eISBN: 978-1-68108-520-3
ISBN: 978-1-68108-521-0

eISSN: 2543-2249
ISSN: 2543-2257

RECENT ADVANCES IN PEDIATRIC MEDICINE

VOLUME 1

SYNOPSIS OF GENERAL PEDIATRIC PRACTICE

Editor:
Seckin Ulualp

Bentham Books

Recent Advances in Pediatric Medicine

(Volume 1)

(Synopsis of Current General Pediatrics Practice)

Edited By

Seckin Ulualp

Division of Pediatric Otolaryngology,
Department of Otolaryngology-Head and Neck Surgery,
University of Texas Southwestern Medical Center,
Children's Health Dallas, Texas, USA

Recent Advances in Pediatric Medicine

Volume # 1

Synopsis of General Pediatric Practice

Editor: Seckin Ulualp

eISSN (Online): 978-1-68108-520-3

ISSN(Print): 978-1-68108-521-0

eISBN (Online): 2543-2249

ISBN (Print): 2543-2257

© 2017, Bentham eBooks imprint.

Published by Bentham Science Publishers – Sharjah, UAE. All Rights Reserved.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (**"Work"**). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.org.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it. The following DRM (Digital Rights Management) policy may also be applicable to the Work at Bentham Science Publishers' election, acting in its sole discretion:

- 25 'copy' commands can be executed every 7 days in respect of the Work. The text selected for copying cannot extend to more than a single page. Each time a text 'copy' command is executed, irrespective of whether the text selection is made from within one page or from separate pages, it will be considered as a separate / individual 'copy' command.
- 25 pages only from the Work can be printed every 7 days.

3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of the U.A.E. as applied in the Emirate of Dubai. Each party agrees that the courts of the Emirate of Dubai shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.
3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Ltd.
Executive Suite Y - 2
PO Box 7917, Saif Zone
Sharjah, U.A.E.
Email: subscriptions@benthamscience.org

CONTENTS

PREFACE

The field of pediatric medicine encompasses a rapidly expanding volume of information. This book has been prepared by a diverse group of authors from a range of pediatric subspecialists to create a platform to review the recent advances quickly and efficiently. With authors from pediatric subspecialties, duplication of the information was reduced to a minimum by integrating the chapters effectively. The authors clearly explain etiology, pathophysiology, and management of commonly encountered pediatric disorders.

The book does not pretend to describe the all aspects of the management of the various problems discussed. Each contributor presented the scientific evidence and discussed the practice pathways to enhance effectiveness of readers in approaching commonly encountered medical problems in children. Concise information about the approach of pediatric subspecialists to common medical problems, that are frequently very complex, enhances the educational value of the book for everyone involved in the care of children.

It is my hope that, by presenting the breadth and depth of many of the typical problems encountered while caring for children in an evidence-based format, *Recent Advances in Pediatric Medicine; Synopsis of Current General Pediatrics Practice* will become a valuable asset for the pediatric practitioner, specialists, medical students, and others involved in the care of children.

A book like this is the result of the effort of many people. I am very grateful to my wife, Zerrin, for having gracefully accepted that many weekends were absorbed by the preparation of this book. Many thanks go to all authors trying the impossible and sparing time to write this book within their endless working schedule.

Seckin Ulualp
Division of Pediatric Otolaryngology
Department of otolaryngology-Head and Neck Surgery
University of Texas Southwestern Medical Center
Children's Health
Dallas, Texas
USA

List of Contributors

Abha Choudhary Department of Otolaryngology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Amal Isaiah Department of Otolaryngology— Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

Amine Daher University of Texas Southwestern (UTSW) Medical Center, Dallas Children's Health, Dallas, TX, USA

Anil Gungor Department of Otolaryngology – Head and Neck Surgery, Louisiana State University School of Medicine, Shreveport, LA, USA

Anthony Sheyn Department of Otolaryngology, University of Tennessee Health Science Center, LeBonheur Children's Hospital, St. Jude Children's Research Hospital, TN 38105, USA

Bailey LeConte Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA

Bethany A. Auble Department of Pediatrics, Division of Endocrinology, Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI, USA

Carisse Orsi Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA

Catherine Blanchet Department of ENT and Head and Neck Surgery, University of Montpellier, Montpellier, France

Dayton Young Department of Otolaryngology, University of Texas Medical Branch, Department of Otolaryngology, Galveston, TX, USA

Derek L. Pepiak Department of Pediatrics, Ochsner for Children and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA, USA

Elia Escaname Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA

Emily Tignor Department of Otolaryngology, University of Texas Medical Branch, Department of Otolaryngology, Galveston, TX, USA

Eric Velazquez Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI, USA

Harold Pine Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA

Issam Saliba Division of Otorhinolaryngology Head & Neck Surgery, University of Montreal, Otology and Neurotology, Sainte-Justine University Hospital Center (CHUSJ) and University of Montreal Hospital Center (CHUM) Montreal, Quebec, Canada

Jamie Flor Section of Pediatric Psychology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Jayne Bellando Section of Pediatric Psychology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Jesica F. Ramirez	Centro Javeriano de Oncologia - Hospital Universitario San Ignacio, Bogota, Columbia Department of Pediatrics, University of Texas Health Science Center, San Antonio, TX, USA
Jessica Hutchins	Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA
Joshua L. Kennedy	Department of Internal Medicine, Department of Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Kathleen R. Billings	Division of Pediatric Otolaryngology-Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
Kristine H. Schmitz	Department of General and Community Pediatrics, Washington, DC, USA
Leandra Godoy	Department of Psychology, Children's National Health System, Washington, DC, USA
Maria C. Veling	Department of Otolaryngology – Head and Neck Surgery, Division of Pediatric Otolaryngology, University of Texas Southwestern Medical Center, Dallas, TX, USA
Maria Rayas	Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA
Maya Lopez	Section of Pediatric Psychology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Melissa Frei-Jones	Department of Pediatrics, Division of hematology and Oncology, University of Texas Health Science Center, San Antonio, TX, USA
Michel Mondain	Department of ENT and Head and Neck Surgery, University of Montpellier, Montpellier, France
Mi-Young Rhee	Department of Psychology, Children's National Health System, Washington, DC, USA
Mohamed Akkari	Department of ENT and Head and Neck Surgery, University of Montpellier, Montpellier, France
Musaed Alzahrani	Department of Surgery, Division of Otolaryngology, King Fahad Specialist Hospital, Dammam, Saudi Arabia
Neslihan Gungor	Department of Pediatrics, Division of Endocrinology, Louisiana State University-Health Sciences Center/University Health, Shreveport, LA, Shreveport, LA, USA
Olga Hardin	Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Ricardo Medina-Centeno	Department of Pediatrics, Division of Gastroenterology and Hepatology, University of Texas Southwestern Medical Center, Dallas, TX, USA
Rinarani Sanghavi	Department of Pediatrics, Division of Gastroenterology and Hepatology, University of Texas Southwestern Medical Center, Dallas, TX, USA
S. Kamal Naqvi	Division of Respiratory and Sleep Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA

Seckin O. Ulualp	Department of Otolaryngology- Head and Neck Surgery, Division of Pediatric Otolaryngology, University of Texas Southwestern Medical Center, Children's Health, Dallas, TX, USA
Suparna N. Shah	Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA
Tanya M. Martinez-Fernandez	University of Texas Southwestern (UTSW) Medical Center, Dallas Children's Health, Dallas, TX, USA
Tomoko Makishima	Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA
Yadira M. Rivera-Sanchez	University of Texas Southwestern (UTSW) Medical Center, Dallas Children's Health, Dallas, TX, USA

CHAPTER 1

Update on the Management of Otitis Media

Emily Tignor, Bailey LeConte, Dayton Young and **Tomoko Makishima***

Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA

Abstract: This chapter discusses the difference between acute otitis media, recurrent otitis media, and otitis media with effusion as well as the etiology, epidemiology, diagnosis and treatment of the distinct diseases. New 2016 guideline updates on Otitis Media with Effusion from the American Academy of Otolaryngology are incorporated.

Keywords: Antibiotics, Cholesteatoma, Ear, Effusion, Hearing, Infection, Myringosclerosis, Otitis media, Otorrhea, Tube, Tympanostomy.

INTRODUCTION

Ear infections are one of the most common reasons for which children seek the care of a pediatrician before the age of three [1]. Parents know that ear infections are common and attribute a multitude of symptoms to the ears- fever, fussiness, pulling at ears, delayed speech, failure to respond when called. Therefore, it is vital for every clinician to have a strong knowledge of how and why ear infections occur, what distinguishes different types of infections and what is the standard of care management for these infections.

Definition

Acute Otitis Media (AOM) is defined as inflammation of the middle ear associated with middle ear effusion [2]. It has a rapid onset and includes symptoms of pain and fever. The tympanic membrane (TM) may be erythematous and bulging outward from middle ear purulence or ruptured due to excessive middle ear positive pressure.

Otitis Media with effusion (OME) is defined as middle ear effusion without acute inflammatory signs or symptoms [3 - 5]. This has a longer duration with gradual onset and includes symptoms of conductive hearing loss and speech delay. Signs

* **Corresponding author Tomoko Makishima:** Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA; Tel: 409.772.9946; Fax: 409.772.1715; E-mail: tomakish@utmb.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

include middle ear effusion with decreased tympanic membrane mobility and flat tympanogram.

Therefore, acute otitis media (AOM) is a separate entity from otitis media with effusion (OME) even though both are forms of middle ear effusion [2].

PATHOPHYSIOLOGY

Middle ear disease stems from many interacting factors including anatomy, environment, infectious agents, and genetics.

Anatomic Causes

The middle ear is an air-filled space medial to the tympanic membrane and lateral to the inner ear [6]. It has a mucosal lining of respiratory epithelium and contains three bones that form a lever mechanism (malleus, incus, and stapes). This lever mechanism is important for the conduction of sound. If the mechanism is damaged or function is decreased, a conductive hearing loss may follow.

The Eustachian tube (ET) plays an important role in middle ear pressure equalization and, therefore, middle ear disease [7]. The ET originates in the anterior middle ear space and courses anteriorly to empty into the lateral nasopharynx. The tensor veli palatini muscle controls opening and closing of the ET during swallow [6, 8, 9]. The Eustachian tube is essential to maintain a functional middle ear by providing ventilation, protection, and clearance. If any of these are impaired, otitis media may develop. Ventilation is the active process of regulating middle ear pressure which is accomplished by contraction of the tensor veli palatine during swallowing, jaw movements, and yawning [6]. This function is poor in children and improves with age [9]. Children who are prone to otitis media are more likely to have deficient active ET function *versus* children who are not [8]. Closure of the ET is a passive process which protects the middle ear from pharyngeal reflux [6].

The Eustachian tube is lined with ciliated respiratory epithelium. Mucociliary clearance contributes to ET function by propelling mucus and fluid from the middle ear into the nasopharynx. Known disorders of mucociliary clearance lead to an increase in middle ear disease [6].

The ET opens laterally in the nasopharynx and can be obstructed by midline adenoid growth or seeded by biofilm from chronic adenoiditis. Orientation of the ET affects reflux of fluid in the nasopharynx into the middle ear as well as drainage of fluid from the middle ear to the nasopharynx. In adults, the Eustachian tube empties into the nasopharynx at a 45 degree angle, while in children, this

angle is closer to 90 degrees. In addition, any excess tissue in the nasopharynx can lead to ET obstruction (*e.g.* adenoid hypertrophy) and, in turn, middle ear disease.

However, despite the common acceptance and logical association of ET dysfunction to middle ear disease, much controversy still exists on causal relationship [9].

Environmental Causes

Irritants

Tobacco smoke is the leading preventable risk factor for the development of otitis media. Studies have consistently shown that tobacco smoke exposure, including second and third hand smoke, is associated with an increased incidence of otitis media and recurrent otitis media [10]. In addition, tympanic membrane perforation, cholesteatoma and other OME complications are increased in children exposed to smoke [11]. Suppression or modulation of the immune system, enhancement of the bacterial adherence factors, impairment of the mucociliary apparatus of the respiratory tract, or enhancement of toxins are suggested mechanisms related to tobacco smoke exposure [12].

Daycare

Daycare is a well-studied risk factor for recurrent AOM: children enrolled in daycare are twice as likely to have AOM due to increased exposure to bacterial pathogens and viral infections [13].

Allergy

Allergies are often blamed for middle ear effusion, and patients with skin test proven atopy and history of recurrent middle ear disease show resolution or significant improvement of middle ear disease after initiation of immunotherapy. This is explained by Th2 inflammatory response mediators (normally increased in the allergic response pathway) which have been found in the fluid of chronically diseased middle ears. No direct evidence exists linking ear disease and allergy at this time [14, 15].

Breast Feeding

Breast feeding may be a protective factor; lower rates of otitis media have been seen in breastfed children for the first 11 months of life. In addition, these children have been noted to have increased serum IgG which may protect against AOM [13].

CHAPTER 2

Contemporary Management of Children with Hearing Loss

Musaed Alzahrani[1] and **Issam Saliba**[2,*]

[1] *Department of Surgery, Division of Otolaryngology, King Fahad Specialist Hospital, Dammam, Saudi Arabia*

[2] *Division of Otorhinolaryngology Head & Neck surgery, University of Montreal, Otology and Neurotology, Sainte-Justine University Hospital Center (CHUSJ) and University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada*

Abstract: Hearing loss has a significant impact on children's ability to develop adequate language and communication skills and often interferes with educational performance as well as limits long-term employment opportunities. Hearing loss is categorized into three broad categories: Conductive, Sensorineural, and Mixed. Audiology workup aims to identify the category and the level of hearing loss; evaluation is divided into subjective and objective tests. Rehabilitation is available to almost all kinds and degrees of hearing loss if diagnosed and managed in a timely manner. For that, we need to increase the awareness of the families and health care providers as well about the screening programs and advocate its implementation in all maternity and child care centers. In this chapter, we discuss acquired and congenital causes of hearing loss. We will also address the diagnostic workup, and finally will discuss in detail the recent developments in pediatric hearing rehabilitation.

Keywords: Cochlear implant, Congenital, Genetics, Hearing aids, Hearing loss, Pediatrics, Syndrome.

INTRODUCTION

Pediatric hearing loss is the most common sensory deficit with an estimated incidence of 1-4 per 1000 newborns [1, 2]. Clinically, 20 dB HL in both ears is considered the normal hearing threshold for children, adolescents, and adults [1]. Any increase in the threshold level is regarded as hearing loss and is classified according to specified degrees of increase (*i.e.,* mild (20 to 40 dB HL), moderate (41to 55 dB HL), moderately severe (56 to 70 dB HL), severe (71 to 90dB HL) and profound (91 to dB HL) as shown in Fig. (**1**). In a recent fact sheet, the WHO

* **Corresponding author Issam Saliba**: Department of Otolaryngology, Sainte-Justine University Hospital Center (CHU SJ), 3175, Côte Sainte-Catherine, Montreal (QC) H3T 1C5, Canada; Tel: (514) 507-7722; Fax: (514) 507-9014; E-mail: issam.saliba@umontreal.ca

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

has estimated that about "360 million people worldwide have disabling hearing loss, 32 million (9%) of these are children" [3].

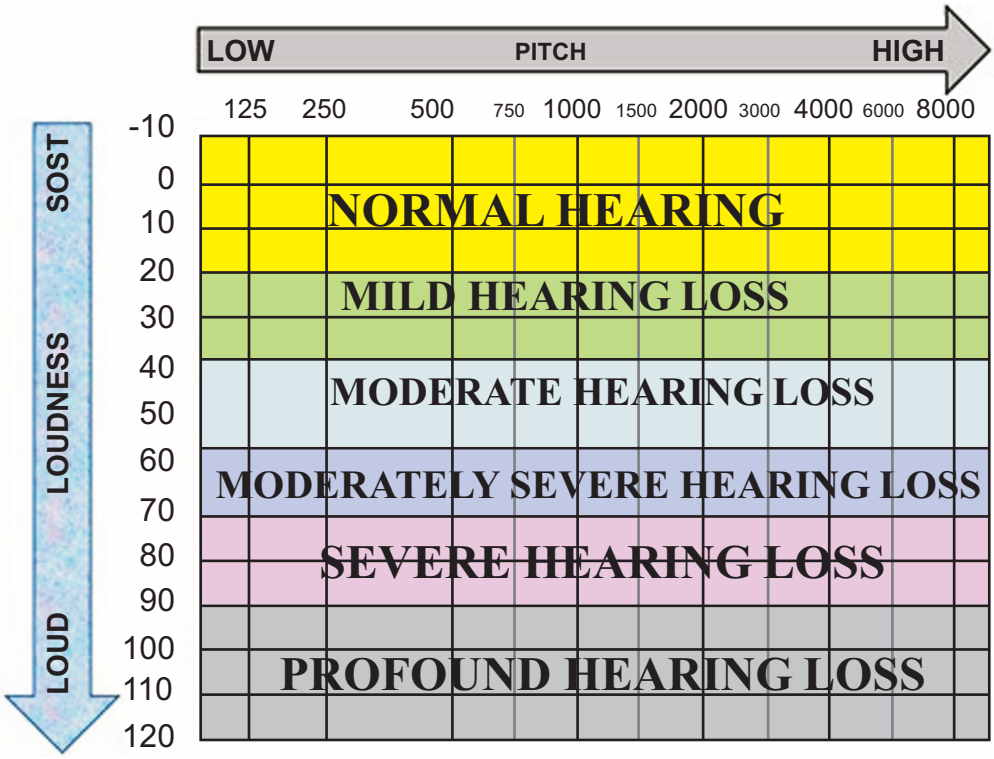

Fig. (1). An illustration showing the levels of hearing loss.

Hearing loss has a significant impact on children's ability to develop adequate language and communication skills [4, 5]; and often interferes with educational performance as well as limits long-term employment opportunities [2]. This impact can be reduced by early diagnosis through neonatal hearing screening programs and childcare clinics, as well as providing adequate educational and social services to affected children and their families [6].

Children diagnosed as clinically deaf have no or very little hearing, do not develop normal speech, and have no other recourse but to use sign language for communication. They may however, benefit from cochlear implants and develop variably normal speech if implanted during the speech development period, which is roughly before the age of five years [7]. However, "hard of hearing" children who suffer from mild to severe bilateral hearing loss develop spoken language and may benefit from hearing aids that amplify incoming sound signals [5, 7].

