

**Urinary Concentrations of Eosinophil-Derived  
Neurotoxin in Children with Atopic  
Dermatitis**

**Thesis**

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Pediatrics**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْحَكِيمُ ﴾ (٣٢)

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*Amal EL Awady EL Deep*

DEDICATION

To

My Mother

My Father

and my Sister

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## List of Abbreviations

<b>AAEDS</b>	Allergic IgE associated atopic dermatitis/eczema syndrome
<b>ACD</b>	Allergic contact dermatitis
<b>AD</b>	Atopic dermatitis
<b>AEC</b>	Absolute eosinophilic count
<b>AEDS</b>	Atopic eczema/dermatitis syndrome
<b>APC</b>	Antigen presenting cell
<b>BLN</b>	Bi lobed nucleus
<b>CBC</b>	Complete blood count
<b>CCR</b>	Chemokine receptor
<b>CD</b>	Cluster of differentiation
<b>CML</b>	Chronic myeloid leukemia
<b>COX</b>	Cyclo oxygenase
<b>CRTH2</b>	Chemoattractant receptor homologous molecule expressed on Th2 cells
<b>DC</b>	Dendritic cell
<b>DNA</b>	Deoxy ribonucleic acid
<b>ECP</b>	Eosinophil cationic protein
<b>EDN</b>	Eosinophil derived neurotoxin
<b>EPO</b>	Eosinophil peroxidase
<b>EPX</b>	Eosinophil protein X
<b>FPR</b>	Formyl peptide receptor
<b>GM-CSF</b>	Granulocyte macrophage colony stimulating factor
<b>HIV</b>	Human immunodeficiency virus
<b>HLA</b>	Human leucocytic antigen
<b>ICAM</b>	Intercellular adhesion molecule

<b>IDEC</b>	Inflammatory dendritic epidermal cell
<b>IFN-<math>\gamma</math></b>	Interferon gamma
<b>IgA</b>	Immunoglobulin A
<b>IgE</b>	Immunoglobulin E
<b>IgG</b>	Immunoglobulin G
<b>IL</b>	Interlukin
<b>ILTs</b>	Ig like transcripts
<b>IQR</b>	Interquartile range
<b>ITIM</b>	Immunoreceptor tyrosine –based inhibitory motif
<b>LB</b>	Lipid bodies
<b>LC</b>	Langerhans cells
<b>LFA</b>	Leucocyte function-associated antigen
<b>LO</b>	Lipo oxygenase
<b>LPL</b>	Lysophospholipase
<b>LTR</b>	Leukotriene receptor
<b>MBP</b>	Major basic protein
<b>MIP</b>	Macrophage inflammation protein
<b>MPDs</b>	Myeloproliferative disorders
<b>mRNA</b>	Messenger ribonucleic acid
<b>NAAEDS</b>	Non allergic IgE associated atopic dermatitis/eczema syndrome
<b>Obj</b>	Objective
<b>PAF</b>	Platelet-activating factor
<b>PGE2</b>	Prostaglandin E2
<b>PMD</b>	Piecemeal degranulation
<b>P. ovale</b>	Pityrasis ovale
<b>RANTES</b>	Regulated upon activation normal T-cell expressed and secreted

<b>RSV</b>	Respiratory syncytial virus
<b>SCORAD</b>	Scoring atopic dermatitis index
<b>SD</b>	Standard deviation
<b>SG</b>	Small granules
<b>SIT</b>	Specific immunotherapy
<b>SNAP</b>	Soluble N-ethylmaleimide –sensitive factor attachment protein
<b>SNARE</b>	SNAP receptor
<b>TGF-<math>\beta</math></b>	Transforming growth factor- $\beta$
<b>Th cells</b>	T helper cells
<b><i>TNF</i></b>	Tumor necrosis factor
<b>TNF-NGF</b>	Tumour necrosis factor-nerve growth factor
<b>T Regs</b>	T regulatory cells
<b>TSLP</b>	Thymic stromal lymphopoietin
<b>VCAM-1</b>	Vascular cell adhesion molecular-1



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# INTRODUCTION AND AIM OF THE WORK

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## Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that is characterized by cutaneous hyperactivity to environmental triggers that are innocuous to non-atopic individuals (*Leung et al., 2004*). AD is often the first step in the atopic march resulting in asthma and allergic rhinitis (*Leung and Bieber, 2003*). There are at least 13 scoring systems and indices for assessment of disease severity in children with AD (*Chairman and Williams, 2000*). Problems with inter and intrapersonal variability become an unavoidable issue when using subjective clinical indices to assess the severity of AD. Thus, it would be useful for clinicians to have objective laboratory markers that correlate with clinical aspects of AD to assess the disease severity to manage it properly (*Leung et al., 2004*).

Eosinophils have a unique contribution in initiating inflammatory and adaptive responses, due to their bidirectional interactions with dendritic cells and T cells, as well as their large panel of secreted cytokines and soluble mediators (*Blanchard and Rothenberg, 2009*). Eosinophils play an effector role in AD because they migrate from blood into lesional skin of AD and release cytotoxic mediators such as cytotoxic proteins (eosinophil cationic protein and eosinophil

protein X) (*Nassenstein et al., 2003*), lipid mediators, oxygen metabolites and cytokines (*Barouch et al., 2000*).

Understanding the complex pathophysiology of allergic diseases has been a main challenge of clinical and experimental research for many years. During allergic inflammation, a bidirectional regulation of neuronal stimulation and allergic inflammation has been prospected. Neuromediators (neurotrophins and neuropeptides) represent the key factor of this process, working on either immune or structural cells and exerting neuroimmunomodulatory functions (*Nockher and Renz, 2006*). Eosinophils are potentially able to express cell surface receptors for all neurotrophins (*Nassenstein et al., 2003*). When eosinophils were cultured in the presence of neurotrophins, an antiapoptotic effect of neurotrophins was observed (*Braun et al., 1999*).

The eosinophil-derived neurotoxin (EDN, also known as eosinophil protein-X) is best-known as one of the four major proteins found in the large specific granules of human eosinophilic leukocytes. Although it was named for its discovery and initial characterization as a neurotoxin, it is also expressed constitutively in human liver tissue and its expression can be induced in macrophages by proinflammatory stimuli. EDN and its divergent orthologs in rodents have ribonuclease activity, and are members of the extensive RNase A superfamily, although the relationship between the

characterized physiologic functions and enzymatic activity remains poorly understood. Recent explorations into potential physiologic functions for EDN have provided us with some insights into its role in antiviral host defense, as a chemoattractant for human dendritic cells, and most recently, as an endogenous ligand for toll-like receptor (*Rosenberg ,2008*).