64]

ADR agreement matrix containing observed classification (O_{ij}) and assigned weighted (w) for disagreements:

Method A	Method B				Total
	1	2	3	4	
1 (Unlikely)	O_{11} (0)	O_{12} (1)	O_{13} (2)	O_{14} (3)	r_1
2 (Possible)	O_{21} (1)	O_{22} (0)	O_{23} (1)	O_{24} (2)	r_2
3 (Probable)	O_{31} (2)	O_{32} (1)	O_{33} (0)	O_{34} (1)	r_3
4 (Highly Probable)	O_{41} (3)	O_{42} (2)	O_{43} (1)	O_{44} (0)	r_4
Total	C_1	C_2	C_3	C_4	N

Chance-expected frequencies: $E_{ij} = \frac{r_j c_j}{N}$

Percentage agreement observed: $P_o = \frac{(O_{11} + O_{22} + O_{33} + O_{44})}{N}$

Percentage agreement expected: $P_c = \frac{(E_{11}+E_{22}+E_{33}+E_{44})}{N}$

Observed proportion of weighted disagreement: $q_{o'} = \frac{(\sum wO_{ji})}{N}$

Chance-expected proportion of weighted disagreement: $q_{e'} = \frac{(\sum wE_{ji})}{N}$

Weighted Kappa: $\kappa_w = \frac{1 - q_{o'}}{q_{e'}}$

SE_o of κ_w: $\sigma = \sqrt{[N(\sum w^2 E_{ji}) - (\sum wE_{ji})^2] / (\sum wE_{ji})^2 N}$

95% CI $\kappa_w = \kappa_w \pm 1.96\ SE_o$; where SE_o is a standard error of $\kappa_w = 0$

Example:

Table D.1 *shown ADR agreement matrix containing observed classification and assigned weighted for* ***agreements****.*

Consensus expert diagnosis	New Clinical Scale				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	18 (g-1=3)	1 (2)	0 (1)	0 (0)	19
Possible	3 (g-2=2)	7 (3)	2 (2)	0 (1)	12
Probable	0 (g-3=1)	5 (2)	15 (3)	1 (2)	21
Highly probable	0 (g-4=0)	1 (1)	4 (2)	1 (3)	6
Total	21	14	21	2	58

Note: Numbers in cells represent observed frequencies (f_o); numbers in parentheses are assigned weighted (w_i) for ***agreement*****;** g is the number of categories contained the scale (g of this scale is 4).

$$\text{Percentage agreement} = \left[\frac{18+7+15+1}{58}\right](100)$$

$$= 70.69\ \%$$

$$\text{Percentage weighted agreement} = \frac{\sum x_i w_i}{N(g-1)}(100)$$

$$= \left[\frac{(18+7+15+1)(3) + (3+1+5+2+4+1)(2) + (0+1+0+0)(1) + (0)(0)}{58(3)}\right] \text{X } 100$$

$$= 89.66\ \%$$

Table D.2 *shown ADR agreement matrix containing observed classification and assigned weighted for* ***disagreement****.*

Consensus expert diagnosis	New Clinical Scale				Total
	Unlikely	Possible	Probable	Highly probable	
Unlikely	18 (6.88) 0	1 (4.59) 1	0 (6.88) 2	0 (0.66) 3	19
Possible	3 (4.34) 1	7 (2.9) 0	2 (4.34) 1	0 (0.41) 2	12
Probable	0 (7.60) 2	5 (5.07) 1	15 (7.60) 0	1 (0.72) 1	21
Highly probable	0 (2.17) 3	1 (1.45) 2	4 (2.17) 1	1 (0.21) 0	6
Total	21	14	21	2	58

Note: Numbers in cells represent observed frequencies (f_o); numbers in parentheses indicate chance-expected cell frequencies (f_c); numbers in upper right corner are assigned weighted (w) for ***disagreement***.