In this chapter, we discuss acquired and congenital causes of hearing loss. We will also address the diagnostic workup, and finally will discuss in detail the recent developments in pediatric hearing rehabilitation.

DEFINITIONS

Hearing loss is caused by different etiologies affecting the external, the middle or the inner ear thus obstructing or damaging a part of the auditory system. The different types of hearing loss are categorized into three broad categories: Conductive, Sensorineural, and Mixed.

Conductive hearing loss refers to an impairment of the conductive part (*i.e.*, external and middle ears) of the auditory system in which the inner ear is usually normal, but air conducted sound is inadequately delivered or prevented from reaching the sensorineural apparatus of the inner ear in a normal way. Although sensitivity to sound is diminished, it may be perceptible if produced at a sufficient tone.

In this form of hearing loss, the bone conduction threshold is normal (less than 20 dB HL) while the air conduction threshold is increased resulting in what is called an air/bone gap (ABG). By definition, an ABG of more than 15 dB HL averaged over 500, 1000 and 2000 Hz is considered a conductive hearing loss [8].

Sensorineural hearing loss is associated with a pathological change, damage, or dysfunction in the structures within the inner ear or in the cochlear nerve. When the neural elements involved in the conduction or interpretation of nerve impulses originating in the cochlea are damaged or are dysfunctional, then either the perception or the interpretation of sound is impaired. The pure tone audiometry shows an increase of air and bone conductions thresholds (more than 20 dB HL), however, the ABG is less than 15 dB HL [8]. Sensorineural hearing loss may further divided into the following subcategories:

a. Sensory hearing loss occurs from an impairment confined to cochlea.
b. Neural hearing loss is related to the impairment of the cochlear nerve.
c. Central hearing loss (a rare occurrence of sensorineural) is a result of a deformity of the central nerve system rostral to the cochlear nerve.

Mixed hearing loss refers to hearing loss of a mixed nature, conductive and sensorineural. On pure tone audiometry, air and bone conduction thresholds are greater than 20 dB with an ABG of 15 dB HL or more.

Some forms of hearing loss may follow certain pattern according to the involved frequencies, such as low frequencies hearing loss (affecting selectively

CHAPTER 3

Overview of Management of Recurrent Tonsillitis

Suparna N. Shah and **Harold Pine***

Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA

Abstract: An understanding of the anatomy and physiology of Waldeyer's tonsillar ring is important to learning as how to diagnose and treat diseases in the upper aerodigestive tract. The physician should have an understanding of the many disease processes that can affect this region and how to treat them. The clinician should be aware of the possible complications of diseases in Waldeyer's ring and the common presentations so these can be recognized and immediate treatment can be initiated. The physician should be knowledgeable of the current indications for tonsillectomy and adenoidectomy and be aware of the potential complications during the postoperative course.

Keywords: Adenoidectomy, Adenoids, Clinical guidelines, Nonsuppurative complications, Palatine tonsils, Pharyngitis, Post-tonsillectomy hemorrhage, Suppurative complications, Tonsillectomy, Tonsillitis, Waldeyer's tonsillar ring.

INTRODUCTION

Infectious and inflammatory diseases of the pharynx, tonsils, and adenoids make up a large portion of childhood illnesses and health care expenditures resulting in two of the most common pediatric surgical procedures today in the United States, tonsillectomy and adenoidectomy. The most common indications for adenotonsillectomy or tonsillectomy currently are obstructive sleep apnea followed by recurrent tonsillitis. In this chapter, we will review pharyngitis and adenotonsillar disease processes. We will review current guidelines to help ensure appropriate referral to specialists. Finally, we will review some pitfalls in taking care of children with tonsillar disease as well as some pearls for those who need help with post-operative management.

Anatomy

The palatine tonsils laterally, the lingual tonsils anteriorly, and the pharyngeal tonsils also known more commonly as the adenoids posterosuperiorly making up

* **Corresponding author Harold Pine**: Department of Otolaryngology, University of Texas Medical Branch, Galveston, TX, USA; Tel: 409-772-2701; Fax: 406-772-1715; E-mail: hspine@UTMB.EDU

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

a ring of lymphoid tissue around the upper part of the pharynx known as Waldeyer's tonsillar ring which is illustrated in Fig. (**1**). All three of the aforementioned structures in Waldeyer's tonsillar ring have similar histology, which leads to the probability of similar function [1].

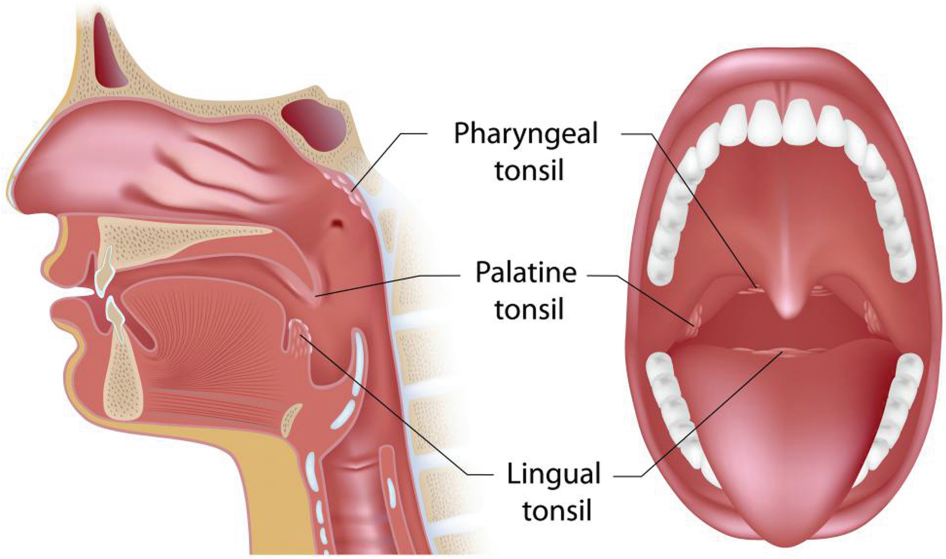

Fig. (1). Anatomy of Waldeyer's tonsillar ring, lateral and anterior views [4].

The palatine tonsils are the largest accumulations of tissue and the only structure in this ring with a capsule. The palatine tonsil is more compact than the other structures and consists of tonsillar crypts, which are blind tubules lined with stratified squamous epithelium that extend deep into its core [2]. The crypts are designed to maximize exposure to surface antigen, but they can also hold debris and bacteria causing recurrent infections [3]. The fibrous capsule, which is a specialized portion of the pharyngobasilar fascia, covers the tonsil and forms septa extending deep into the tonsil to conduct the nerves and vessels [1]. Therefore, when surgically excising the tonsils from the tonsillar fossa in which they are housed, the dissection should occur along the loose connective tissue plane between the capsule and the tonsillar bed since the capsule is not easily separated from the tonsillar tissue.

The tonsillar fossa consists of 3 muscles predominantly. The anterior pillar is made up of the palatoglossus muscle, the posterior pillar is the palatopharyngeal muscle, and the base of the fossa is made up of the pharyngeal constrictors, mainly the superior constrictor muscle [3]. The muscular wall of the tonsillar bed is thin and immediately under is the glossopharyngeal nerve and deeper the

neurovascular structures of the carotid sheath. Great care needs to be taken to avoid violating the

muscular wall and damaging the nerve during a tonsillectomy [1]. Even without actual damage to the nerve, patients can still experience transient loss of taste over the posterior third of the tongue and referred otalgia caused by edema after a tonsillectomy [3].

The arterial blood supply of the palatine tonsils is primarily based at the inferior pole and consists of several branches from the external carotid artery. The inferior pole is supplied by the tonsillar and ascending palatine branches of the facial artery and the tonsillar branch of the dorsal lingual artery. The superior pole gets its blood supply from the ascending pharyngeal artery and the palatine branches of the maxillary artery. The main blood supply however is the tonsillar branch of the facial artery [5]. Venous blood drains through a peritonsillar plexus into the lingual and pharyngeal veins, which subsequently drain into the internal jugular vein [3]. Lymphatic drainage is to the superior deep cervical and jugular digastric lymph nodes. The nerve supply of the tonsillar region is primarily through the tonsillar branches of the glossopharyngeal nerve and there is lesser contribution from the descending branches of the lesser palatine nerve [1].

The adenoids or pharyngeal tonsils are located on the posterior wall of the nasopharynx and the lingual tonsils are located at the base of the tongue, still within the ring of lymphoid tissue that surrounds the oropharyngeal opening. The adenoids and lingual tonsils are covered by a specialized, pseudostratified, ciliated columnar epithelium that forms plicated surface folds similar to the tonsillar crypts to maximize the surface area of the tissue [3].

The blood supply of the adenoids includes the ascending pharyngeal artery, the ascending palatine artery, the pharyngeal branch of the maxillary artery, the artery of the pterygoid canal, and contributing braches from the tonsillar branch of the facial artery. Venous drainage is to the pharyngeal plexus communicating with the pterygoid plexus and all draining into the internal jugular and facial veins. Lymphatic drainage is to the retropharyngeal and pharyngomaxillary lymph nodes and nerve supply is from the pharyngeal plexus [1].

Physiology

The lymphoid tissue of Waldeyer's tonsillar ring consists predominantly of B-cell lymphocytes with some T-cell lymphocytes and mature plasma cells. These cells are found in four distinct zones of the adenoids and tonsils, the reticular cell epithelium, the extrafollicular area, the mantle zone of the lymphoid follicle, and the germinal center of the lymphoid follicle [3].

CHAPTER 4

Therapies for Pediatric Chronic Rhinosinusitis

Anthony Sheyn*

University of Tennessee Health Science Center, Department of Otolaryngology, LeBonheur Children's Hospital, St. Jude Children's Research Hospital, TN 38105, USA

Abstract: Pediatric Chronic Rhinosinusitis (PCRS) is a common condition in otolaryngological practice. PCRS remains ill-defined as a condition as it remains difficult to establish as a diagnosis. PCRS may co-exist with other widespread conditions such as allergic rhinosinusitis and adenoiditis. Recent efforts have been targeted at defining this condition and to develop stepwise treatment. A consensus of statement was recently put out defining PCRS as at least 90 continuous days of nasal symptoms with corresponding endoscopic and/or image findings in a patient who is 18 years old or younger. With a working definition, research has focused on developing stepwise treatments ranging from medical management to endoscopic sinus surgery. This chapter focuses on discussing the developed treatments for PCRS.

Keywords: Adenoiditis, Balloon sinuplasty, Chronic rhinosinusitis, Endoscopic Sinus surgery.

INTRODUCTION

Pediatric chronic rhinosinusitis (PCRS) is a difficult, but common problem in the otolaryngologic practice arising mainly from poor understanding of the disease. The differential diagnosis for PCRS includes viral upper respiratory infections, acute bacterial sinusitis, allergic rhinitis, nasal foreign body, and congenital abnormalities such as choanal atresia and pyriform aperture stenosis. Arriving at a diagnosis is often difficult, but a recent clinical consensus statement from the American Academy of Otolaryngology has developed a working definition of PCRS with the intent of helping with diagnosis and guiding treatment strategies. PCRS is defined as at least 90 continuous days of symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough with corresponding endoscopic and/or CT findings in a patient who is 18 years of age or younger [1].

PCRS may also co-exist with other widespread conditions such as allergic rhinitis

* **Corresponding author Anthony Sheyn**: University of Tennessee Health Science Center, Department of Otolaryngology, LeBonheur Children's Hospital, St. Jude Children's Research Hospital, TN 38105, USA; Tel: (513) 225-2288; Email: tsheyn@gmail.com

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

and adenoid disease [2] and has the potential to exacerbate asthma, which affects approximately 2-20% of children [3]. Improvements in asthma have been observed in children following surgery for PCRS.

The pathogenesis of PCRS in poorly understood and is likely multifactorial. Mucociliary clearance defects, allergic rhinitis, chronic bacterial infection, environmental factors and social factors all contribute to the development of disease. Over the past 10-15 years, bacterial biofilms have been identified as an additional factor in disease progression [4]. A recent study indicated that a hereditary contribution exists as well. Siblings of patients with PCRS had a 57.5 fold increased risk, first cousins had a 9.0 increased risk and second cousins had a 2.7 increased risk [5].

Anatomic variants may also contribute to the disease process, although controversy still exists. The most frequent anatomic variants noted in CRS are pneumatized middle turbinate, uncinate hyperplasia, deviation of the uncinate, large ethmoid bulla, large agger nasi cells, and Haller cells. Nasal polyps in children are rare, except in cases of CF. Antrochoanal polyps are more likely but still quite rare and may cause obstructive symptoms and rhinorrhea.

In addition to health related problems, the treatment of PCRS is a prominent public health issue and incurs a high financial cost. PCRS visits are second to well child visits for pediatricians. The actual cost of treating chronic sinusitis is difficult to estimate, but over $2 billion is spent annually on over-the-counter medications alone [6].

As our understanding of PCRS grows, treatment options are improved and now occur in a step wise fashion. Currently, long term antibiotic therapy is the first line therapy. Alternatives to oral antibiotic therapy and treatment of refractory disease include a variety of surgical therapies. Adenoidectomy is generally considered the primary surgical therapy. Additional procedures include endoscopic sinus surgery and balloon catheter dilation.

DIAGNOSIS

The diagnosis of PCRS is based on the presence of specific symptoms present for 3 months or more with associated image or endoscopic findings. The major and minor criteria used for diagnosis are the same as those used for diagnosing acute bacterial rhinosinusitis (Table **1**). The usual symptom complex for children includes cough, nasal congestion, and rhinorrhea [7].

Physical examination should always include an anterior rhinoscopy and a nasal endoscopy. Anterior rhinoscopy is quite often unreliable and very non-specific.

Nasal endoscopy is more sensitive procedure for examining a patient in the office. It allows for evaluation of septal, turbinate, meatal, and nasopharyngeal abnormalities. These areas should be carefully inspected for presence and quality of secretions, presence of inflammation, patency of choanae, nasopharyngeal masses, and adenoid hypertrophy.

Table 1. Major and Minor Criteria for Bacterial Sinusitis.

Major Criteria	**Minor Criteria**
Facial pain or pressure	Headache
Facial congestion or fullness	Fever (for chronic)
Nasal congestion or obstruction	Halitosis
Nasal discharge, purulence, or discolored nasal discharge	Fatigue
Hyposmia or anosmia	Dental pain
Fever (for acute)	Cough
Purulence on intranasal examination	Ear pain, pressure, fullness.

Radiologic studies are not routinely indicated in the initial management of suspected PCRS. If necessary, imaging should be CT Maxillofacial scan without contrast to examine the paranasal sinuses. While plain radiographs have been described as having a sensitivity of 84.2% and a specificity of 76.6% when compared to nasal endoscopy, it is a challenge to differentiate between a mass, polyp, infection, or mucosal disease in opacified sinuses [8, 9]. With CT, the Lund-McKay scoring system can be used to increase the predictive value of imaging. It is important to consider that in children, a score of 5 is the cutoff for being consistent with the presence of sinus disease [10]. While MRI is better at examining soft tissues, it has worse bony resolution when compared to CT, and is inadequate for surgical planning or intraoperative guidance if sinus surgery is necessary. Finally, it is important to remember that abnormal imaging findings may persist for some time after symptom resolution [11]. In cases of complicated PCRS, especially with suspicion of cystic fibrosis or primary ciliary dyskinesia, additional lab work may be necessary and will be discussed in a later section.

MEDICAL MANAGEMENT OF PCRS

PCRS is a very difficult disease to treat due to difficulties with diagnosis and the many contributing factors to the pathophysiology of the disease. There is agreement that a step wise approach should be adopted to the treatment of children with this disease, beginning with medical management. Treatment generally begins with antibiotics and adjuvant medical management, progressing to surgical treatment in recalcitrant cases. A recent consensus has also been

CHAPTER 5

Practical Management of Children with Stridor

Anil Gungor*

Department of Otolaryngology- Head and Neck Surgery, Louisiana State University School of Medicine, Shreveport, LA, USA

Abstract: Stridor is one of the most common reasons for referral to a pediatric ENT subspecialist. This chapter is prepared as technical update for the advanced practitioner (neonatologist, pediatrician, family physician, general ENT) as a supplement to existing classic textbook material. In addition to existing established surgical approaches, newer and more conservative treatment techniques are increasingly successful as the primary or adjunct treatment. Surgical and medical practice continues to be shaped by increased awareness of and demand for conservative procedures and higher risk aversion. Management of stridor now requires a greater variety of updated medical and surgical expertise. Increased collaboration between specialists allows for an extended period of interventions and introduces new challenges and perspectives for all involved. - Practical skills for interview, assessment of the severity and cause of stridor are discussed in detail from the perspective of the pediatric ENT subspecialist collaborating closely with several other subspecialty areas.

Keywords: Conservative, Indications, Stridor, Surgical.

INTRODUCTION

Pediatric stridor management presents challenges that require innovative approaches and comprehensive treatment strategies. Reconstruction of craniofacial malformations, obstructive anomalies of the tongue base, nasal vault and choanae are addressed by subspecialists from various clinical and surgical academic traditions who practice variable levels of required communication. Hypopharyngeal, laryngeal, glottic, subglottic, and tracheobronchial obstructions are solely treated by pediatric otolaryngologists who have additional expertise and/or pediatric ENT fellowship training. The increasing viability of children with multiple levels of obstruction and synchronous airway lesions requires close collaboration for intelligent and effective airway management.

