



بسم الله الرحمن الرحيم

∞∞∞∞

تم رفع هذه الرسالة بواسطة / مني مغربي أحمد

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى

مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد





Serious Drug Induced Hypersensitivity Reactions among Hospitalized Infants and Children

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

By

Saeid Fawzey Turkey

M.B., B.Ch., Ain Shams University (2014).

Under Supervision of

Dr. Rasha Hassan El-Owaidy

Associate Professor of Pediatrics

Faculty of Medicine, Ain Shams

University

Dr. Ahmed Rezk Ahmed

Lecturer of Pediatrics

Faculty of Medicine, Ain Shams

University

Faculty of Medicine

Ain Shams University

2022



سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to **Allah**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Rasha Hassan EL-Owaidy**, Associate Professor of Pediatrics, Faculty of Medicine, Ain-Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made the completion of this work possible.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Ahmed Rezk Ahmed** Lecturer of Pediatrics, Faculty of Medicine, Ain-Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I would like to express my hearty thanks to all **my family** for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Saeid Turkey

LIST OF CONTENTS

Title No.	Page
List of Tables	i
List of Figures	iv
List of Abbreviation	vi
Introduction	1
Aim of the work	5
Review of literature	6
Definition of "Adverse drug reaction".....	6
Definition of "Drug hypersensitivity reactions(DHRs)".....	7
Definition of "Serious drug hypersensitivity reactions".....	8
Epidemiology of DHRs.....	9
Factors that may affect DHRs in children.....	12
Types, pathogenesis and clinical presentation of DHRs.....	26
Diagnosis of DHRs.....	32
Management of DHRs.....	49
Prevention of future reactions.....	58
Prognosis of DHRs.....	58
Patients and methods	60
Results	70
Discussion	101
Recommendations	118
Summary	119
References	123
Arabic summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Studies on the epidemiology of adverse drug reaction, drug hypersensitivity, and drug allergy in children.....	13
Table (2):	Risk factors for drug hypersensitivity reactions.....	15
Table (3):	Modern classification of hypersensitivity reactions.....	33
Table (4):	Reading criteria of the ICDRG.....	42
Table (5):	Maximum nonirritant drug concentration of drugs used for SPT and IDT.....	65
Table (6):	Dilutions of the drugs used for DPT.....	67
Table (7):	Reading criteria for patch test according to the ICDRG.....	68
Table (8):	Demographic characteristics of the study cohort.....	70
Table (9):	Family history of the study cohort.....	71

Table (10): Associated allergic disorders among the study cohort.....	72
Table (11): Medication class and the underlying illness.....	74
Table (12): Culprit medication in the study cohort.....	75
Table (13): Chronological relation between development of allergy and admission to hospital in the study cohort.....	78
Table (14): Clinical presentation and type of allergy in the study cohort.....	80
Table (15): Time from administration of medication to onset of reaction in the study sample.....	81
Table (16): Results of hematological workup in the study cohort..	82
Table (17): Management and outcome of allergic reactions in the study cohort.....	83
Table (18): Post-discharge workup in the study cohort.....	85
Table (19): Demographic characteristics of patients suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	86

Table (20): Family history in patients suffering from SJS, severe
urticaria/angioedema or
anaphylaxis.....**87**

Table (21): Past history in patients suffering from SJS, severe
urticaria/angioedema or
anaphylaxis.....**88**

Table (22): Culprit medication in patients suffering from SJS,
severe urticaria/angioedema or
anaphylaxis.....**89**

Table (23): Chronological relation between allergy and admission
and time to onset of reaction in patients suffering from SJS, severe
urticaria/angioedema or
anaphylaxis.....**92**

Table (24): Clinical presentation in patients suffering from SJS,
severe urticaria/angioedema or
anaphylaxis.....**96**

Table (25): Hematological work-up in patients suffering from SJS,
severe urticaria/angioedema or
anaphylaxis.....**98**

Table (26): Management and outcome in patients suffering from
SJS, severe urticaria/angioedema or
anaphylaxis.....**99**

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Revised Gell and Coombs classification of drug reactions.....	34
Figure (2):	General diagnostic approach for drug hypersensitivity reactions.....	36
Figure (3):	Representation of the general mechanisms drug hypersensitivity reactions indicating the most used in vitro tests used for diagnosis.....	44
Figure (4):	Skin prick test.....	66
Figure (5):	Intradermal testing technique.....	66
Figure (6):	Culprit medication in the study cohort.....	76
Figure (7):	Class of culprit medication in the study cohort....	76
Figure (8):	Previous exposure to the culprit medication.....	77
Figure (9):	Chronological relation between development of allergy and admission to hospital.....	78
Figure (10):	Clinical manifestations of drug hypersensitivity among the studied patients.....	81

Figure (11): Management of the drug hypersensitivity reactions among the study cohort.....	84
Figure (12): Percentage of patients presenting with vancomycin allergy among those suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	91
Figure (13): Percentage of patients presenting with antipyretic-analgesic allergy among those suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	91
Figure (14): Chronological relation between allergy and admission in patients suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	93
Figure (15): Box plot illustrating time from administration of medication to onset of reaction in patients suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	94
Figure (16): Kaplan-Meier curves for time to onset of reaction to medication in patients suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	95
Figure (17): Percentage of patients presenting with clinical manifestation among those suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	97
Figure (18): Lines of management offered to patients suffering from SJS, severe urticaria/angioedema or anaphylaxis.....	100