Observed proportion of weighted disagreement: $q_{o'} = \frac{(\sum wO_{ji})}{N}$

$$= \frac{(18+7+15+1)(0) + (3+1+5+2+4+1)(1) + (0+1+0+0)(2) + (0+0)(3)}{58}$$

$$= 0.31$$

Chance-expected proportion of weighted disagreement: $q_{e'} = \frac{(\sum wE_{ji})}{N}$

$$= \frac{(6.88+2.90+7.60+0.21)(0) + (4.34+4.59+5.07+4.34+2.17+0.72)(1) + (7.6+1.45+6.88+0.41)(2) + (2.17+0.66)(3)}{58}$$

$$= 1.076$$

Weighted Kappa: $\kappa_w = 1 - \frac{q_{o'}}{q_{e'}}$

$$= 1 - \frac{0.31}{1.076}$$

$$= 0.712$$

SE_o of κ_w: $\sigma = \sqrt{[N(\sum w^2 E_{ji}) - (\sum wE_{ji})^2] / (\sum wE_{ji})^2 N}$

$$= 0.09796$$

95%CI $\kappa_w = \kappa_w \pm 1.96\ SE_o$

$$= 0.712 \pm 1.96\ (0.09796)$$

$$= 0.712 \pm 0.192$$

APPENDIX K

Application of the clinical scale

Example: A 65-year-old, Thai female, presented with 4 days of low-graded fever, myalgia and fatigue. She had no cough, no rhinorrhea, and no sore throat. After that, she went to the out patient clinic of a private hospital and received home medications. Two days prior to admitted at Chulalongkorn Memorial Hospital, she went to that private hospital again due to her existing symptoms, she also had chest pain at the sternal area. At that hospital, her hematocrit was 42%, 2300 cells/mm^3 of WBC with 72% neutrophil and 19% of lymphocyte, her platelet was 44,000 cell/mm^3 and LDH was 678 U/L. Her EKG presented non-specific T-wave change. Her attending physician diagnosed her of bicytopenia and she was referred to Chulalongkorn Memorial Hospital for further work up.

Her past medical history was dyslipidemia and she has taken gemfibrosil 300 mg 1 capsule daily for 2-3 years. One year PTA, she had osteoarthritis (OA) at both knees and received meloxicam (30mg) 1 tablet daily for her OA. After taking meloxicam for 4-5 months, she complained bleeding per gum during tooth brushing. Medications on admission were gemfibrosil and meloxicam.