* **Corresponding author Anil Gungor**: Department of Otolaryngology- Head and Neck Surgery, Louisiana State University School of Medicine, Shreveport, LA, USA; Tel: 318 6756262; Fax: 318 6756260; Email: entforkids@yahoo.com

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

Definitions

Stridor, simply, is noisy breathing caused by airflow obstruction. In general practice, it is used as a catch all term for all abnormal respiratory noise including stertor, snoring, and mouth-breathing. There may be an academic benefit for a more refined description that distinguishes between stertor (upper nasopharyngeal, palatal), inspiratory (more supraglottic noise), bi-phasic (glottic), and expiratory (more subglottic noise) stridors but these have not become part of the descriptive and diagnostic language use of general practitioners. The same descriptive confusion exists for laryngomalacia (more inspiratory stridor) and tracheomalacia (more expiratory stridor); conditions with very different dynamics and etiology. Many practitioners use tracheomalacia to describe any and all stridor. Since all abnormal respiratory noises require attention, using stridor for all as a starting point is perfectly acceptable for referrals. In addition, stridor, especially in very young babies is not present in classical pure form, nor does it stay the same over time. Feeding, secretion control, reflux, body position, fatigue, intervening respiratory illness as well as growth and maturation all change the quality, phase and, severity of stridor.

Evaluation of the Stridorous Child

Acute stridor in a child is an airway emergency and needs immediate attention. The differential diagnosis includes foreign body aspiration (FBA), epiglottitis, croup, bacterial tracheitis (Table **1**), among others (seizures, trauma, shaken baby, reflux, aspiration *via.*).

Table 1. Clinical Diagnosis of Inflammatory Stridor.

	Epiglottitis	**Croup**	**Bacterial Tracheitis**
Microbiology	H inf type B	Parainfluenza	S Aureus, Strep
Age	2-6 yrs	<3 yrs	Wide
Onset	Rapid (hours)	Slow (days)	Slow (days)
Cough	Absent	Barking cough	Brassy
Dysphagia	Severe	None	None
Stridor	Inspiratory	Biphasic	Variable
Temperature	Elevated	Elevated	Elevated
Posture	Sitting forward	Lying back	Lying back
Drooling	Marked	None	None
Voice	Muffled	Hoarse	Hoarse
X-ray	Thumbprint sign	Steeple sign	Narrow tracheal lumen

All FBA suspects need to have an airway evaluation under anesthesia (AE). Epiglottitis is diagnosed clinically and is best managed conservatively avoiding diagnosis in the operating room if possible. Croup and bacterial tracheitis may need AE if diagnostic uncertainty exists.

Congenital stridor suggests an airway anomaly. Mild stridor can be observed while more clinical information is gathered. Feeding assessment, clinical examination of the palate, tongue, jaw, and their proportionality, features suggestive of syndromic associations (low set ears, webbed neck, limb anomalies *via*.) are important. Meanwhile, cardiac and neuromotor evaluations are conducted. If all is normal, and the stridor remains mild, respiration, voice and feeding are not compromised, no apneas, cyanosis or ALTE's are reported, then careful observation is recommended. Most likely cause of this is mild laryngomalacia. Over time, especially about a month after birth, as the child becomes stronger and is able to command larger and faster air exchange, stridor may increase. Careful assessment of apnea, cyanosis, ALTE's, feeding, weight gain, retractions is performed in the office. Assessment of feeding by a specialist is very helpful especially if uncertain about caregivers' report. Feeding assessment should include an evaluation of protective reflexes (cough, gag, palatal elevation), coordination of sucking, swallowing, breathing, detection of atypical suck/swallow ratio, pacing difficulty, and fatigue. If the length of feedings exceed 30 minutes, and non-nutritive suckling is detected, stridor is no longer considered mild.

At this time, careful auscultation of respiratory sounds in the chest and the neck is performed. Most babies tolerate a distress position that accentuates any pre-existing respiratory compromise and provides important information to the practitioner. This position is obtained by placing baby face up on caregivers' knees and thighs while the examiner sits across, facing the caregiver. The caregiver holds baby tightly on her thighs by his arms and elbows to the side. Gentle traction is applied on the mandible by the examiner, causing extension of the neck and blocking baby's view of the caregiver. This position reduces thoracic volume through abdominal shift, and increases respiratory demand in addition to mild emotional distress due to immobilization and inability to see caregivers' face. Most babies will get agitated and/or start crying in a short while, providing the examiner with valuable time for observation and auscultation. The bell portion of the baby stethoscope is then used to listen to various areas in the neck, (both supra- and subglottic) and chest. Phase of stridor, location, closure (complete, incomplete), ability to clear secretions, ball-valving foreign bodies *via*. can be assessed.

CHAPTER 6

Update on the Management of Laryngomalacia

Mohamed Akkari[*], **Catherine Blanchet** and **Michel Mondain**

Department of E.N.T. and Head and Neck Surgery, University Hospital Gui de Chauliac, University of Montpellier, 80 avenue Augustin Fliche 34295 Montpellier Cedex 5, France

Abstract: Laryngomalacia (LM) is the most common cause of stridor in children. It presents during the first days of life with inspiratory stridor often associated with feeding difficulties. Diagnosis must be confirmed by performing a flexible fiberoptic laryngoscopy. LM is classified in mild, moderate and severe LM depending on respiratory and feeding severity symptoms. LM usually goes with gastroesophageal reflux disease, and can also be associated to synchronous airway lesions, neurological disorders, heart disease and congenital syndromes. Identification and management of co-morbidities using appropriate complementary examinations are essential as they influence LM severity and treatment outcomes. Medical management of LM includes lifestyle/dietary measures and anti-acid treatment. Supraglottoplasty, including several technique variants, is the mainstay of severe LM treatment, with numerous studies reporting high success and low complications rates. Tracheotomy and non-invasive ventilation are indicated in case of supraglottoplasty failure, most of the time due to associated neurological disorder and congenital syndromes.

Keywords : Gastroesophageal reflux disease, Inspiratory supraglottic collapse, Laryngomalacia, Lifestyle/dietary measures, Neonates and infants, Non-invasive ventilation, Stridor, Tracheotomy, Trans-oral supraglottoplasty.

INTRODUCTION

Laryngomalacia (LM) is defined as an inspiratory supraglottic collapse causing stridor. It typically presents during the first 10 days of life with inspiratory high-pitched stridor worsening with feeding, agitation, crying and supine positioning [1]. Feeding difficulties are often associated.

The pathophysiological mechanisms involved in LM are the infant's specific laryngeal anatomy [2], an abnormally integrated peripheral and central nervous system mechanism of laryngeal function and tone involving the superior laryngeal nerve [3], and the occurrence of mucosal posterior oedema induced by

[*] **Corresponding author Mohamed Akkari**: Department of E.N.T. and Head and Neck Surgery, University Hospital Gui de Chauliac, University of Montpellier, 80 avenue Augustin Fliche 34295 Montpellier Cedex 5, France; Tel: +33 4 67 33 68 25; Fax: +33 4 67 33 67 28; Email: m-mondain@chu-montpellier.fr

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

gastroesophageal reflux disease (GERD) and mucosal trauma during inspiration [4]. Consequently, the increased airflow through an area of obstruction creates turbulence and vibrations of supraglottic structures leading to stridor. LM is responsible for 60-70% of all congenital stridors [5].

After a peak at 6-8 months, it is commonly admitted that in most of the cases, spontaneous resolution of LM and its symptoms occurs after 24 months old [6, 7]. In a recent review of the literature, Isaac *et al* [8] have highlighted the paucity of the literature regarding the natural history of LM, with an uncertainty concerning the rate and time to resolution, and suggested caution when informing parents about the evolution of the symptoms.

In 10-20% of cases, LM is associated with respiratory and/or feeding signs of severity that require a more specific management. These cases need an early identification in order to provide the most appropriate treatment, including surgical procedures. LM Consensus recommendations have recently been published by the International Pediatric ORL Group (IPOG) [9].

The aim of this chapter is to present an update on the diagnostic and therapeutic management of LM according to the most recent literature.

DIAGNOSTIC MANAGEMENT

All children with stridor must benefit from an ENT evaluation. The objectives are to confirm the diagnosis of LM, to determine its severity and to identify potential associated lesions.

History

Medical history must be detailed: birth term, obstetrical and neonatal medical events, associated congenital diseases. Parents questioning will specify the timing and circumstances of stridor appearance, stridor characteristics and aggravating factors. Feeding difficulties, usually due to swallowing dysfunction (trouble to coordinate the suck swallow breath sequence) [10] or association with GERD (regurgitation, emesis, cough, and slow feedings) must be sought-after, and their intensity needs to be evaluated: milk rations, meal frequency, and above all weight gain.

Physical Examination

A complete pediatric clinical examination must be performed, including height and weight measurement, respiratory sound and rate evaluation, chest movements and deformation analysis, lung auscultation, and search for associated morbidities.

As stridor is not a specific symptom of LM [11], direct visualization of the larynx using flexible fiberoptic laryngoscopy (FFL) is essential to confirm the diagnosis and eliminate others causes of inspiratory stridor [12, 13]. Nasal FFL is easily performed in the office with the help of a caregiver, usually without local anesthesia. In children with cardiorespiratory fragility, this exam must be performed in a medical environment including resuscitation equipment [4].

Olney *et al* [14] have proposed a classification of LM based on FFL usual endoscopic findings:

-Type 1 (57%): anterior prolapse of mucosa and corniculate cartilages overlying the arytenoid cartilages. This prolapse will be favored in case of mucosal oedema induced by GERD and mucosal trauma during inspiration.
-Type 2 (15%): foreshortened aryepiglottic folds
-Type 3 (13%): posterior displacement of the epiglottis which is usually omega-shaped.
-Combined types (15%)

Severity Classification

LM can be classified into mild, moderate and severe categories [9], which are not based on the intensity of the stridor but rather on the associated respiratory and feeding symptoms [15].

Mild LM accounts for 40% of cases at the time of presentation. Symptoms are an inspiratory stridor with occasional feeding symptoms (cough, chocking and regurgitation) without swallowing dysfunction. According to Landry *et al* [15], approximatively 30% of the children presenting mild LM will progress to the moderate category, mainly due to the evolution of the GERD symptoms.

Moderate LM accounts for 40% of cases at the time of presentation. Children present stridor with frequent and additional more intense feeding symptoms (slow feeding, swallowing dysfunction). Approximatively 30% of the children presenting moderate LM will progress to the severe category despite an appropriate medical treatment [15].

Severe LM accounts for 20% of cases at the time of presentation and will require surgical treatment [16]. Respiratory signs of severity are: episodes of respiratory distress, malaise, recurrent cyanosis, permanent inter or subcostal retraction that can lead to pectus excavatum, obstructive sleep apnea, chronic respiratory failure with pulmonary artery hypertension, cor pulmonale and heart failure. Feeding signs of severity are: iterative suffocation during feeding, failure to thrive due to insufficient caloric intake and heightened metabolic expenditure, major

CHAPTER 7

Synopsis of Management of Diabetes Mellitus Types 1 and 2

Eric Velazquez and **Bethany A. Auble***

Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, Wisconsin, USA

Abstract: Diabetes involves pancreatic dysfunction due to autoimmune destruction of the beta cells and insulin deficiency. The prevalence and incidence of Type 1 and Type 2 are increasing in the general population. Type 1 Diabetes often begins in childhood and requires lifelong insulin replacement therapy and monitoring of blood glucose levels. Long and short-acting insulin allows for adjustment of therapies around patients' lives, but close medical observation and a good patient-provider relationship is necessary for optimal management. Type 2 Diabetes is characterized by severe insulin resistance and partial deficiency that has become more prevalent in pediatric patients, often occurring around puberty. Therapy involves lifestyle changes to promote active weight loss, healthy eating habits, and exercise. Few pharmacological therapies are approved, but many are being studied for pediatric use.

Keywords: Artificial Pancreas, Bariatric Surgery, Closed Loop Control, Continuous Glucose Monitoring, Continuous Subcutaneous Insulin Injection, Glucagon, Insulin, Lifestyle Changes, Metformin, Multiple Daily Insulin Injections, Type 1 Diabetes, Type 2 Diabetes.

INTRODUCTION

Diabetes Mellitus is a life-altering diagnosis, requiring adjustment of a patient's life and schedule. In pediatric patients, it also changes the entire family's focus. Loss of insulin-secreting beta cells results in loss of glycemic control with subsequent hyperglycemia in Type 1 diabetes. Insulin replacement therapy remains the mainstay of current therapy. Advances in insulin pumps, continuous glucose monitors, and closed loop control systems have resulted in long-term improved glycemic control. New advancements in pancreatic transplant, stem cell therapy, biomarker screenings, and prevention strategies are being published yearly. Type 2 Diabetes requires an alternative approach to management with a

* **Corresponding author Bethany A. Auble**: Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, Wisconsin, USA; Tel: 414-337-8717; Fax: 414-266-6749; Email: bauble@mcw.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

strong emphasis placed on diet, exercise, and lifestyle modifications. The medical therapies for the treatment of Type 2 Diabetes are a growing field of research, but pharmacotherapy must be combined with lifestyle changes if lasting health improvements are to be achieved.

Epidemiology

In the United States, the prevalence of Type 1 Diabetes is estimated for 0.25% of the population [1]. From 2001–2009, prevalence of Type 1 diabetes increased by nearly 20%, with projections suggesting that from 2010 to 2050, the number of youth with Type 1 diabetes may triple. In this same time period, the prevalence of Type 2 diabetes increased by nearly 30% and accounts for 45% of newly diagnosed cases of diabetes in the pediatric population. Projections suggest that from 2010 to 2050, a nearly 4-fold increase might occur of patients with Type 2 diabetes. While still relatively uncommon, the rates of new cases of type 2 diabetes were greater among peripubertal individuals aged 10–19 years than in younger children, with higher rates among U.S. minority populations than in non-Hispanic whites.

Physiology

The pancreas is both an exocrine gland and an endocrine gland. Endocrine cells are located within scattered Islets of Langerhans and divided into three categories: alpha-cells (produce glucagon), beta-cells (produce insulin and amylin) and delta-cells (produce somatostatin). Insulin stimulates cells to uptake free glucose, glycogenesis in the liver, and uptake amino acids, proteins and fat from the bloodstream. Humans are born with a varying amount of beta-cells, and even within these cells, there is variation to susceptibility to auto-immune attack [2]. In Type 1 Diabetes, autoimmune destruction of beta-cells produces gradual dysregulation of glucose and its symptoms develop after >80-90% of cells are lost. Type 2 Diabetes is caused by the relative deficiency of insulin due to severe peripheral tissue resistance.

Glucagon works primarily in the liver to convert glycogen into glucose to raise blood glucose. Its function becomes dysregulated in type 2 diabetes, leading to postprandial hypersecretion, worsening overall hyperglycemia. Amylin is a neuroendocrine peptide hormone that is co-secreted with insulin, uses the same processing enzymes, and works to suppress release of glucagon, slows digestion and slows rate of insulin entering the bloodstream. The benefit of delayed gastric emptying is creating a slower rise, and overall lower peak level of blood glucose [3]. Somatostatin is a peptide hormone that has many GI effects but is active in slowing gastric emptying, suppressing insulin and glucagon release, and suppressing exocrine pancreatic secretions. Incretins are small hormones released

by intestinal mucosa that stimulate insulin release, delay gastric emptying and inhibit glucagon release. While native molecules have short half-lives, synthetic versions last much longer and are being looked at as therapeutic alternatives.

TYPE 1 DIABETES MELLITUS

The "event" of stage II most likely is not a single event but some combination of environmental and genetic triggers. The time period of stage III-IV is highly variable, the reasons for why are being closely studied [2]. Patients most often present with classic symptoms of onset: polyuria, polydipsia, hyperglycemia and ketonuria during Stage V (some present in full diabetic ketoacidosis). The "honeymoon period" between Stage V and VI is called such as very low supplemental insulin is required to maintain normoglycemia Fig. (**1**).

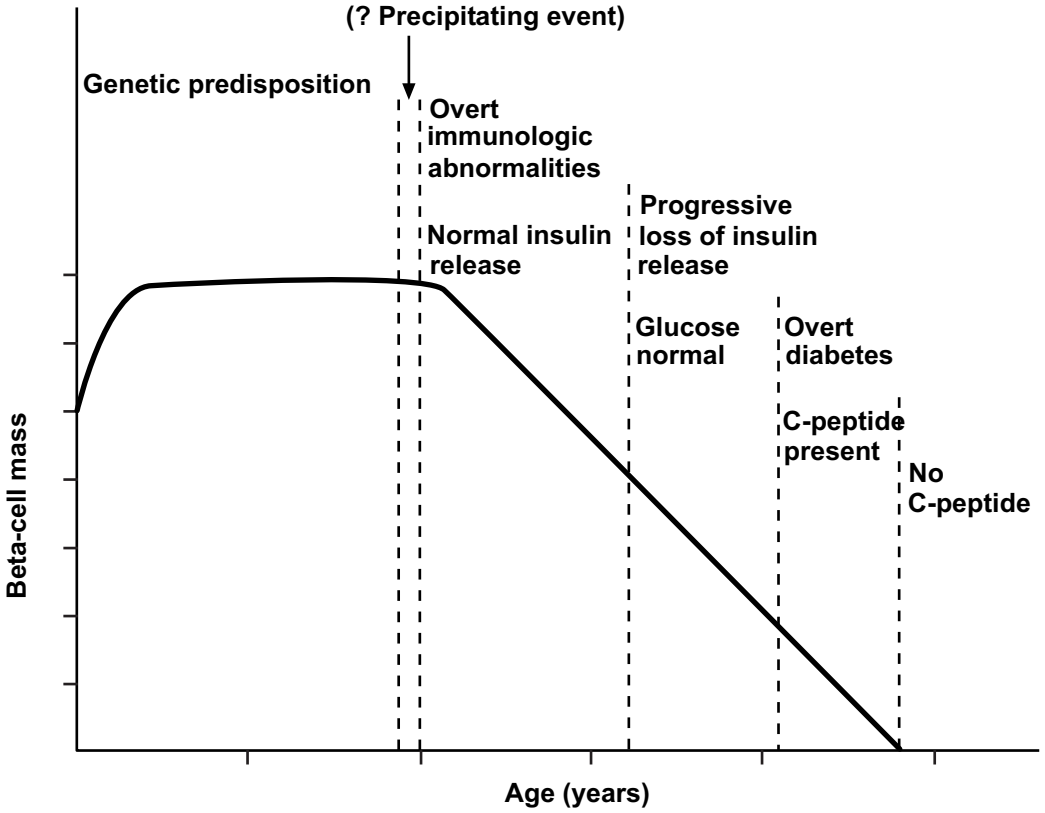

Fig. (1). The Eisenbarth model for the development of Type 1 Diabetes is divided into six stages: 1. Genetic Predisposition, 2. Triggering "Event," 3. Activation of Autoimmune Response, 4. Immunologic Response with progressive loss of insulin secretion with maintenance of normal blood sugar level, 5. Symptoms develop, but residual insulin secretion is maintained, 6. Loss of residual insulin secretion to a point of glucose dysregulation [4].