List of Abbreviations

Abb.	Full term
ADR.....	Adverse drug reaction
AGEP.....	Acute generalized exanthematous pustulosis
AR.....	Allergic rhinitis
BA.....	Bronchial asthma
BAT.....	Basophil activation test
CLV.....	Clavulanic acid
CMPA.....	Cow's milk protein allergy
CRP.....	C- reactive protein
CXCL8.....	C-X-C Motif Chemokine Ligand 8
CYP.....	Cytochrome P450
DA.....	Drug allergy
DH.....	Drug hypersensitivity
DHRs.....	Drug hypersensitivity reactions
DPT.....	Drug provocation test
DRESS.....	Drug reaction with eosinophilia and systemic symptoms

ESR.....	Erythrocyte sedimentation rate
FcR.....	Fc receptor
GM-CSF.....	Granulocyte monocyte colony-stimulating factor
HB.....	Haemoglobin
HLA.....	Human leukocyte antigen
ICDRG.....	International Contact Dermatitis Research Group
I-DHR.....	Immediate drug hypersensitivity reaction
IDT.....	Intradermal test
IFN- γ	Interferon gamma
IL.....	Interleukin
IQR.....	Interquartile range
LGALS3.....	Galectin-3 lectin domain
MDH.....	Multiple drug hypersensitivity syndrome
MPE.....	Maculopapular exanthema
N/A.....	Not assessed
NAT.....	N-acetyltransferase
NI-DHR.....	Non-immediate drug hypersensitivity reaction
NMBA.....	Neuromuscular blocking agents
NOD2.....	Nucleotide-binding oligomerization domain genes
NSAID.....	Nonsteroidal anti-inflammatory drugs

PTs.....Patch tests
RCM.....Radiocontrast media
SCARS.....Severe cutaneous adverse reactions
SJS.....Stevens-Johnson syndrome
SPT.....Skin prick test
SSLR.....Serum sickness-like reactions
STs.....Skin testing
TEN.....Toxic epidermal necrolysis
Th.....T helper cells
TNF.....Tumor necrosis factor
UGT.....Diphosphate glucuronosyltransferase
WBCs.....White blood cells

ABSTRACT

Background: There are very limited data concerning the epidemiology of drug hypersensitivity in Egypt. **Aim:** We sought to investigate the magnitude of serious drug hypersensitivity reactions among hospitalized infants and children in a tertiary hospital over a period of one year. **Patients and methods:** This is a cross-sectional study that was conducted over a period of one year from the middle of October 2020 to the middle of October 2021. The study was carried out in Children's Hospital, Ain Shams University. We screened for patients with serious drug hypersensitivity reactions among a total of 10440 hospital admissions over a period of 12 months. Positive cases were further assessed with complete clinical and laboratory assessment. **Results:** Out of total admissions of 10440 patients over the study period, 35 (0.335%) patients had clinical manifestations of serious drug hypersensitivity reactions. Concerning those 35 patients, they were 21 (60%) males and 14 (40%) females with age ranging between 3 to 193 months with median (IQR) = 50 (24-96) months. In our study different medications were accused of causing serious drug hypersensitivity reactions. Antibiotics in general showed the highest frequency (54.3%) especially vancomycin (20%) followed by blood products (20%). Other drugs included antipyretics-analgesics, antiepileptic, cytotoxic and biological agents were suspected also to be the trigger of a serious drug hypersensitivity reactions but with lower frequencies (11.4%, 5.7%, 5.7% and 2.9% respectively). Four patients (11.4%) were known to be allergic; with 1(2.9%) having allergic rhinitis, 1 (2.9%) having urticaria, and 2 (5.7%) having cow milk protein allergy. Ten patients (28.6%) had family history of allergic disorders. Eleven patients (31.4%) had manifestations of anaphylaxis, 18 (51.4%) severe urticaria/angioedema, while the remaining 6 (17.1%) had manifestations of Stevens-Johnson syndrome. Concerning results of laboratory investigations, anemia was found in 29 (82.9%) patients, leukocytosis in 9 (25.7%) patients, leukopenia in 8 (22.9%) patients and thrombocytosis in 4 (11.4%) patients, while none of them had eosinophilia. CRP and ESR were elevated in 24 (68.6%) and 15 (42.9%) patients respectively. All of the 35 patients could overcome the drug hypersensitivity reaction with proper management. **Conclusions:** Although drugs hypersensitivity was rarely reported in our study, but they are potentially life threatening in many cases and should be clearly well reported. Proper education of the nursing staff and doctors in different specialties about different presentation and management of drugs hypersensitivity are essentially important. This would greatly help to prevent morbidity and mortality.

Key words: Drug-Induced Hypersensitivity, Hospitalized Infants, Children

INTRODUCTION

An adverse drug reaction (ADR) is defined as any harmful or unintended reaction to a drug that occurs at doses used for prevention, diagnosis, or treatment. Adverse drug reactions (ADRs) are broadly divided into predictable (related to pharmacologic actions of the drug in otherwise normal individuals) and unpredictable reactions (related to individual's immunological response and, on occasion, to genetic differences in susceptible patients) (*Khan and Solensky, 2010*). Drug allergy encompasses a spectrum of immunologically mediated hypersensitivity reactions with varying mechanisms and clinical presentations. This type of adverse drug reaction not only affects patient quality of life, but may also lead to delayed treatment, unnecessary investigations, and even mortality (*Johansson et al., 2004*).

Drug hypersensitivity reactions (DHR) may be IgE or non-IgE mediated. In IgE-mediated reactions, (e.g., urticaria, angioedema, anaphylaxis), drug allergens bind to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of