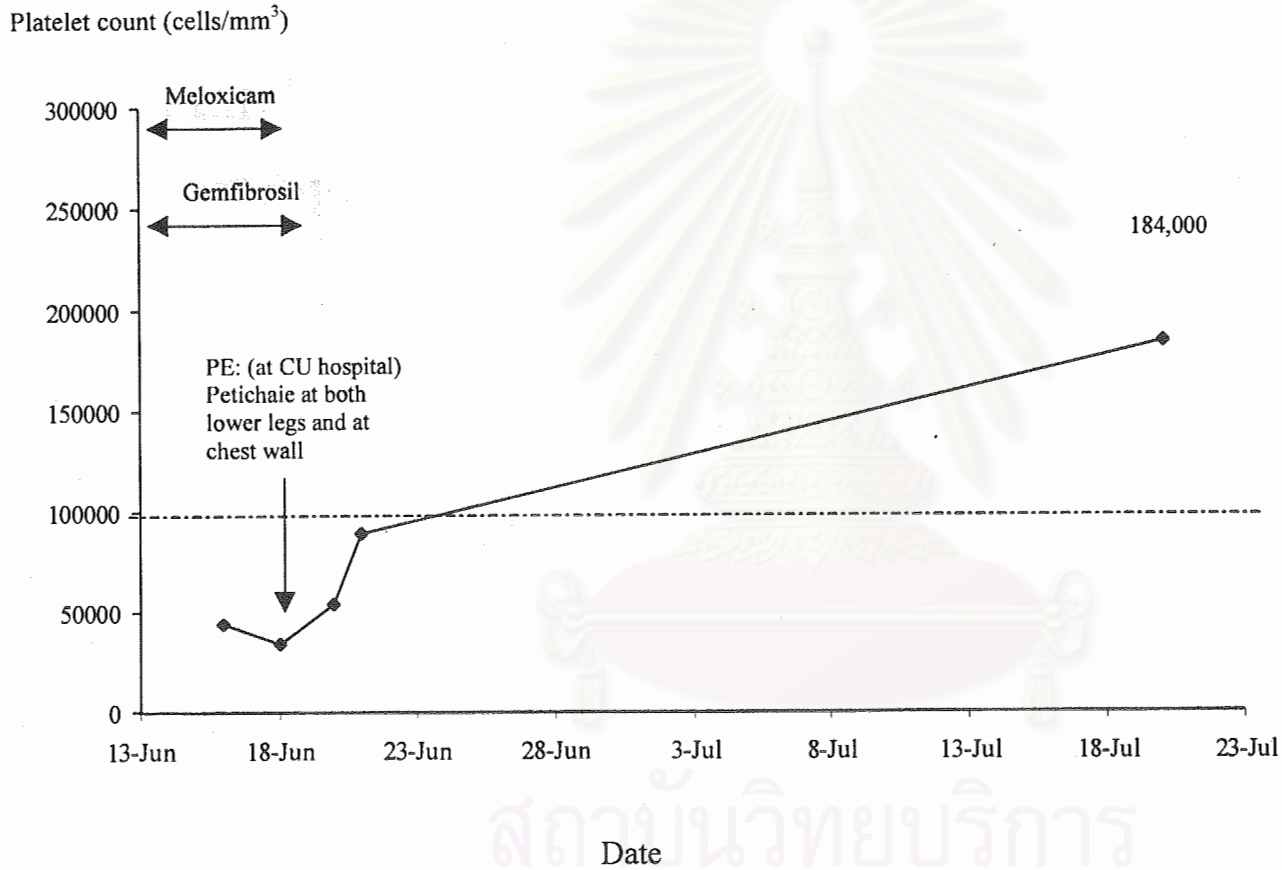
At Chulalongkorn Memorial Hospital, her body temperature was 36.6 °C, her blood pressure was 118/74 mmHg, her heart rate was 84 beats/min and respiratory rate was 16 breaths/min. Skin examination revealed diffuse petechiae at both lower legs and chest wall. She had no pale, no jaundice, no oral ulcer and negative cervical lymph node. Her lung sound was clear and no adventitious sound. Cardiac examination was normal S_1, S_2 and no murmur. She had normal bowel sound with no abdominal tenderness, mass or hepatospleenomegaly. She had no edema or deformity of body. Examination of neurologic system was grossly intact. Admission laboratory studies showed hematocrit 37.7%, white blood cell count 3700/mm^3, platelet count 34,000/mm^3, creatinine 0.4 mg/dL and blood urea nitrogen 9 mg/dL.

Meloxicam was discontinued on hospital day 2 (19/6). On day 3, gemfibrosil was withheld and her WBC count was 3980/mm^3, platelet count was 54,000/mm^3. On day 4, her platelet count increased to 89,000/mm^3. The platelet count trended upward during

hospitalization and the patient was discharged on hospital day 5. Discharged medications were tramadol 1 capsule prn for pain and diazepam (2mg) 1 tablet at bed time. One month after discharge, the platelet count returned to normal value of 184,000/mm^3.