CHAPTER 8

Pediatric Type 2 Diabetes Mellitus

Carisse Orsi[*], **Maria Rayas, Jessica Hutchins** and **Elia Escaname**

Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA

Abstract: Pediatric Type 2 Diabetes Mellitus (T2DM) is an increasing medical concern for the pediatric community. It is most commonly diagnosed in adolescents but has also been seen in patients as young as 5 years of age. Presentation of T2DM can range from mild symptoms of polyuria, polydipsia and nocturia to diabetic ketoacidosis. Guidelines by the American Diabetes Association are used to diagnose and treat children with diabetes. Early diagnosis and aggressive treatment is critical in delaying complications of diabetes. Poorly controlled diabetes can lead to significant increase in morbidity and mortality with development of hypertension, nephropathy and retinopathy. In this chapter, a review of the epidemiology of Type 2 diabetes, diagnosis and treatment options will be discussed.

Keywords: A1c, Acanthosis nigricans, Hypertension, Insulin resistance, Metformin, Nephropathy, OGTT, Pediatric, Pediatrics, Rosiglitazone, T2DM.

INTRODUCTION

When diabetes is discussed in the pediatric setting, one primarily thinks of Type 1 diabetes mellitus (T1DM). In the past decade, more physicians caring for pediatric patients are encountering an increase in the number of overweight and obese patients. These subset of patients bring along co-morbidities that are considered uncommon in general pediatrics. Now the pediatric provider must be able to identify patients at risk for not only Type 2 diabetes mellitus (T2DM), but also conditions such as hypertension, dyslipidemia and non-alcoholic fatty liver disease.

EPIDEMIOLOGY

Although initially referred to as adult onset diabetes, T2DM is now commonly diagnosed by physicians in the pediatric population. The increase in T2DM in

[*] **Corresponding author Carisse Orsi**: Department of Pediatrics, University of Texas San Antonio Health Science Center, San Antonio, TX, USA; Tel: 210-567-5283; Fax: 210-567-0492; Email: orsic@uthscsa.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

children coincides with the rising childhood obesity rate. In a study conducted through Yale Pediatric Obesity clinic, impaired glucose tolerance (prediabetes) was reported in 25% of children and 21% of adolescents with a BMI >95% for age and sex [1]. The worrisome concern in this particular population is that the progression from impaired glucose tolerance to overt T2DM seems to occur at an accelerated pace in children compared to adults [2]. Additional factors that may contribute to the increase in childhood T2DM are exposure to diabetes in utero and endocrine disrupting chemicals, such as organophosphates and nicotine [3].

The SEARCH study is the largest to date registry for diabetes in youth <20 years of age. This study evaluated the prevalence of T1DM, T2DM, maturity onset diabetes (MODY) and "uncertain type". Ten years ago, T2DM accounted for less than 3% of all new cases of diabetes in adolescents, but now accounts for 20-50%. Comparing data from 2001 and 2009 reveals a 30.5% increase in T2DM diagnosed in children <20 years of age [4].

The prevalence of T2DM by race is highest in American Indians, followed by blacks, Hispanics, Asian Pacific Islanders and lastly whites [4]. The prevalence is higher in ages 15-19 years compared to ages 10-14 due to the increase in insulin resistance appreciated during puberty [2]. Females are more likely to be diagnosed with T2DM than males. Of the children diagnosed with T2DM, 75% have a first or second degree relative with T2DM [2].

DIAGNOSIS

With the increasing number of T2DM cases, it is imperative that the pediatric provider identifies children at risk for T2DM in hope to prevent or at least delay the diagnosis. A thorough family history is important to determine risks factors, as well as, distinguish risks for other types of diabetes like MODY. Based on the 2016 ADA diabetes guidelines, screening for T2DM in the pediatric population is indicated in patients that have a BMI >85% for age and sex plus two other additional risk factors (Table **1**) [5]. Screening should begin at 10 years of age or earlier depending on the onset of puberty. The timing of puberty is important given its association with increased insulin resistance. Patients at risk should be screened every 3 years. They may be screened more often if they exhibit symptoms consistent with T2DM, such as polyuria or polydipsia.

Another risk factor includes the presence of acanthosis nigricans (AN). AN refers to darkening of the skin associated with insulin resistance that is usually appreciated on the back of the neck or other skin folds. It is a helpful physical finding that health care providers may use to identify children at risk for diabetes. It is also a non-invasive tool utilized in the school setting to increase the screening

of children that may not be receiving regular health care. It can be graded on a scale described by Burke *et al*. (Table **2**) [6]. Its regression can be a sign of improved glycemic control and insulin resistance. There does not appear to be any correlation between the degree of AN and the development of T2DM.

Table 1. Risk factor for diabetes.

Testing for Type 2 Diabetes or Prediabetes in Asymptomatic Children (<18 years)
Criteria: □ Overweight (BMI >85% for age and sex, weight for height >85%, or weight >120% of ideal for height)
Plus any two of the following risk factors: □ Family history of T2DM in fort or second degree relative □ Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) □ Signs of insulin resistance or condition associated with insulin resistance (acanthosis, hypertension, dyslipidemia, polycystic ovarian syndrome, SGA birth weight) □ Maternal History of diabetes or GDM during the child's gestation

Table 2. Grading system for Acanthosis Nigricans.

Acanthosis Nigricans Score	Acanthosis Nigricans Description
0	Absent
1	Present on close visual inspection
2 (mild)	Present at the base of the skull (does not extend to lateral neck)or axillae
3 (moderate)	Extends to lateral margins of the neck; in axillae it is visible only with arms raised
4 (severe)	Extends to anterior neck; in axillae it is visible without arms raised

Once a child is identified as being at risk for developing T2DM, then screening for diabetes using fasting plasma glucose levels, 2 hour oral glucose tolerance test (OGTT) or hemoglobin A1c (A1c) can be performed. There is debate as to whether the A1c is a reliable screening tool in the pediatric population. Given the variability of fasting glucoses and the convenience of obtaining an A1c when compared to an OGTT, many health care providers prefer to use an A1c. A provider should be aware of medical conditions that can interfere with the accuracy of the A1c. In conditions such as sickle cell anemia, hemoglobinopathies and cystic fibrosis, the A1c can be falsely low and therefore an unreliable tool. Table **3** is adapted from the 2016 ADA Standards of Medical Care in Diabetes and discusses the criteria for the diagnosis of both T1DM and T2DM.

CHAPTER 9

Practical Guide for Management of Children with Obesity

Neslihan Gungor*

Department of Pediatrics Division of Endocrinology, Louisiana State University-Health Sciences Center/University Health, Shreveport, Louisiana, USA

Abstract: The worldwide prevalence of pediatric obesity has increased remarkably over the past three decades turning pediatric obesity into a serious and challenging public health concern. One in three children and adolescents in the US are overweight or obese. Pediatric obesity is associated with numerous comorbidities, cardiovascular risk factors, and adulthood obesity. Obesity has been a major contributor to increasing healthcare expenses. Increasing awareness of pediatric obesity in the public as well as the healthcare platform is essential to tackle the problem and plan primary and secondary prevention. Given the limited pharmacotherapy options for pediatric obesity, a multifaceted approach of lifestyle changes involving nutrition, physical activity and behavior modification is needed. In order to make a meaningful impact, collaboration among the government, employers, schools, healthcare and other organizations from the community is required. This chapter intends to provide a comprehensive yet concise review of evaluation and management of pediatric obesity.

Keywords: Adolescent, Cardiovascular risk, Child, Diabetes, Dyslipidemia, Lifestyle modification, Obesity, Overweight, Pediatric, Prevention, Type 2 diabetes mellitus, Weight management.

INTRODUCTION

The prevalence of pediatric obesity has increased substantially in the past three decades turning it into a major public health problem [1, 2]. Childhood obesity is a multifactorial condition which can adversely affect nearly every organ system. It has been associated with serious physical and psychosocial comorbidities [1 - 3]. This chapter intends to review the definition, determinants, epidemiology and comorbidities of pediatric obesity and provide a practical approach to clinical evaluation and treatment.

* **Corresponding author Neslihan Gungor**: Department of Pediatrics Division of Endocrinology, Louisiana State University-Health Sciences Center/University Health, Shreveport, Louisiana, USA; Tel: (318) 675-6076; Email: ngungo@lsuhsc.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

DEFINITION

The term obesity refers to excess of body fat or adiposity. However, the methods used to directly measure body fat are not available in routine clinical practice. In clinical practice and population health surveillance systems, obesity is defined by the body mass index (BMI), a mathematical formula of weight-for-height index. The BMI is calculated by weight in kilograms divided by height in meters squared (kg/m^2). The BMI has a high correlation with adiposity and excess weight at the population level. However, the BMI does neither quantify total body adiposity, nor distinguish between fat and muscle on an individual basis. Furthermore, the BMI does not predict body fat distribution. Therefore it may overestimate adiposity in a child with increased muscle mass (*e.g.*, an athlete) and underestimate adiposity in a child with reduced muscle mass (*e.g.* sedentary child) [3 - 5]. In the pediatric age group gender-specific BMI-for-age, percentile charts are used to define overweight and obesity. Children and adolescents with a BMI over the 85^{th} but less than the 95^{th} percentile for age and gender are considered overweight, and those with a BMI equal to or greater than the 95^{th} percentile are considered obese. The term "severely obese" has been used to refer to children and adolescents with a BMI greater than the 99th percentile [3, 6]. In the United States (US), the gender-specific Growth Charts, released in May 2000 by the Centers for Disease Control are available to assess Body Mass Index for children 2 to 20 years of age [6]. The International Obesity Task Force (IOTF) has developed an international standard growth chart which enables comparison of prevalence globally [7]. The World Health Organization has published growth standards for infants and children from birth to 5 years of age [8] and growth reference curves for BMI for children 5–19 years of age [9]. However, many countries have elected to use country-specific growth charts.

ETIOLOGY AND RISK FACTORS

In broad terms, obesity is the result of a chronic imbalance between energy intake and expenditure, with more calories being consumed than expended. In general a lack of physical activity in the presence of unhealthy eating patterns result in excess energy intake. Obesity is a complex, multi-factorial condition affected by genetic and non-genetic factors and interactions between these [1, 5, 10, 11]. Due to the extensive nature of this topic and space restrictions, the reader is referred to additional references. Energy consumption and expenditure are impacted upon by epigenetic programming, environmental and social factors. Specific causes for the increase in prevalence of childhood obesity are not clear. To date, the effects of a single factor has not been identified. (Fig. **1**) provides a general overview of the determinants [1, 5, 10, 11] of pediatric overweight/obesity (Fig. **1**).

As seen in the figure, there are multiple social, environmental, behavioral and biological determinants. There are interindividual differences in susceptibility or resistance to the obesogenic environment [5, 10, 12]. Genetic variation plays a major role in this. Various hormones, most of which originate from the gastrointestinal tract, play role in appetite regulation and energy homeostasis [5, 10, 12 - 15]. For example ghrelin is currently the only known appetite-stimulating (orexigenic) gut hormone, secreted by the oxyntic glands of the stomach. Ghrelin levels rise shortly before mealtimes. Peptide tyrosine tyrosine (PYY), pancreatic polypeptide, oxyntomodulin, amylin, glucagon, glucagon-like peptide-1 (GLP-1), and GLP-2 are the anorexigenic gut hormones which decrease appetite and food intake.

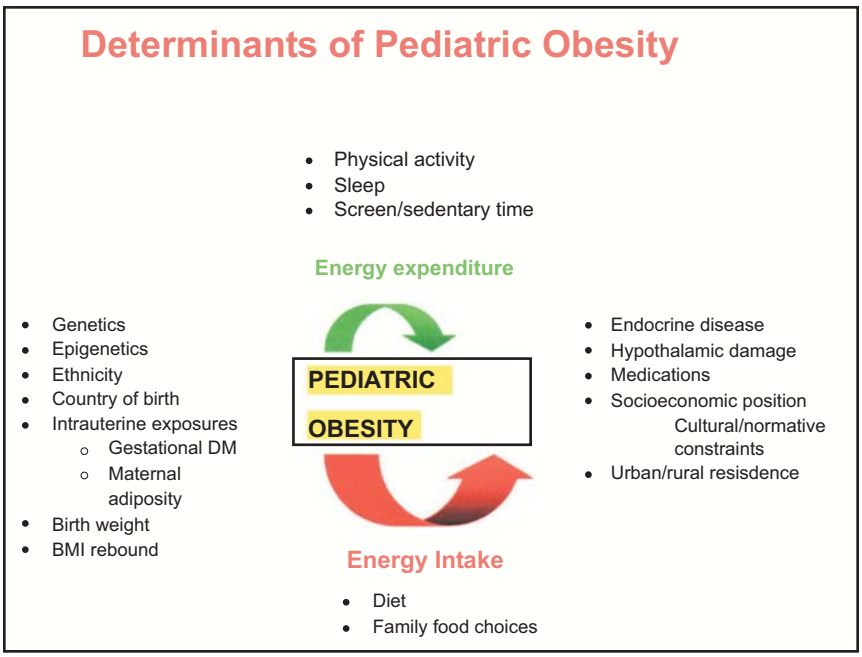

Fig. (1). Determinants of pediatric obesity. Pediatric obesity is a multifactorial condition of positive energy balance, stemming from both genetic and non-genetic factors, as well as complex interactions among these (Adopted from Reference 11, with permission).

Endocrine causes of obesity account for less than 1% of obesity in the pediatric age group. Hypothyroidism (primary or central), growth hormone deficiency or resistance and cortisol excess are the potential endocrine conditions leading to obesity. Polycystic ovarian syndrome (PCOS) is closely associated with obesity. Obesity may also be seen in pseudohypoparathyroidism (caused by Gsα inactivating mutation) [1, 5, 11]. Albright hereditary osteodystrophy (AHO) is an

CHAPTER 10

Current Concepts in the Management of Hyperthyroidism

Abha Choudhary*

Division of Pediatric Endocrinology, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA

Abstract: Graves' disease (GD) is the most common cause of hyperthyroidism in children and adolescents. It is an autoimmune disorder, caused by immunologic stimulation of the thyroid stimulating hormone receptor (TSHR). Thyrotropin stimulating immunoglobulin (TSI) binds to TSHR and leads to thyroid hormone overproduction. Clinical features include fatigue, tremors, palpitations, heat intolerance and poor school performance. The diagnosis is by findings of increased heart rate and goiter in the setting of suppressed thyrotropin stimulating hormone and elevated free thyroxine. Radioactive iodine uptake and serum antibody measurements help to determine the cause of hyperthyroidism. Treatment options for GD include antithyroid drugs, radioactive iodine or surgery. Lasting remission occurs in 15 to 30% of children with GD. Thus, a majority of children will require definitive therapy with radioactive iodine or thyroidectomy. A discussion of advantages and risks of each therapeutic option is essential to help the patient and family select a treatment option.

Keywords: Adolescents, Children, Graves' disease, Hashitoxicosis, Hepatotoxicity, Hyperthyroidism, Methimazole, Radioactive iodine, Radioactive iodine uptake, Thyroidectomy.

INTRODUCTION

Epidemiology

Graves' disease (GD) accounts for 10 to 15% of the childhood thyroid diseases. It is the most common cause of hyperthyroidism in children. The incidence of hyperthyroidism in adults worldwide has been reported to be 23-93/100,000 inhabitants per year [1]. The incidence in children is estimated to be 0.9 per 100,000 in national prospective surveillance study from the United Kingdom and Ireland. Autoimmune thyrotoxicosis accounted for 96% of the cases [2]. The incidence of GD is estimated to be 0.1 per 100,000 person-years in young

* **Corresponding author Abha Choudhary**: Division of Pediatric Endocrinology, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA; Tel: 214 648 3501; Fax: 214 456 2940; Email: AChoudhary@uams.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

children, while it is 3 per 100,000 person-years in adolescents. The prevalence in United States is 1 in 10,000 person-years. GD is rare in less than 5 years of age and has a peak incidence at 10 to 15 years of age, more common in females than males (5:1). GD is more common in children with other autoimmune conditions and in those with family history of autoimmune thyroid disease [3, 4].

Pathogenesis

The cause of GD is unclear, but it is thought to result from a complex interaction of genetic, immune and environmental factors. The immune system produces the thyroid stimulating hormone receptor antibody (TRAb), which is directed against the thyroid stimulating hormone receptor (TSHR). The TRAb can either stimulate or inhibit thyroid hormone secretion. GD occurs from formation of stimulating antibodies to the TSHR called the thyrotropin stimulating immunoglobulins (TSI). It is a functional assay which measures the production of cyclic adenosine monophosphate in cultured thyroid follicular cells. TSI binds to and also stimulates the TSHR on the thyroid follicular cells, leading to increased vascularity of the gland, follicular hypertrophy/ hyperplasia and increased production of the thyroid hormone. The thyroid gland displays lymphocytic infiltration with T-lymphocyte abnormalities and an absence of follicular destruction. T cells activate local inflammation and tissue remodeling by producing cytokines, leading to B-cell dysregulation and autoantibody formation. An imbalance between pathogenic and regulatory T cells is thought to be involved in both the development of GD and its severity [3].

Graves' ophthalmopathy, an immune mediated condition is caused by cross-reactivity of TSI with a TSHR like protein in retro-orbital tissue and extraocular muscle. This leads to local inflammation and infiltration of glycosaminoglycans resulting in edema, muscle swelling and increase in intraorbital pressure causing the characteristic eye findings [5, 7].

Transient hyperthyroidism may result from destruction of thyroid follicular cells by an autoimmune or infectious process, which leads to unregulated release of preformed hormone into the circulation. Subacute thyroiditis occurs from an infection or inflammation and usually resolves in a few months with normalization of thyroid functions. Hyperthyroidism is also seen in McCune-Albright syndrome (somatic-activating mutation of the GNAS gene). It results in increased stimulatory G protein signaling that causes hyperfunction of glycoprotein hormone receptors, autonomous cell proliferation and hormone hypersecretion. Thyrotropin stimulating hormone (TSH) secreting pituitary adenoma and pituitary resistance to thyroid hormone are caused by unregulated overproduction of TSH [6, 7].

Etiology

The most common cause of hyperthyroidism in children is GD. Other causes include acute or sub-acute thyroiditis, T4 ingestion and thyrotoxic phase of chronic lymphocytic thyroiditis (Hashitoxicosis). Hyperthyroidism is also seen in autonomously functioning thyroid nodule, toxic adenoma, multinodular goiter, McCune Albright syndrome, struma ovarii and TSH producing pituitary adenomas [5, 7, 8]. Etiology is listed in Table **1**.

Table 1. Causes of Hyperthyroidism.

Condition	Mechanism	Thyroid Exam	Antibody	RAIU
Increased Secretion of Thyroid Hormone				
Graves' disease	Thyrotropin receptor-stimulating antibodies (TRAb)	Symmetric, non tender goiter	TSI+ Anti-thyroglobulin and thyroid peroxidase antibody +/-	Diffusely ↑
Toxic multinodular goiter	Autonomous overproduction of thyroid hormone	Multiple nodules	Negative	↑ multifocal uptake
Toxic adenoma	Autonomous overproduction of thyroid hormone	Single nodule	Negative	↑ uptake in a single focus
TSH secreting pituitary adenoma	Autonomous production of TSH	Normal or symmetric goiter	Negative	↑
Pituitary resistance to thyroid hormone	Overproduction of TSH	Symmetric goiter	Negative	Diffusely ↑
Excess Secretion of Preformed Thyroid Hormone				
Chronic lymphocytic thyroiditis (Hashitoxicosis)	Autoimmune Release of preformed hormone	Firm goiter	Anti-thyroglobulin and thyroid peroxidase antibody +	↓
Subacute thyroiditis	Viral Release of preformed hormones	Painful goiter	Negative	↓
Drug Induced Hyperthyroidism				
Factitious thyroiditis	Intake of thyroxine	No goiter	Negative, low TSH	↓
Iodine induced	Exposure to contrast agent	Often multinodular	Negative	↑

TSH: Thyroid stimulating hormone; TSI: thyrotropin stimulating immunoglobulins; TRAb: thyroid stimulating hormone receptor antibody.

CHAPTER 11

Recent Advances in Pediatric Asthma

Amine Daher, Tanya M. Martínez Fernández and **Yadira M. Rivera-Sánchez***

University of Texas Southwestern (UTSW) Medical Center, Dallas Children's Health, Dallas, Texas, USA

Abstract: In the past decade, there have been great advances in the approach to and management of pediatric asthma. Recent progress includes improved definitions, established guidelines, and novel therapeutic modalities. There is growing recognition that asthma is a heterogeneous entity and as such, individualized therapy is now standard when creating intervention plans. Asthma severity is classically categorized based on the concepts of impairment and risk. As more specific data is gathered on asthma subgroups, molecular pathways and cluster analysis, there has been a movement for categorizing patients into asthma phenotypes, which could serve to tailor therapies and optimize clinical response. This chapter will review the pathophysiologic processes involved in asthma; expose the latest definitions of asthma and management guidelines; discuss the implications of the "phenotypic" approach in pediatric asthma and present an overview of pertinent recent therapeutic advances.

Keywords: Asthma guidelines, Asthma pathophysiology, Asthma phenotypes, Inhaled corticosteroids, Macrolides, Mepolizumab, Omalizumab, Pediatric asthma, Type 2 Hi asthma, Type 2 Lo asthma, Vitamin D.

INTRODUCTION

Asthma is the most common chronic disease in children and affects over 6 million children in the US [1]. It has been increasingly recognized as a heterogeneous disorder in terms of its phenotypic presentation, pathophysiology and response to therapy. Asthma patients experience recurrent symptoms of airflow obstruction due to airway inflammation, bronchial hyper-responsiveness and in some cases progressive permanent changes [1]. The essence of asthma therapy is control of symptoms and inflammation coupled with treatment of bronchospasms and exacerbations while giving proper consideration to potential contribution from comorbidities. We will briefly review common established therapies as well as

* **Corresponding author Yadira M. Rivera-Sánchez**: University of Texas Southwestern (UTSW) Medical Center, Dallas Children's Health, Dallas, Texas, USA; Tel: (214) 456-4630/(214) 456-5406; Email: Yadira.Rivera-Sanchez@utsouthwestern.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

novel and developing therapies in the care of pediatric patients with asthma.

DEFINITION OF ASTHMA AND CURRENT STANDARD OF CARE

Asthma is a global health concern with prevalence estimated at 1-18% of the world's population. The Global Initiative For Asthma (GINA) established in 2002, defines asthma as a heterogeneous disease, usually characterized by chronic airway inflammation in which patients have a history of wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [2]. A definition for severe asthma was recently developed by both the European Respiratory Society and the American Thoracic Society [3]. It includes patients greater than six years of age who require at least high dose inhaled corticosteroids (ICS) augmented by a second controller to achieve adequate control [3].

Current guidelines offer a standardized approach to asthma therapy. The overall strategy includes assessment of severity and control of symptoms as well as contributing co-morbidities such as obesity, gastroesophageal reflux, psychiatric disorders and rhinosinusitis. Long-term therapeutic goals focus on use of controller medications, relievers and add-on therapies in order to achieve good symptom control as well as a reduction in exacerbations, lung function limitation and side effects of treatment. We refer the reader to a published standardized stepwise approach for the use of inhaled corticosteroids, short acting beta agonists, long acting beta agonists and leukotriene antagonists in the management of asthma [1]. More novel and developing therapies are discussed in later sections of this chapter.

ASTHMA PATHOPHYSIOLOGY

Asthma symptoms stem from airflow limitation due to bronchoconstriction, airway hyper-responsiveness and edema. These, in the setting of chronic inflammation, can progressively lead to airway remodeling. In this section, we will define those processes as well as discuss the various chemical and cellular participants in the pathophysiology of asthma.

Acute bronchoconstriction is the rapid narrowing of airways resulting from airway smooth muscle constriction. Airway hyper-responsiveness is the unbalanced bronchoconstriction response of airways to various stimuli. Airway edema participates in airflow obstruction through mucosal swelling, increased mucus secretions and plug formation. In some asthma patients, permanent histologic changes such as smooth muscle and mucus glands hyperplasia as well as angiogenesis can occur. These histologic changes are collectively referred to as airway remodeling and account for the lack of complete reversibility often seen in

chronic asthma [1, 4].

Neonates have a predominant Th2 phenotype. With time, various exposures tend to shift the immune system towards the Th1 system. In children with asthma, there is an imbalance between the Th1 and Th2 immune pathways manifested by high prevalence of atopic conditions. The hygiene hypothesis proposes for example, that among other exposures, having older siblings and or attending day care can lead to beneficial effects by decreasing the risk of developing atopic diseases. This decrease in atopy is the direct result of infectious exposures balancing in turn the Th1 and Th2 components of the immune system [4].

Inhalation of allergens leads to an inflammatory cascade in asthma patients that is, in most cases, eosinophilic and IgE mediated. Allergens cross-link IgE bound to mucosal mast cells and trigger the release of preformed histamines and leukotrienes. This is known as the "early phase reaction" leading to acute bronchoconstriction [4]. The inflammation seen in asthma requires the interaction of many cell lines, each with characteristic contributions. Upon activation, mucosal mast cells release pre-formed histamines and other mediators leading to bronchoconstriction. Airway eosinophils also release several pro-inflammatory cytokines. In atopic asthma patients, the degree of eosinophilia often correlates with the severity of asthma and decreases with the use of steroid therapy. Some patients with asthma have a predominance of airway neutrophils. Neutrophils contribution to inflammation in asthma is not well understood. Data suggests, however, that in asthma patients, the presence of neutrophils as the predominant cell line correlates with steroid resistance [1, 4].

In addition, asthma inflammation strongly depends on the interplay of a multitude of signaling molecules such as IgE, cytokines and leukotrienes. These molecules are the target of many research and established therapies. IgE is an allergen specific antibody essential to the allergic inflammation of asthma. It binds mast cells as well as other inflammatory cells and promotes bronchoconstriction as well as the release of other inflammatory cytokines [1]. Key Th2 cytokines include: IL-5 promotes bone marrow proliferation of eosinophils and survival in the periphery; IL-4 and IL-13 promote a Th2 response and IgE production [1]. Leukotrienes are released upon activation of mast cells and lead to bronchoconstriction [1].

In summary, in asthma there is an imbalance between the Th1 (protective) and Th2 (allergic) immune systems. The inflammatory cascade is the product of the interaction of many Th2 cell lines and signaling molecules. Clinical symptoms of asthma result from airflow limitation due to acute bronchoconstriction in the early phase followed by inflammation, increased mucus secretion and airway hyper-

CHAPTER 12

Evaluation and Treatment of Bronchiolitis

Derek L. Pepiak*

Department of Pediatrics, Ochsner for Children and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, Louisiana, USA

Abstract: Bronchiolitis is the most common cause of hospitalization in infants and children less than 2 years of age. Patients typically present with signs of an upper respiratory tract infection that then progress to symptoms consistent with a lower respiratory tract infection. The key to diagnosis is the history and physical examination; labs and chest radiography are not routinely necessary or recommended. Treatment is largely supportive as many of the therapies that are effective in other respiratory diseases are ineffective in the treatment of bronchiolitis. Emphasis should therefore be on prevention and reducing transmission of the disease. Areas of focus for the prevention of bronchiolitis include administration of palivizumab prophylaxis in selected infants and children, hand hygiene, elimination of tobacco smoke exposure, encouragement of breastfeeding, and family education.

Keywords: Breastfeeding, Bronchiolitis, Bronchodilators, Children, Corticosteroids, Hand hygiene, Hypertonic saline, Infants, Oxygen, Palivizumab, RSV, Respiratory distress, Respiratory syncytial virus, Smoking.

INTRODUCTION

Bronchiolitis is a clinically diagnosed condition in patients less than 2 years of age that usually begins with symptoms of an upper respiratory tract infection. Initial presentation with coryza and low-grade fever is common. Typically this progresses to a lower respiratory tract infection manifesting as cough, tachypnea, retractions, nasal flaring, wheezes, and/or crackles. The pathogenesis of bronchiolitis includes acute inflammation, edema, sloughing and necrosis of epithelial cells of the small bronchi and bronchioles, increased mucus production, bronchospasm, obstruction of small airways, and atelectasis [1]. Multiple viruses have been isolated as the cause of bronchiolitis. Respiratory syncytial virus (RSV) is by far the most common cause of bronchiolitis, accounting for 50%-80% of cases [2]. Ninety percent of children are infected with RSV within the first 2 years

* **Corresponding author Derek L. Pepiak**: Department of Pediatrics, Ochsner for Children and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, Louisiana, USA; Tel: 504-390-0245; Email: dpepia@lsuhsc.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

of life [3]. The highest incidence of RSV bronchiolitis occurs in North America between December and April [4]. Other viral etiologies of bronchiolitis include rhinovirus, parainfluenza virus type 3, human metapneumovirus, influenza, adenovirus, coronavirus, and enterovirus [5]. In North America, bronchiolitis is the most common cause of hospitalization in infants less than 12 months of age, accounting for approximately 100,000 admissions per year at an estimated cost of $1.73 billion [6 - 8].

CLINICAL FEATURES

Clinical Presentation and Course

During the first few days of illness, most infants present with a 1- to 3-day history of mild upper respiratory tract infection symptoms such as conjunctivitis, otitis media, nasal congestion, rhinitis, pharyngitis, and fever [9]. Decreased oral intake may also be present. Up to 40% of patients then progress to a lower respiratory tract infection with tachypnea, retractions, wheezing, and/or crackles on days 2-3 of illness [10]. Symptoms usually peak on days 5-7 and then gradually resolve. The mean duration of illness is 15 days with resolution of symptoms within 3-4 weeks [11, 12].

Criteria for Admission

No clear criteria exist for determining which infants should be admitted to the hospital. Generally, hospitalization is considered for infants who present with lethargy, dehydration, apnea, or moderate to severe respiratory distress, manifested as nasal flaring, retractions, or a respiratory rate greater than 60-70 breaths per minute [13, 14]. Risk factors for more severe disease presentation requiring admission include prematurity, age less than 12 weeks, chronic lung disease, congenital and anatomical defects of the airway, congenital heart disease, immunodeficiency, and neuromuscular disorders [5]. The average length of stay in the hospital is 3-4 days [15, 16].

Short-term Complications

While bronchiolitis has a high degree of morbidity, it is associated with a low degree of mortality. Mortality rates are estimated to be around 1% [17 - 19]. However, mortality rates can increase to 3.5% in patients with bronchiolitis when additional cardiac or chronic lung conditions are present [20]. The risk of apnea is increased in infants with RSV bronchiolitis, with rates ranging from 1.2% to as high as 23.8% [21, 22]. The risk for intubation in bronchiolitis, either secondary to disease progression or due to apnea, is approximately 5% [18]. Acute otitis media may be present in 50%-60% of patients with bronchiolitis [23, 24].

Secondary bacterial infection, with the exception of acute otitis media, is uncommon in infants with bronchiolitis [25]. Children with bronchiolitis have been reported to have inappropriate secretion of antidiuretic hormone, and close monitoring of fluid status is recommended [26, 27].

Long-term Complications

Most infants with bronchiolitis recover with no long-term sequelae. However, long-term complications may include development of bronchiolitis obliterans, allergic sensitization, and recurrent wheezing [28]. Some studies have shown an association between bronchiolitis in infancy and subsequent development of atopic illnesses such as asthma later in life [29]. However, the connection between bronchiolitis and asthma is controversial as other studies have not supported a relationship between the two [30, 31].

EVALUATION AND DIAGNOSIS

The diagnosis of bronchiolitis is essentially a clinical one. The typical history has been discussed earlier. Physical examination findings can vary between patients and can also fluctuate over time in the same patient; serial assessment of an infant with bronchiolitis is often necessary to monitor the progression and resolution of the disease. Patients often present with excessive nasal secretions leading to upper airway obstruction, manifesting as transmitted inspiratory and expiratory wheezing. Nasal obstruction from secretions may limit the ability of the infant to take adequate nutrition, ultimately leading to dehydration. Work of breathing is usually increased as shown by nasal flaring, intercostal retractions, subcostal retractions, and use of accessory muscles. Auscultation of the chest often reveals diffuse bilateral crackles and wheezes, as well as a prolonged expiratory phase of respiration. Hyperinflation of the lungs from air trapping may allow the liver and spleen to be palpable in the abdomen on examination.

The main goal for the history and physical examination is to determine which infants who present with wheezing and other respiratory symptoms likely have viral bronchiolitis versus another disorder [32]. In addition to bronchiolitis, the differential diagnosis of infants less than 2 years of age who present with wheezing and/or other lower respiratory tract symptoms includes adenoidal hypertrophy, retropharyngeal abscess, croup, asthma, recurrent viral-induced wheezing, bacterial pneumonia, cystic fibrosis, malacia of the airways, foreign body aspiration, aspiration pneumonia, congenital heart disease, congestive heart failure, and vascular rings [33, 34].

In 2014, the American Academy of Pediatrics (AAP) updated their guidelines for diagnosis, management, and prevention of bronchiolitis [32]. The guidelines

CHAPTER 13

What is New with Management of Pediatric Central Sleep Apnea?

S. Kamal Naqvi*

Division of Respiratory and Sleep Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, Texas, USA

Abstract: Central Sleep Apnea (CSA) in children is a far less studied and understood abnormality compared to Obstructive Sleep Apnea (OSA). It is seen more often in younger patient population mostly with co-morbidity. There are structural abnormalities in the brain, spinal cord, airway and chest wall or functional disorders in respiratory control, hemoglobin concentration, swallowing or cardiovascular system, resulting in CSA. Clinical observation of central apneic events prompts further evaluation ideally done by performing Polysomnography testing (sleep study) to confirm the presence and estimate the severity.

Various medical and surgical treatment options result in improvement or resolution of the central apneic events. Majority of the patients show a gradual resolution of the disorder with age. However a minority of patients continue to manifest the disorder and require longer term treatment mostly by using respiratory support in the form of invasive or non-invasive ventilation. More research is needed to explore treatment options for children.

Keywords: Central sleep apnea, Pediatrics, Polysomnographic study, Sleep disordered breathing.

INTRODUCTION

Sleep disordered breathing encompasses conditions from the more common obstructive sleep apnea (OSA) to obstructive hypoventilation, sleep related hypoxemia and central sleep apnea.

Central sleep apnea results from absent respiratory drive from breathing centers in the brainstem during sleep. There is a difference in the definition of CA for children and adults. The American Academy of Sleep Medicine (AASM) defines CA in children as cessation of breathing during sleep without any breathing effort

* **Corresponding author S. Kamal Naqvi**: Division of Respiratory and Sleep Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, Texas, USA; Tel: 214-456-8348; Fax: 214-456-5406; Email: kamal.naqvi@utsouthwestern.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

for duration of 20 seconds or longer, or lasting at least 2 breaths' duration with 3% oxygen desaturation or arousal [1].

Definitions

In children including infants, the CA is at least 2 breaths in duration and is associated with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds, or less than 60 beats per minute for 15 seconds. Periodic breathing has been described as greater than 3 episodes of CA lasting 3 seconds separated by no more than 20 seconds of normal breathing.

Apnea following a sigh is not considered pathologic unless it is associated with arousal or desaturation. Isolated central apnea (Fig. **1A**), CA following post-arousal sigh breathing (see Fig. **1B**), and periodic breathing patterns (see Fig. **1C**) can be seen in healthy infants and children [2].

Fig. (1A). Sixty-second-long epoch showing central sleep apnea.