Table 6.1 *Laboratory Data*

Date	**Jun 16**	**Jun 18**	**Jun 20**	**Jun 21**	**Jul 20**
Temp		37.3	36.8	37.2	
BP		20	20	20	
RR		140/80	120/70	110/70	
PR		63	84	88	
Date	**Jun 16**	**Jun 18**	**Jun 20**	**Jun 21**	**Jul 20**
RBC (4.6-6.2 /4.2-5.4 x10^6)				4.39	4.60
Hemoglobin (13-18/12-16)	13.8	12.9	13.6	13.3	14.5
Hematocrit (40-54/37-47)	42	37.7	39.9	39.8	44
MCV (80-100)		88	89	91	95
MCH (27-34)		30.0	30.4	30.3	31
MCHC (33-35)		34.2	34.1	33.4	32
RDW		12.5	14.8	12.4	
WBC (4500-11000)	2300	3700	3980	3680	5100
PMN (40-75%)	72	39.2	25	30	46
Lymphocytes (20-50 %)	19	41.1	41	54	42
Monocytes (2-10 %)		17.8	2	9	9
Baso (<1%)					
Eosinos (1-6 %)					3
Platelets (15-450 000/mm^3)	44000	34000	54000	89000	184000
ESR					
Date	**Jun 16**	**Jun 18**	**Jun 20**	**Jun 21**	**Jul 20**
Total bilirubin			1.35		0.7
Direct bilirubin			0.83		0.1
Bleeding time					
PTT (28-42 sec) (Pt/control)				9.6/11.0	
INR				0.8	
BUN/SCr	10.1/0.8	5/0.4			12.4/0.4
Alb					4.5
SGOT/SGPT			211/202		58/96
LDH	678				



A 65-year-old, Thai female, presented with 4 days of low grade fever, myalgia and fatigue

Concurrent illness

1. Dyslipidemia x 2-3 years
2. Osteoartitis x 1 year

Figure 0.1 *Time relationship of meloxicam-induced thrombocytopenia*

Axis I: Chronological relationship

Approach Question			Scores
I. Chronological criterion: *Is the timing of the event related to administration of suspected drug? And, does the problem improve when discontinue the offending drug?*			
- Discovery of event before take the suspected drug or more than 1 month after stop the drug			Unrelated
-Time from drug intake until the onset of first clinical or laboratory manifestation	**Initial Treatment**	**Subsequent Treatment**	
		≤ 7 days	+3
	≤ 1 month	8-30 days	+2
	> 1 month	> 1 month	+1✗
	Within 1 month after stopping		0
- Time from withdrawal of the drug until normalization of manifestation	**Without stopping**	**After stopping**	
	Continuing ↓ in platelet	Recovery within 3 weeks with or without treatment	+1
	Disappearance of thrombocytopenia	Recovery after 3 weeks with or without treatment	0 ✗
	-	Relapse after 3 weeks.	-3

Discussion: In this patient, thrombocytopenia occurred after taking meloxicam. The timing of this abnormality may be approximately 4-5 months after taking the first dose of suspected drug, which was assumed by the minor clinical bleeding evidence, such as bleeding per gum. This adverse event resolved after discontinuation of meloxicam for approximately 1 month without other treatment.

Axis II: Alternative Causes

Approach Question	Scores
II. Alternative Cause: *Are there any common alternative causes (e.g., aplasia, blood disorder; liver disease with or without alcoholism; bacterial or viral infection; Idiopathic thromcytopenic purpur:ITP, etc.) that could explain this event?*	
Complete excluded	+3
Partial excluded with no evidences that rule in another causes	+1 ✗
Not investigated	0
Possible another cause detected	-1
Probable another cause detected	-2
Highly probable another cause detected	-3

Discussion: [64,79] The 4 general major types of thrombocytopenia are platelet underproduction, increased platelet destruction, platelet sequestration, and hemodilution. Platelet underproduction is usually seen in disorder related to bone marrow dysfunction such as malignancy and toxic exposure, which usually causes pancytopenia. Platelet sequestration is inconsistent in our patient because she had no spleenomegaly and her platelet count had

never been low either before or after exposure to meloxicam. Also, there was no clinically apparent infection or malignancy discovered in this patient during taking meloxicam.

Hemoditlution by blood product transfusion and fluid administration is impossible because she had never been received transfusion of fluid or blood product before her clinical bleeding symptom appearred. In, addition, her hemoglobin level and clinically volemic state were normal.