[1A,1B] Sixty-second-long [1C] 120 seconds-long epoch of the polysomnography of a 4-month-old child born at full term, referred for evaluation of sleep apnea because of observation by parent of apneic episodes. [1*A*] Central sleep apnea without arousal. [*B*] Central sleep apnea after arousal during Quiet sleep. [*C*] Periodic breathing during Active sleep. abdm, abdominal plethysmography; C4, central electroencephalogram leads; CHIN, chin electromyogram; EOG, L&R eye electromyogram; EKG, electrocardiogram; ETCO, end-tidal carbon dioxide tracing; F4, frontal electroencephalogram leads; O2, Occipital electro-encephalogram, FLOW, tracing of oral thermistor; Nasal Pressure for measurement of nasal air pressure; SNOR, snore micrograph; SpO2, continuous

pulse oximetry; thor, thoracic plethysmography.

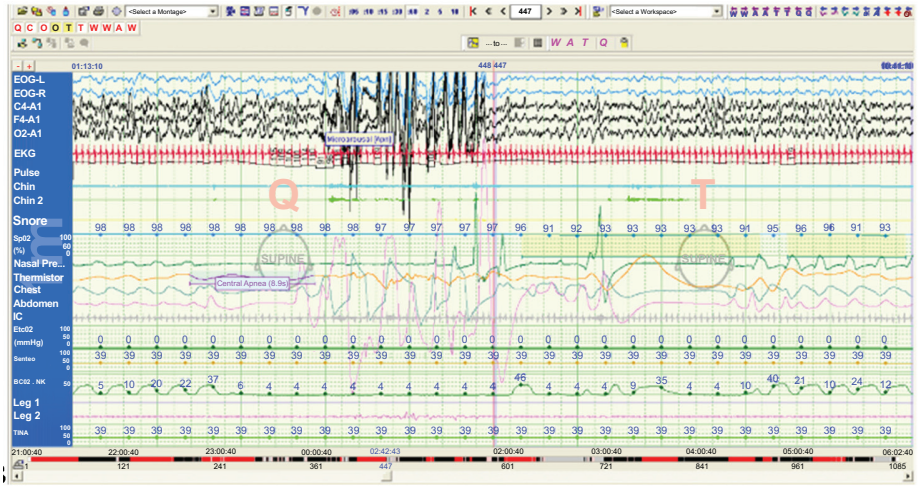

Fig. (1B). Sixty-seconds-long epoch showing central sleep apnea after arousal during Quiet sleep.

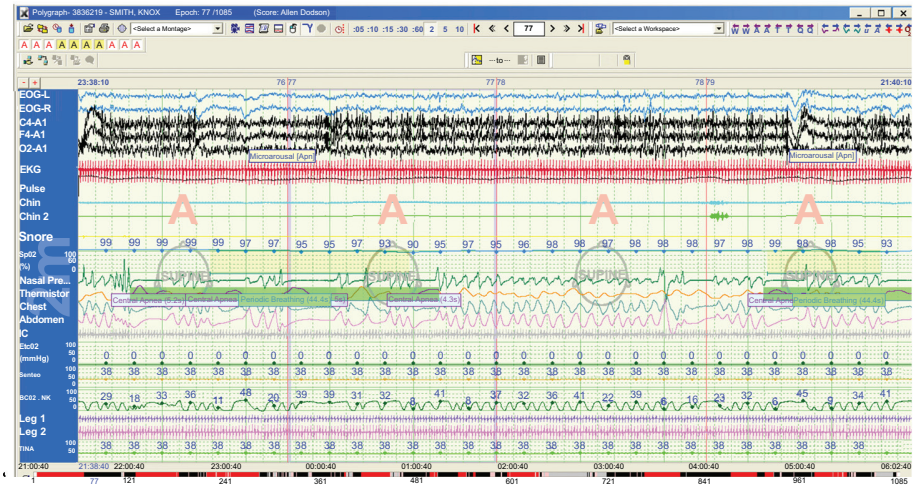

Fig. (1C). 120 seconds-long epoch showing periodic breathing during Active sleep.

Generally, it is common to see CA in healthy infants and children, but on rare occasions it can be a sign of significant pathologic consequences, such as congenital central hypoventilation syndrome or Arnold-Chiari malformation [3].

The severity of CA can be characterized using the central apnea index (CAI) while apnea-hypopnea index (AHI) usually refers to the obstructive type of the disorder and is the total number of events overnight divided by hours of sleep. There is no clear description in the literature of pathologic central apnea index but

CHAPTER 14

Practical Considerations in the Treatment of Pediatric Obstructive Sleep Apnea

Amal Isaiah and **Seckin O. Ulualp***

Department of Otolaryngology— Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Abstract: Obstructive sleep apnea syndrome (OSAS), affecting about 5% of all children, has positioned itself to be a major epidemiological problem in the United States. The prevalence of this condition appears to be increasing over time, in parallel with the growth in childhood obesity. Pediatric OSAS belongs to a spectrum of respiratory disorders called sleep-disordered breathing (SDB), caused by varying degrees of paroxysmal upper airway obstruction during sleep. Left untreated, OSAS has potential to progress over time, leading to not just fragmented sleep, but also neurocognitive problems, and in the most severe instances, serious cardiopulmonary adverse effects. The treatment of OSAS involves a structured series of steps spanning medical and surgical approaches, including adenotonsillectomy, which is considered the gold standard for management of childhood OSAS. This chapter provides a review of the epidemiology of OSAS, followed by a discussion of natural history, treatment and follow up.

Keywords: Adenotonsillectomy, Obesity, Pediatric obstructive sleep apnea, Snoring.

INTRODUCTION

Sleep is a physiological state of quiescence that facilitates recovery of body functions. Most cardiopulmonary parameters are minimized to conserve energy expenditure during sleep. As a consequence, ventilatory drive reaches an expected nadir compared to wakefulness. Relaxation of upper airway musculature also increases the preponderance towards airflow obstruction. These changes principally manifest in an overall reduction in ventilatory volumes [1].

Previous studies have clearly shown that despite the tendency towards upper airway obstruction, healthy infants and children still maintain normal airflow

* **Corresponding author Seckin O. Ulualp**: Department of Otolaryngology—Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA; Tel: (214) 456-3862; Fax: (214) 648-9122; Email: Seckin.ulualp@utsouthwestern.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

without significant hindrance. However, as function of age, development and changes in body physiology, the tendency towards obstruction is not uniform across all age groups [2].

Sleep-disordered breathing (SDB) represents a broad spectrum of clinical disorders, all of which have pathologic upper airway obstruction as the common factor. SDB has continued to grow in prevalence over time, and accounts for a significant amount of public health burden [3], with estimates ranging from 1-15% by various studies [4]. It is therefore of paramount importance to maintain a strong degree of clinical suspicion when children present with history of snoring.

Sleep-Disordered Breathing

The term SDB encompasses three principal categories, based on the severity of upper airway obstruction, and includes (i) primary snoring, (ii) upper airway resistance syndrome (UARS) and (iii) obstructive sleep apnea syndrome (OSAS). It is to be noted that accurate distinction between these three conditions requires diagnostic testing, specifically polysomnography (PSG), also called a sleep study [5].

In the mildest form of SDB, called primary snoring, there is intermittent nocturnal airflow obstruction that results in turbulence (snoring); however there are no clinical features that suggest that duration and architecture of sleep are abnormal. Primary snoring has a conservative estimate of around 7% according to one study based on administration of a questionnaire to parents of children in primary school [6]. In the same study, the authors also described an association of the condition with (i) presence of asthma and (ii) exposure to cigarette smoking. However, the utility of clinical history alone to distinguish between primary snoring alone and more severe forms of SDB has been questioned in the past [7], and this is important given that snoring seems to be associated with significant neurobehavioral deficits in a subset of children, possibly related to increased susceptibility to sleep fragmentation [8]. Others have demonstrated that primary snoring does not progress significantly over time [9].

Upper airway resistance syndrome occupies an intermediate position in the spectrum of SDB. This term was coined to describe a subset of patients who do not meet the criteria for OSAS by PSG standards, yet they present with symptoms that most closely resemble chronic upper airway obstruction. The pathophysiology of UARS has been related to abnormal maxillomandibular anatomy, and may respond to orthodontic treatment [10].

Epidemiology

The prevalence of pediatric SDB and OSAS continue to grow since there has been a recent increase in awareness of the problem, yet the vast majority remain undiagnosed. Epidemiologic estimates place the population burden to be at about 7.45% when estimated by examining the prevalence by parental reports of snoring [11]. The same meta-analysis by strict criteria of *always snoring* reported SDB to be in the range of 1.5-6% and when the criteria changed to *often*, the prevalence increased to 3.2-14.8%. It is to be noted that the prevalence of OSAS parallels the prevalence of SDB, as the latter requires a PSG for diagnosis.

Race is an independent risk factor for SDB, with African-American children having greater preponderance towards developing the condition [12]. Hormonal influence on SDB manifests in a slight increase in prevalence among prepubertal boys, however this association has not been consistently demonstrated [6]. Despite a paucity of data from very young children, it is generally regarded that SDB decreased over time between 4 and 12 years of age [13].

The association between obesity and SDB and/or OSAS is unambiguous. Most studies that investigated this relationship have generally concluded that obesity increases the risk of SDB as well as the non-response to treatment [14, 15].

Environmental factors play a role in increased susceptibility to pediatric OSAS, and generally also include indicators of neighborhood disadvantage—specifically factors that span (i) second hand smoke exposure and (ii) low socioeconomic status [16]. These factors remained even after controlling for the effects of prematurity and obesity.

Pathophysiology of OSA

A complex interplay of anatomical and physiologic factors is hypothesized to contribute to development of upper airway obstruction as seen in pediatric OSAS. Fixed anatomical obstruction may be attributed to narrowing at the level of the lumen, soft tissue or the craniofacial skeleton [17]. Secondary risk factors originate from disordered control of neuromuscular tone responsible for maintaining upper airway patency during sleep.

The upper airway in children with pediatric OSAS is thought to be modeled as a *Starling* resistor [18], in which airflow obstruction occurs as a function of the closing pressure within the airway lumen, termed critical closing pressure (P_{crit}). This index is a composite measure of both viscoelastic and neuromuscular properties of the upper airway. When P_{crit} falls below threshold, airflow obstruction occurs consistently. Children with OSAS are known to have higher

CHAPTER 15

State of the Art of the Diagnosis and Management of Gastroesophageal Reflux Disease

Ricardo Medina-Centeno and **Rinarani Sanghavi***

Department of Pediatrics, Division of Gastroenterology and Hepatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract: Involuntary passage of gastric contents into the esophagus may be physiologic (Gastroesophageal Reflux-GER) or may be associated with troublesome symptoms (Gastroesophageal Reflux disease-GERD). GER is common in infants and is related to immature anti reflux mechanisms. On the other hand, GERD needs further evaluation. Presenting features of both include esophageal symptoms like vomiting and extra esophageal symptoms such as irritability, reflux laryngitis, pharyngitis and dental erosions. Upper GI series is not recommended for diagnosing GERD. Traditional pH probe examinations have been replaced largely by combined multi-channel Impedance –pH monitoring which helps establish a temporal relationship between symptoms and pathological reflux, as well as ascertain the acidic *versus* non acidic, solid *versus* liquid or gas nature of the refluxate. Proton pump inhibitors remain the mainstay of treatment, along with H2 receptor antagonists and prokinetic agents. Surgical intervention should be reserved for selected severe cases.

Keywords: Antacids, Bravo pH monitoring, Combined Multiple Intraluminal Impedance (MII) and pH Monitoring, Endoscopy, Esophageal manometry, GER, GERD, Lifestyle changes, Manifestations, PH monitoring, Prevalence, Prokinetics, Upper GI imaging.

Definitions

Gastroesophageal reflux (GER) is a normal physiological process in which there is an involuntary passage of gastric contents into the esophagus. Most of the reflux episodes are asymptomatic, having short duration, occurring several times per day, particularly after meals and limited to the distal esophagus. Commonly, a reflux episode results from a transient relaxation of the lower esophageal sphincter (LES). Other causes include increased abdominal pressure not accompanied by an increase in the pressure of the LES or conditions when the

* **Corresponding author Rinarani Sanghavi**: Department of Pediatrics, Division of Gastroenterology and Hepatology, University of Texas Southwestern Medical Center, Dallas, TX, USA; Tel: (214) 456-3862; Fax: (214) 648-9122; Email: rina.sanghavi@utsouthwestern.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

LES pressure is reduced. Physiologic GER is a reflux episode associated with regurgitation or occasionally vomiting during the first months of life or in the absence of symptoms. GER is a frequently encountered problem in infancy and tends to self-resolve [1]. Gastroesophageal reflux disease (GERD) is when reflux of gastric contents is the cause of troublesome symptoms and/or complications such as esophagitis, nutritional compromise, respiratory complications or poor weight gain. Pathologic GERD may be primary or secondary. Secondary GERD is associated with a number of genetic syndromes such as Cornelia de Lange, chromosomal abnormalities such as Trisomy 21, birth defects such as congenital diaphragmatic hernia, omphalocele and gastroschisis, and neurologic conditions such as myotonic dystrophy [2].

Regurgitation, a common manifestation of reflux in infant and older children, is defined as effortless passage of refluxed gastric contents into the oropharynx or above, while vomit is defined as forceful expulsion of the refluxed gastric contents from the mouth [3]. On the other hand, rumination is defined as voluntary contraction of the abdominal muscles resulting in regurgitation of recently ingested food that is subsequently spitted up or re-swallowed. This requires a different diagnostic and treatment algorithm than reflux and is beyond the scope of this review. The reader is referred to the Rome III criteria for further reading on rumination in children [3].

Epidemiology

GER is extremely common in healthy infants occurring 30 or more times a day [4, 5].

Many, but not all, episodes of these reflux episodes result in regurgitation into the oral cavity. Commonly, the frequency of reflux episodes decreases with increasing age, and is unusual in children older than 18 months old [1, 6, 5]. The prevalence of GER in older children and adolescent is estimated to be as high as 10% with 6% having GERD [7]. There is a higher prevalence of GERD in patients with neuromuscular disorders such as muscular dystrophy and cerebral palsy.

Pathophysiology

Transient lower esophageal sphincter relaxations (TLESRs) or inadequate adaptation of the sphincter tone due to changes in abdominal pressure are the most common mechanisms causing GER at any age [8]. This relaxation is a neural reflex, through the vagal nerve causing activation of intramural inhibitory neurons, releasing nitric oxide locally promoting relaxation of the LES. GER is influenced by genetic (Table **1**), environmental (alcohol, smoking, drugs, food,

weight), anatomic, hormonal and neurogenic factors. In infants, GER is most common as they ingest more than twice the volume than adults per kilogram body weight and feed more frequent causing more TESLRs. Delayed gastric emptying, abnormal gastric accommodation has been described in patients with GERD [9, 10]. Anatomical causes include hiatal hernia which increases the number of reflux episodes and delays esophageal clearance.

Table 1. Genetic factors.

1	Increased GER-symptoms in relatives of GERD patients [11]
2	Concordance for GER is higher in monozygotic compared to dizygotic twins [12]
3	Some studies have suggested association with chromosomes 9 and 13 [13]

There are three major tiers of defense that serve to limit the degree of GER and minimize the risk of reflux-induced injury. The first line is the antireflux barrier consisting of the LES, diaphragmatic pinchcock and angle of His. The second line is the esophageal clearance consisting of gravity, esophageal peristalsis, salivary and esophageal secretions. The third line is the esophageal mucosal defense (bicarbonate, mucin, prostaglandin E2, tight junctions, *etc.*).

Clinical features of GERD

Symptoms of GERD may be divided into esophageal and extra esophageal symptoms. (Table **2**). Esophageal symptoms include typical symptoms such as heartburn, vomiting, water brash (sour taste at the back of mouth), and epigastric abdominal pain especially worse after eating spicy foods. Dysphagia is also thought to be a symptom of GERD, especially common in younger children (< 1 year of age). Arching of the back (Sandifer syndrome) is a common presentation of GERD in infants. It is difficult to rely on symptoms in children less than 1 year of age due to their inability to accurately verbalize symptoms. These symptoms also do not always resolve with acid suppression therapy in the first year of life, making the diagnosis even more challenging [14].

Extra esophageal symptoms of GERD have been documented for several years now. Irritability, coughing [15, 16]. Choking, wheezing, sore throat, voice hoarseness, dental erosions and reflux associated laryngitis or pharyngitis have been implicated in various studies [17 - 20].

In any patient with suspected GERD not responding to adequate therapy, particularly in children with dysphagia and choking, eosinophilic esophagitis should be considered in the differential diagnosis. Eosinophilic esophagitis has a clinical presentation similar to GERD, and as of the writing of this paper, the only

CHAPTER 16

Essentials of Sickle Cell Disease Management

Jesica F. Ramirez[1] and **Melissa Frei-Jones**[2,*]

[1] *Centro Javeriano de Oncologia - Hospital Universitario San Ignacio, Bogota, Columbia*

[2] *Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas, USA*

Abstract: Sickle cell disease (SCD) is the most common inherited disorder identified by newborn screening programs with an estimated 100,000 individuals living with SCD in the United States (US). The most severe phenotype of SCD is seen in patients with homozygous hemoglobin SS (HbSS) also known as sickle cell anemia. Common morbidities include invasive pneumococcal infection due to loss of splenic function, pulmonary sickling causing acute chest syndrome, cerebrovascular stroke, acute pain episodes and the development of chronic pain syndromes. Life expectancy for SCD has improved and children born with SCD today have a greater than 90% chance of survival to adulthood. Disease modifying therapies including the use of simple and chronic transfusions and oral hydroxyurea to both treat and prevent disease complications such as pain, stroke and acute chest syndrome. The only curative option for SCD remains hematopoietic stem cell transplantation with the best outcomes from a matched sibling donor.

Keywords : Acute chest Syndrome, Anemia, Asplenia, Avascular necrosis, Dactylitis, Electrophoresis, Hemoglobin S, Hydroxyurea, Newborn screen, Pain crisis, Pneumococcus, Prophylaxis, Sepsis, Sickle cell disease, Splenic sequestration, Stroke, Transcranial doppler ultrasound, Transfusion, Vaso-occlusive crisis.

INTRODUCTION

Sickle cell disease (SCD) is the most common inherited red blood cell (RBC) disorder worldwide [1]. It is a life threatening condition resulting from a single base pair mutation in the β-globin gene. Hemoglobin polymerizes in its deoxygenated state, causing the RBC to take on a crescent or sickled conformation that alters blood viscosity and vascular endothelium, leading to vaso-occlusion, an exuberant inflammatory response and early death of RBC [2, 3].

* **Corresponding author Melissa Frei-Jones**: Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas, USA; Tel: 210-567-7477; Email: freijones@uthscsa.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

Approximately 312,000 infants with SCD are born each year in the world. Although survival and life expectancy for children with SCD in the first world has increased due to universal newborn screening for early disease detection and initiation of prophylactic penicillin to prevent early complications, infants born in the United States (US) and Europe together represent only 2% of the annual SCD births worldwide [4]. The majority of cases of SCD are found in developing countries with limited resources for preventive care and treatment [5].

New approaches to sickle cell management with disease modifying treatments including hydroxyurea and chronic transfusions are being studied [6, 7]. Advances in early detection of complications and methods for improved survival of patients undergoing transplant have also been described [8]. In this chapter, we discuss the current guidelines for early diagnosis and management of SCD and its complications, hoping to help physicians identify the presentation of SCD, treat acute sequelae and know when to refer to a SCD specialist for chronic management.

GENERAL CONCEPTS

Genetics

SCD is caused by a mutation in the β-globin gene and demonstrates autosomal recessive inheritance. Given that a single HbS allele produces a phenotypic change in the hemoglobin profile, an autosomal co-dominant fashion has also been proposed [9].

"Sickle cell disease" is the term used to refer to various genotypes that cause the characteristic clinical syndrome. The most frequently occurring genotype is the homozygous state (HbSS) also known as sickle cell anemia, which has the most severe clinical phenotype. More than ten other genotypes have been described, although most are rarer [10].

Classification of Variants

The different forms of SCD result from the coinheritance of HbS with other abnormalities in the β-globin gene. The most common variants include: Sickle-hemoglobin C disease (HbSC), Sickle-β+-thalassemia (HbSβ+), and Sickle-β--thalassemia (HbSβ0) [9].

The most severe forms of the disease are HbSS and HbSβ0. Patients with these variants have been described to have higher markers of hemolysis, lower mean hemoglobin values, and increased prevalence of complications including: vaso-occlusive pain crisis, acute chest syndrome, acute cerebrovascular stroke, leg

ulcers and priapism [9, 11]. The lower the expression of β-like chains in the thalassemic allele, the more complications experienced by the patient [12]. The most common genotypes of SCD, and the associated typical peripheral blood findings in untreated SCD are shown in Table **1**.

Table 1. Common Genotypes of Sickle Cell Disease.

Common Genotypes of Sickle Cell Disease					
Name /Genotype	Main Hemoglobin present	Hemoglobin level (g/dL)	Mean Corpuscular Volume (fL)	Reticulocyte %	Severity
Sickle cell anemia (Hb* SS) BS/BS	S	6 to 9	Normal	10 to 25	+++
Sickle β0 thalassemia (Hb SB0) BS/BO	S	6 to 9	Decreased	10 to 25	+++
Sickle Hb C disease (Hb SC) BS/BC	Sc	9 to 12	Normal	5 to 10	++
Sickle β+ Thalassemia (Hb SB+) BS/B+	Sa	10 to 13	Decreased	2 to 10	+

Most common genotypes that cause sickle cell disease are listed, resulting from one or more mutations on the β-globin gene and the laboratory findings associated with each of the presentations when left untreated.
*Abbreviations: Hb, hemoglobin. (Modified from Pediatr Clin North Am, 2013 Dec; 60(6):1363-81).

Epidemiology

SCD is the most common genetic disorder identified through newborn screening. Approximately 300,000 infants are born with SCD-HbSS each year in the world. Sickle cell trait (SCT) is frequently found in individuals of African ancestry (sub-Saharan, equatorial Africa) but it has spread throughout the world due to migration [13]. An estimated 230,000 HbSS births occur annually in sub-Saharan Africa [4].

Approximately 100,000 people with SCD live in the US [11]. The disease is more common in African-Americans with 1 in 12 carry SCT and 1 in 365 individuals are affected with disease [11, 14]. For Hispanics the incidence is lower, 1 in every 36,000 births affected with the disease [5].

Survival to adulthood is currently between 93.9% and 95% in children enrolled in comprehensive care programs. The average age of death for patients with SCD has been estimated to be 39 years, and the mortality in pediatric patients is 0.52 per 100 patient-years. On the other hand, the developing world still has an estimated mortality rate of 50-90% before age 5; most commonly as a result of streptococcal sepsis, acute severe anemia and splenic sequestration [4, 15].

CHAPTER 17

Management of Recurrent Epistaxis

Kathleen R. Billings*

Division of Pediatric Otolaryngology-Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Abstract: Objective: To describe the etiology, diagnostic examination, and management options of recurrent epistaxis in children, to help clinicians better delineate which patients might benefit from conservative *versus* more aggressive therapies.

Results: Epistaxis occurs frequently in children, and affected children are often seen by primary care, emergency department, and otolaryngology physicians. Knowledge of the underlying etiology, diagnostic examination techniques, and available treatment options is essential for clinicians. A review of the current literature was performed, and this chapter provides information about epistaxis management. Most cases of epistaxis are self-limited and respond well to conservative treatments, such as lubricants and antiseptic ointments; however, some cases will require hematologic testing, diagnostic imaging, and intraoperative assessment and management.

Conclusions: Epistaxis is a common diagnosis in children. Clinicians should be familiar with the etiology and management of this condition in children.

Keywords: Epistaxis diagnosis, Epistaxis etiology, Epistaxis management, Pediatric epistaxis.

INTRODUCTION

Epistaxis (nosebleed) is defined as acute bleeding from the nostril, nasal cavity, or nasopharynx [1 - 5]. The condition is very common in children, although it rarely occurs in those under 2 years of age. Reports site the incidence of at least one episode of epistaxis to be around 30% among children aged 0-5 years, 56% among those aged 6-10 years, and 64% among those aged 11-15 years. [1, 5] Most bleeding episodes are minor and self-limited, requiring no medical attention. However, bleeding can be unpredictable and may have an impact on the quality of life for the child and family. Families may fear excessive blood loss due to

* **Corresponding author Kathleen R. Billings**: Division of Pediatric Otolaryngology-Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; Tel: 312-227-9414; Fax: 312-227-6230; Email: KBillings@luriechildrens.org

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

recurrent epistaxis [2]. Many seek medical attention from primary care or emergency department physicians and otolaryngologists for the management of epistaxis. A general understanding of the etiology, examination, and treatment options for epistaxis is essential for all clinicians caring for children. This chapter will provide a review of the current diagnostic and treatment strategies for children with recurrent epistaxis.

ETIOLOGY

In the majority of children, spontaneous bleeding is almost always venous and arises from "Little's area," the anterior region of the nasal septum. A number of arteries anastomose in this region, forming a plexus of vessels under the thin septal mucosa called Kiesselbach's plexus. Bleeding can occur in this area when exposed to dry air or minor trauma. Crusting and scabbing in the area can cause itching, leading to repetitive trauma to the region by picking and rubbing. Recurrent epistaxis, referred to as "idiopathic epistaxis," in children is usually attributed to crusting, nasal vestibulitis and/or digital trauma, although no direct cause can be established in many cases. [1, 3 - 5] Allergic rhinitis is thought to contribute to epistaxis due to nasal mucosal inflammatory changes, leading to friable, irritated mucosa that is more apt to bleed. Nasal colonization with *Staphylococcus aureus* has been shown to be more common in children with epistaxis than in control subjects, and the bacterial colonization has been postulated to cause inflammation and new vessel formation, leading to epistaxis [6 - 8]. Irritation in the nasal cavity can lead to digital trauma and subsequent epistaxis. Kamble *et al* [7] found that the presence of *S. aureus* colonization in the anterior nasal cavity was associated with significant crusting and dilated blood vessels on the anterior septum in children with epistaxis. Other causative factors for epistaxis include trauma, anatomic abnormalities, medications, neoplasms, and coagulopathies [9, 10].

The incidence of epistaxis is thought to be greater in the cold, winter months in northern climates, when upper respiratory infections are more frequent and when indoor humidity decreases to low levels [1,11]. Nosebleeds may also occur more often in hot, dry climates with low humidity; however, given the commonality of epistaxis in children, ambient temperature may have little impact on the overall rate of bleeding.

There is no general consensus on the best approach for the evaluation of pediatric epistaxis. A thorough review of the patient's history and physical examination, including anterior rhinoscopy are recommended. History should include frequency of nose bleeds, laterality (important when considering cautery), duration of bleeding, and the presence of easy bruising or bleeding easily with

other minor traumas (both possibly suggestive of coagulopathies). Documentation of prior trauma to the area, history of allergic rhinitis, and a review of medications (*i.e.*, aspirin use) may help elucidate the cause of bleeding. A family history of epistaxis is important when considering the diagnosis of hereditary hemorrhagic telangiectasia (HHT) and coagulopathies, such as hemophilia and von Willebrand disease. At physical examination, the nasal cavity is assessed for the source of bleeding. Visible vessels on the anterior septum are often apparent, in addition to drying and crusting of the nasal mucous membranes. Oral cavity examination might reveal the presence of telangiectasia in patients with HHT. Rigid or flexible nasal endoscopy is appropriate in those in whom the source is uncertain or when there is suspicion for a neoplasm, such as juvenile nasopharyngeal angiofibroma (JNA) [3, 4]. Imaging studies, such as computed tomography (CT) or magnetic resonance (MR) imaging, are not recommended in the routine examination of a child with epistaxis. When confirming or considering the diagnosis of JNA or another nasal neoplasm, imaging is necessary to assess the extent of involvement of the surrounding structures.

Knowing when more aggressive diagnostic testing should be used can be challenging. In a study by Patel *et al* [4], laboratory testing, including a complete blood count and a prothrombin time/activated partial thromboplastin time (PT/PTT), was performed in 131 of 175 (74.9%) pediatric patients with epistaxis. Twenty-seven (20.6%) patients were found to be anemic at testing, although only 2 had hemoglobin levels less than 10 mg/dL and 3 had hematocrit less than 30%. No patient required a blood transfusion for anemia or severe bleeding. A study by Elden *et al* [10] demonstrated anemia in 4 of 47 (8.5%) patients in an analysis of predictors of bleeding disorders in children with epistaxis. The study included children with severe epistaxis who had experienced medical management failure and who were undergoing intraoperative cautery. Anemia was associated with younger age in both studies mentioned (5.9 years and 6.4 years, respectively), which may reflect the impact of blood loss on lesser overall blood volume of younger children.

Sandoval *et al* [9] found duration, severity, and the presence of other bleeding symptoms to have no predictive value for the diagnosis of coagulopathy in 178 pediatric patients referred to a hematology clinic for a diagnosis of coagulopathy. The authors diagnosed coagulopathy in 59 (33.0%) of the patients analyzed (age range 15-219 months). The coagulopathies diagnosed included von Willebrand disease in 33, platelet aggregation disorders in 10, thrombocytopenia in 7, mild factor VII deficiency in 3, Bernard-Soulier syndrome in 2, and a variety of other factor deficiencies in the remaining patients. Only a family history of bleeding was predictive of the diagnosis of a bleeding disorder, and children who received a diagnosis of coagulopathy had a longer median PTT than did those without the

CHAPTER 18

Update on Management of Allergic Rhinitis

Maria C. Veling*

Department of Otolaryngology – Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA; Tel/Fax: 214-456-7644;

Abstract: Allergic rhinitis (AR), the most common chronic disease in children, is the fifth most common chronic disease in the United States. Otolaryngologists see a large percentage of patient's whose disease process is often associated with, or caused by, upper and lower airway inflammation. Because allergy is a common contributor to airway inflammation, a working knowledge of the treatment options for pediatric allergic rhinitis is essential in the evaluation and management of children presenting to otolaryngologists.

Keywords: Allergic rhinitis, Allergic rhinitis and Allergic conjunctivitis, Allergic rhinitis and Asthma, Allergic rhinitis and Otitis media with effusion, Allergic rhinitis and Rhinosinusitis, Allergic rhinitis and Sleep disturbance, Allergic rhinitis comorbidities, Allergic rhinitis diagnosis, Avoidance, Environmental control, Immunotherapy, Pharmacotherapy, Subcutaneous immunotherapy, Sublingual immunotherapy.

INTRODUCTION

Allergic rhinitis is one of several comorbid conditions often seen in patients who suffer from allergic disease (atopy). The genetic predisposition to develop allergic diseases, *i.e,* atopy, is typically associated with intensified immune responses to common allergens such as inhaled and food allergens.

The phenotype of allergy has a complicated and variable genetic contribution, hence, no single genetic test is used to identify if an individual is allergic. In the light of the genes identified, alterations in both innate and adaptive immunity are critical in allergic disease [1]. Moreover, gene-environment interactions [2], add another layer of variability to the development of allergic disease. To date exposure to cigarette smoke, higher socioeconomic level, first born or only child, and elevated total IgE (>100 IU/L) before age 6 have been identified as risk

* **Corresponding author Maria C. Veling**: Department of Otolaryngology – Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA; Tel/Fax: 214-456-7644; Email: maria.veling@utsouthwestern.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

factors for developing allergic disease [3].

Generally, the first clinical manifestation of allergic rhinitis disease in early childhood is atopic dermatitis. A typical sequence of food allergy, rhinitis and asthma follows atopic dermatitis. The atopic march describes the progression of atopic manifestations from atopic dermatitis to allergic rhinitis and asthma. A number of cross-sectional and longitudinal studies substantiate its validity; however, more data are needed to support the atopic march hypothesis [4 - 7]. The atopic march may not be a simple progression as genetic and environmental factors influence the development of atopic dermatitis, allergic rhinitis and asthma.

ALLERGIC RHINITIS (AR)

Allergic rhinitis, affecting 1 out of 6 Americans, is the most common chronic disease in the United States. AR and related illnesses account for 800,000 to 2 million lost school days on annual basis [8, 9].

Allergic rhinitis is a chronic disorder of the upper airways and is induced by IgE-mediated inflammation after exposure of the nasal membranes in sensitized patients to a specific allergen [10]. The symptoms of allergic rhinitis encompass nasal congestion, nasal drainage, sneezing, nasal itching, and postnasal drainage. Allergic rhinitis has a multiplicity of symptoms with varied clinical presentation in the pediatric patient, depending on the duration of allergy on exposure, age, and presence of comorbid disease. In addition, its symptoms can be similar to those of recurrent upper respiratory infections, a common occurrence in childhood, leading to under treatment of the allergic disease process.

The prevalence of AR varies with factors including, but not limited to, genetics, epigenetics, and environmental exposure. Worldwide prevalence estimates range from 1.5% to 39.7% depending on geographic location [11]. In The Pediatric Allergies in America Survey, otolaryngologists surveyed estimated that 41% of their pediatric patients, aged 4 to 17 years, were diagnosed with allergic rhinitis [12].

Although allergic rhinitis is not life threatening, it can have a significant impact on the quality of life [13], school performance, quality of sleep, and physical and emotional health [12]. In addition, it can have a substantial economic impact including both direct costs to patients and indirect costs that include absenteeism [14] and inefficient school performance [15]

Diagnosis

Allergic rhinitis in children is diagnosed based on history, clinical assessment and allergy testing. Allergy testing in the absence of clinical likelihood of allergic disease yields unacceptable false-positive rates and is not recommended. This was illustrated by a positive skin prick test in 53.9% of 10,509 Americans randomly sampled in Third National Health and Nutrition Survey [16].

Though the recently published Clinical Practice Guideline on Allergic Rhinitis states that skin testing can be used in patients of any age [17], early sensitization to inhalant allergens in infancy occurs infrequently and there is rarely a need to test for them in children less than 4 years of age. Herr and colleagues [18] used a standardized questionnaire in 1850 infants at their 18th-month examination to identify children with allergic rhinitis-like symptoms defined as runny nose, blocked nose, and sneezing apart from a cold. Of the 1850 infants, 9.1% were found to have allergic rhinitis-like symptoms. All children were then assessed with a specific inhalant IgE screen, total IgE, and eosinophilia. There was no difference in eosinophilia or total IgE in the "allergic rhinitis-like symptoms" group compared with the "no allergic rhinitis-like symptoms" group. Only 9 of the 1850 children had both allergic rhinitis-like symptoms and elevated inhalant-specific IgE. In comparison, there were 43 of 1850 infants with elevated inhalant-specific IgE that were identified in the "no AR-like symptoms group." This suggests that allergic rhinitis is rare at 18 months of age and that screening infants for elevated specific IgE would lack specificity in identifying infants with clinical symptoms.

When there is a high degree of suspicion, testing only for indoor allergens, may identify the majority of sensitized children as demonstrated by Sahiner *et al* [19]. In their study, they looked at 432 children, less than 2 years of age, with asthma, and tested them with either a full panel of inhalant allergens, including indoor allergens *vs*. indoor allergens alone. They found the rate of sensitization to be essentially equal between the two groups concluding that in the very young, testing for indoor allergens alone, may identify the majority of affected children.

It is also important to remember that negative allergy skin testing in early childhood does not exclude sensitization and allergic symptoms at a later age [20].

TREATMENT OF ALLERGIC RHINITIS

Treatment of allergic rhinitis in children is similar to treatment in adults, and consists of avoidance, environmental controls, pharmacologic therapy, and specific allergen desensitization.

CHAPTER 19

The Management of Pediatric Allergic Emergencies

Olga Hardin[1] and **Joshua L. Kennedy**[1,2,3,*]

[1] *Department of Internal Medicine, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

[2] *Department of Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

[3] *Arkansas Children's Research Institute, Little Rock, AR, USA*

Abstract: Anaphylaxis is a dangerous condition that must be treated quickly. The prevalence is on the rise, and the diagnosis requires a low index of suspicion in someone experiencing the typical constellation of symptoms involving more than one body system after exposure to a possible allergen. Treatment involves the administration of intramuscular epinephrine before consideration of any other modalities. While treatment of anaphylaxis with epinephrine always comes first, specific laboratory tests including serum tryptase and directed specific IgE tests can be considered to help aid in the diagnosis. Finally, every patient who experiences anaphylaxis should be discharged with injectable epinephrine and an emergency action plan.

Keywords: Anaphylaxis, Drug Allergy, Epinephrine, Food Allergy, Histamine, Tryptase, Venom Allergy.