Disseminated intravascular coagulation (DIC) may be incompatible due to normal PTT value. Also, she had no high-grade fever, thus the sepsis-induced thrombocytopenia may not be the cause of adverse event in this patient. In addition, the classic clinical association of malignacy was not present. Moreover, her underlying diseases have hyperlipidemia and osteoathritis, which did not associated with thrombocytopenia.

For idiopathic thrombocytopenic purpura (ITP), it can only be diagnosed with a proper clinical situation that does not involve the administration of suspected medication. We believe that this cause might not associated with decreased platelet in our patient.

Axis 3: Concomitant Drugs

Approach Question	Scores
III. Concomitant Drug: *Does the patient receive another drug that may be cause of this event?*	
No concomitant drug or Yes, if the onset is incompatible	+1 ✗
No documented or Yes, if the onset is compatible with no reported and drug marketed > 5 years.	0
Yes, if the onset is compatible with no reported and drug marketed ≤5 years.	-1
Yes, if the onset is compatible with known reaction.	-2
Yes, if the onset is compatible with evidence for this event.	-3

Discussion: There was only one concomitant drug which was gemfibrosil. However, this drug had been taken for 1 year prior to taking meloxicam. Thus, we believe the timing of this agent was incompatible.

Axis 4: Clinical Feature

Approach Question	Scores
IV. Clinical Feature*: Does the patient have any clinical features (e.g.,petechia, ecchymoses, epistaxis, hemorrhagic bullae inside the mouth, gingival bleeding, conjuntival or retinal bleeding, GI bleeding, hypermenorrhea, etc.)?*	
Yes	+1✗
None	0

Discussion: On admission date, the patient had petichaie at both lower legs and at chest wall. She also complained of bleeding per gum during tooth brushing which occurred after taking meloxicam for approximately 4-5 months.

Axis 5: Rechallenge

Approach Question	Scores
V. Re-challenge: *Did the problem recur with intentional or accidental re-exposure to suspected drug?*	
Yes, positive rechallenge	+3
Not done or No documented	0 ✗
Yes, negative rechallenge	-3

Discussion: On chart and OPD card reviewed at our hospital, she had not been rechallenged with meloxicam.

Axis 6: Previous Report

Approach Question	Scores
VI. Previous Report: *Has this type of adverse event previously been reported?*	
Yes	+2 ✗
No: drug marketed $\leq$ 5 years	0
No: drug marketed > 5 years	-2

Discussion: To date, there has been only 1 study [80] reporting the thrombocytopenia related to meloxicam which published in 2000. It was found that meloxicam-induced thrombocytopenia was rare event, there were only 2 cases occurred after taking it.

Risk Probability Scale

$\geq$ 9 Highly probable	✗ 6-8 Probable	3-5 Possible	$\leq$ 2 Unlikely

Discussion: According to the information in this case study, the summation of score in each axis was 6 points that indicated a probable relationship between meloxicam and the subsequent thrombocytopenia.

VITAE

Mr. Sarit Namwong was born on June 2, 1973 in Muaklek District of Saraburi Province, Thailand. He received his Bachelor Degree of Science in Pharmacy from Chiang Mai University (CMU). He had worked for several years as a hospital pharmacist at Chiang Rai Prachanookore Center Hospital before moving to Saraburi Center Hospital in 1999. Since June 2000, he had been enrolled in the Master Degree Program of Clinical Pharmacy at Faculty of Pharmaceutical Sciences, Chulalongkorn University (CU). He had principal research interesting in the safety of drug therapy. During this course, he had conducted a study of development of causality assessment criteria in drug-induced blood dyscrasias in Thai patients. In the future, this clinical pharmacy-training course will enable him to involve more in the future pharmacy practice and research program in Saraburi Center Hospital.

Currently, he is the staff clinical pharmacist at Department of Pharmacy Service in Saraburi Center Hospital.