INTRODUCTION

Rapid recognition of allergic emergencies is crucial to a timely and appropriate treatment. Allergic emergencies are synonymous with a complex of symptoms affecting two or more organ symptoms known as anaphylaxis. The National Institute of Allergy and Infectious Disease (NIAID) and The Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" [1]. The incidence of anaphylaxis is increasing in the US and in other Western countries [2 - 6]. In the United States, the lifetime prevalence of anaphylaxis is estimated to be around 0.05% to 2%

* **Corresponding author Joshua L. Kennedy**: Department of Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA; Tel: 501-364-1060; Email: KennedyJoshuaL@uams.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

[7, 8]. Despite the increase in prevalence, there continue to be examples of mis- or under-diagnosis across the United States. In fact, anaphylaxis accounted for 186-225 deaths per year according to the Multiple Cause of Death Database between the years 1999-2009 [9]. This chapter will provide an overview of common causes, pathophysiology, diagnostic criteria, treatment, complications, and follow up recommendations for children during and after anaphylaxis.

Common Causes of Anaphylaxis in Children

Food Allergy

Food is the most common trigger for anaphylaxis among all age groups [2], and eight major foods including peanuts, tree nuts, shell fish, fish, cow's milk, eggs, wheat, and soy are responsible for more than 90% of these reactions in children [1, 10 - 13]. While the true prevalence of food allergy is unknown, studies suggest that physician diagnosis of food allergy is on the rise in the United States affecting approximately 6-8% of children [14, 15]. According to a study done by the Centers for Disease Control and Prevention in 2013, food allergy diagnoses increased 50% between 1997 and 2011 [16]. Perceived food allergy is also on the rise, which makes the diagnosis difficult. Furthermore, the revelation that anaphylaxis to foods can be delayed by several hours when considering the carbohydrate galactose-1,3-alpha-galactose (alpha-gal) found in mammalian meat has made diagnosis even more difficult. Patients with this allergy present with delayed symptoms, including anaphylaxis for 4-6 hours after exposure, to beef, pork, lamb, and other mammalian meats [17 - 21]. This food allergy has been described in children; however, it does not seem to be a problem in infancy, but usually begins around the age of 2 [21]. Avoidance of the allergenic food is the only known treatment for this condition, and patients with known food allergy should always carry an epinephrine autoinjector.

Venom Allergy

Venom allergy accounts for 5-13% of all anaphylaxis events presenting in children [22 - 24]. Stinging insects belong to the insect order Hymenoptera, but less than 1% of this order is responsible for human stings [25 - 27]. Honey bee, yellow jacket, wasp, and hornet stings, as well as fire ant bites can result in a wide range of symptoms ranging from temporary local reactions to anaphylaxis. While local reactions are common, life-threatening systemic reactions only occur in 0.4%-0.8% of children [28 - 31] and account for ~40 deaths annually in the US [32]. However, many clinicians remain unaware that immunotherapy (venom allergy shots) can successfully provide prophylaxis for venom allergic patients against future systemic reactions to hymenoptera [25].

Drug Allergy

Medications account for 5%–12% of anaphylaxis cases [22 - 24]. The most common culprits of drug allergy include antibiotics (penicillin and sulfa drugs, specifically), anticonvulsants, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), and chemotherapy agents. Antibiotics are most common drugs to cause anaphylaxis [23, 24]. In a large study evaluating the incidence of antibiotic allergy incidence, it was found that 25% of patients requiring antimicrobial therapy reported that they had an allergy to an antimicrobial agent. 15.9% of all antibiotic allergic patients in this study reported that they were allergic to penicillin, making penicillin the most commonly reported antibiotic allergy [33]. However, it is important to note that in studies attempting to confirm penicillin allergy in patients who had a reported history of reactions to the medication, an overwhelming 96% of the subjects had negative skin testing and were able to pass an oral challenge, suggesting the number of patients with true allergy to penicillin is much lower than is suspected by the general population [34].

Presentation and Diagnosis

The presenting symptoms of anaphylaxis can be nonspecific, and, thus, a low index of suspicion is required to properly and quickly treat patients. As defined by NIAID and FAAN, the diagnosis of anaphylaxis requires symptoms involving two or more organ systems. Cutaneous (skin) manifestations, such as urticaria (hives), pruritus (itching), erythema (redness), or angioedema (swelling), are present in up to 90% of anaphylaxis cases. Respiratory symptoms are common as well, presenting in ~70% of cases. These symptoms include dyspnea (difficulty breathing), wheezing (musical sound heard in the lungs made by excess mucus and bronchoconstriction of lower airways), cough, congestion, stridor (musical sound made by upper airway constriction), and hoarseness. Gastrointestinal (GI) upset, altered mental status, and/or cardiovascular compromise may be present as well. Many patients experiencing anaphylaxis describe a “feeling of impending doom,” which should be taken seriously [35].

The diagnosis of anaphylaxis may be challenging, given the number of possible signs and symptoms and the variation of severity [7, 36 - 45]. History of events leading to presentation is very helpful in connecting nonspecific symptoms to suspected anaphylaxis. To help with the diagnosis, the NIAID and FAAN have developed diagnostic criteria that are helpful in defining anaphylaxis (Table **1**). Certain conditions have been related to increased risk for severe anaphylaxis and should be considered in a patient with known triggers for anaphylaxis. These conditions include recurrent wheezing or asthma, eczema, atopic dermatitis, and

CHAPTER 20

Autism Spectrum Disorder: What a Pediatrician Should Know

Jayne Bellando[*], **Jaimie Flor** and **Maya Lopez**

Section of Pediatric Psychology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Abstract: It is important for pediatricians to increase their expertise in the area of Autism Spectrum Disorders (ASD). With the increase prevalence rate of ASD and the emphasis on early detection, pediatricians need to be familiar with diagnostic criteria for ASD and know when to refer for a comprehensive evaluation. After a formal diagnosis is given, pediatricians will be "front line" in the medical management of co-morbid medical/psychiatric symptoms of ASD for their patients. They will serve as the medical home for families to guide evidence-based treatment options and to help find community resources for the child with ASD. The goals of this chapter are to provide an overview of ASD diagnostic criteria; to increase knowledge in early detection and diagnosing ASD; provide information about common medical comorbidities for individuals with ASD; and build knowledge in guiding families as they find evidenced-based therapeutic resources for their child with ASD.

Keywords: Alternative treatments for autism, Autism, Autism Spectrum Disorder, Autism early screening, Autism evaluation, Autism identification, Autism interventions, Autism toolkits, Complementary and Alternative treatments, DSM-5, Pediatrician knowledge, Medical co-morbidities, Vaccines.

INTRODUCTION

Autism is a neurodevelopmental disorder that typically presents very early in life [1]. Autism Spectrum Disorders (ASD) have increased in public awareness and in prevalence, based upon most recent estimates of 1 in 68 children [2]. The American Academy of Pediatrics [3, 4] and the American Academy of Neurology [5] have published on the importance of early screening and early detection of ASD in order to obtain services that will yield best outcomes for the child and their families.

[*] **Corresponding author Jayne Bellando**: Section of Pediatric Psychology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; Tel: 501 364-1021; Fax: 501 364-1095; Email: BellandoJayne@uams.edu

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

Given the increased prevalence in ASD, it is certain that pediatricians will encounter children with ASD in their practice. Pediatricians are often the first professionals to assess for developmental concerns and guide the family in obtaining appropriate services. Given that there is no blood test or specific medical markers for an autism diagnosis, the pediatrician is charged with the daunting task of screening and providing consultation for a disorder that is currently diagnosed by behavioral measures and skilled observation. The pediatrician also needs to be able to help guide caregivers as they decide upon treatment options and ways to access and pay for treatments for their child. This in itself can be overwhelming for the family as well as for the pediatrician. Given the ubiquitous access to electronic information, the pediatrician must also be aware of controversial treatments and pop culture information about autism so questions can be appropriately discussed with families.

This chapter attempts to provide information on key diagnostic features of ASD, review screening guidelines and the recommended assessment process for ASD. Information about common co-morbid medical conditions will also be discussed. Resources to find evidenced based information about well-established treatments for ASD will be presented as well as providing resource sites for more alternative interventions for ASD. The goals of this chapter are to help the busy pediatrician build knowledge in identifying and diagnosing ASD; provide information about common medical comorbidities for individuals with ASD; and build knowledge in guiding families as they find therapeutic resources for their child with ASD.

DIAGOSTIC CRITERIA FOR AUTISM SPECTRUM DISORDER

The most recent Diagnostic and Statistical Manual (DSM-5) was published in May 2013 and significantly changed the way autism was classified [6]. Autism was first introduced to the DSM-III under the term Pervasive Developmental Disorder [7] and this has remained until DSM-5. Pervasive Developmental Disorder has been replaced with the term Autism Spectrum Disorder (ASD), which now subsumes the former DSM-IV diagnoses of Autistic Disorder, Asperger Disorder and Pervasive Developmental Disorder, Not Otherwise Specified (PDD, NOS). Given its genetic etiology, Rett's disorder is now included as an associated feature of ASD but does not have its own diagnostic code. The diagnosis of Childhood Disintegrative Disorder has also been eliminated from the DSM-5. Another difference is in diagnostic criteria. Instead of three factors, the DSM-5 has two diagnostic factors: "persistent deficits in social communication and social interactions across multiple contexts and restricted, repetitive patterns of behaviors, interests or activities" [6 p50-59]. Studies have shown that the two factor model is a better fit than the DSM-IV three factor model for a diagnosis of autism [8 - 10]. Like other diagnostic codes in the DSM-5, ASD has specifiers to

capture associated features (language impairment, cognitive impairment) and to indicate severity of symptoms. Severity level ratings can change over time to reflect the trajectory of the patient's course. To receive an ASD diagnosis, differences in development must be seen within the early developmental period; however, the DSM-5 acknowledges that for some individuals the deficits may not manifest until social demands exceed their ability or deficits may be minimized by strategies that have been learned [6]. Criteria now can also be met by current symptom presentation or by history. If a diagnosis based upon DSM-IV criteria has already been given and is well established, the new diagnosis of ASD should be applied. The DSM-5 is also clear that specifiers should not be used to determine eligibility for or for the provision of services [6].

Ozonoff [11] provides a well-articulated rationale behind the research that guided the criteria and theoretical changes for the DSM-5. In the time leading up to the publication of the DSM-5, some studies showed good sensitivity and specificity with the new DSM-5 criteria [12, 13] while other studies reported concerns about the DSM-5's ability to correctly classify individuals with ASD [14 - 16] The rebuttal to studies that were not complementary to the new criteria stated that the final DSM-5 criteria were not used in these studies [17, 18]. Since the publication of the DSM-5 is still relatively recent, some studies have been published to help answer questions about specificity and sensitivity [19 - 21]. with differing results. More research is needed to determine if there are groups of individuals by age or symptom presentation that might be less likely to be captured in the new criteria. The Autism Spectrum Disorder Task Force has described the DSM-5 ASD criteria as a "living document" [6] so it is assumed that new research findings will guide future updates of the Autism Spectrum Disorder diagnostic criteria.

SCREENING AND ASSESSMENT OF ASD

While it is important for pediatricians to know the diagnostic criteria for ASD, it is just as important to apply it to children in your practice to screen for ASD/developmental concerns. In a study of screening practices of PCPs for ASD, it was reported that only 8% of general pediatric providers screened specifically for ASD [22]. Among the reasons cited for this low rate is PCPs' perception that they lack experience with screening tools or that they do not have adequate time to screen within the confines of a PCP visit [22]. The AAP has outlined an algorithm specifically for the identification of ASD in all children [4]. The process involves: surveillance, screening and implementation of an action plan

Surveillance entails listening to parent's concerns about development, actively eliciting developmental concerns from parents, taking a good developmental history, making behavioral observations in the clinic, and identifying risk factors

CHAPTER 21

Treating Anxiety in Children

Kristine Schmitz[1,*], Mi-Young Ryee[2] and **Leandra Godoy[2]**

[1] *Department of General and Community Pediatrics, Children's National Health System, Washington DC, USA*

[2] *Department of Psychology, Children's National Health System, Washington DC, USA*

Abstract: Pediatric providers can play a key role in the early identification and treatment of anxiety. Brief screening tools can be used to enhance detection and differentiation of anxiety symptoms. Once identified, providers can triage concerns to determine the best course of action, including treatment setting (primary care *versus* referral to an outpatient provider) and intervention approach (cognitive-behavioral therapy, medication management). Distraction and parent education can be effective tools to reduce short-term anxiety associated with office-based procedures. More long-term treatment of anxiety, either within primary care or in community-based settings, can vary depending on presenting concerns and the child's age. However, evidence-based approaches typically include psychoeducation, cognitive behavioral therapy, recognition and management of physical cues of anxiety, cognitive restructuring, exposures, relapse prevention, and collaboration with parents and schools. Medication may be a useful way to augment treatment in certain circumstances.

Keywords: Anxiety in children, Anxiety treatment, Co-located mental health, Cognitive-behavioral therapy, Pediatrics, Selective serotonin reuptake inhibitor (SSRI).

INTRODUCTION

Anxiety is one of the most common mental health disorders [1, 2]. Lifetime prevalence of anxiety disorders is 28%, surpassing depression and impulse-control disorders, such as attention deficit hyperactivity disorder [1]. Anxiety disorders present earlier than many other childhood mental health disorders [1] and are associated with later development of depression, substance abuse, and other socio-emotional disorders [1, 2]. Early identification of anxiety and intervention is critical to treating anxiety and preventing co-morbidity.

[*] **Corresponding Author Kristine Schmitz:** 111 Michigan Ave, NW, Washington, DC 20010, USA; Tel: (202) 854-0769; Fax: 202-476-3386; Email: KSchmitz@childrensnational.org

Seckin Ulualp (Ed.)
All rights reserved-© 2017 Bentham Science Publishers

Identifying Anxiety

To facilitate identification of anxiety concerns, pediatricians can combine their observations and clinical interview with a more structured screening tool. Use of a standardized screening tool can be beneficial given that providers often overlook mental health issues and many parents of children with mental health problems do not independently report concerns about their children's behavior [3]. Anxiety may have even lower sensitivity rates of provider identification because the perceived burden on parents and functional impairment can appear less severe than for disruptive behavior disorders [4]. Routine, universal screening can help to identify potential mental health concerns, such as anxiety, earlier among a wider range of families and has therefore been increasingly encouraged within primary care as a way to reduce unmet mental health needs [5, 6]. Screening tools should not be used diagnostically, but rather are most appropriate when used in combination with provider's clinical interview, observations, and judgment.

Several brief screening tools exist and can be been used in primary care to assess for anxiety. These include broad-based screening tools that have questions about anxiety, as well as anxiety-specific tools (Table **1**). Broad-based screening tools are more appropriate for universal screening efforts as a way to identify possible mental health concerns across a large group of children and a variety of areas. In contrast, anxiety-specific screening tools are more appropriate when used as a second stage screener (*e.g.*, when broad-based tool raises concerns about anxiety) or when parents or providers raise concerns about anxiety. For anxiety in particular, it may be important to obtain youth report in addition to parent reported symptoms [7].

Once concerns about anxiety have been raised, either *via* screening tools or clinical interview, providers can triage concerns by asking questions about symptom severity (*e.g.*, frequency, intensity, and duration of anxiety symptoms) and functional impairment—or the extent to which anxiety symptoms get in the way of the child's ability to function at home, at school, and in the community. For younger children in particular, assessing the impact of anxiety symptoms on parents and family members is also important (*e.g.,* determining if parent has had to change work schedule to accommodate child's behaviors). The level of severity and impairment, as well as the provider's own skills and the availability of community-based resources will inform decisions about referral to an outside provider.

Brief Office Interventions

Children can experience significant anxiety during their medical interactions, including both routine preventive care and procedural care. Numerous approaches

may reduce acute anxiety within the office setting, including distraction techniques and parental presence and training. While distraction can exacerbate anxiety symptoms in the long-term, it is a mainstay for addressing acute anxiety caused by medical procedures. Audiovisual approaches, such as offering video cartoons or three-dimensional glasses during immunizations or medical procedures, have demonstrated significant reductions in anxious behavior in children and parental report of their child's anxiety [8 - 11]. Use of cold and vibration during intravenous catheter insertion or immunizations can also reduce anxiety and pain [11, 12]. Use of music appears to be less effective, but may be preferred by patients [13].

Table 1. Sample anxiety screening tools suitable for use in primary care.

Tool	Domains	Ages	Forms/ Questions	Availability
Screen for Anxiety and Related Disorders (SCARED) [73]	Panic/somatic symptoms, generalized anxiety, social anxiety, school avoidance, total anxiety	8-18 years	Parent: 41 Youth: 41	Free
Spence Children's Anxiety Scale (SCAS) [74]	Panic/agoraphobia, social anxiety, separation anxiety, generalized anxiety, obsessions/compulsions, physical injury, total anxiety	2.5-12 years	Parent: 38 Youth: 44	Free
Revised Children's Manifest Anxiety Scale—2nd Edition (RCMAS-2) [75]	Physiological anxiety, worry, social anxiety, defensiveness, inconsistent responding, total anxiety	6-19 years	Youth: 49	$ (Pro-Ed: www.proedinc.com/)
Beck Youth Inventories –2nd Edition (BYI—II)	School performance, the future, negative reactions of others, fears including loss of control, and physiological symptoms	7-18 years	Parent: 20 Youth: 20	$ (www.pearsonclinical.com/)
Multidimensional Anxiety Scale for Children (MASC 2) [76]	Separation anxiety, phobias, generalized anxiety, social anxiety, obsessions & compulsions, physical symptoms, harm avoidance, inconsistency index	8-19 years	Parent: 50 Youth: 50	$ (www.mhs.com/)

Partnering with a parent to reduce their child's anxiety can yield good results, particularly for younger children, though success can depend on the parent's own anxiety. When a parent is calm at the start of an operative procedure and they accompany the child into the operating room, their child may feel significantly less anxious and have fewer anxious behaviors at the onset of anesthesia, even

SUBJECT INDEX

A

All rights reserved-© 2017 Bentham Science Publishers

B

C

D

E

F

G

H

I

J

L

M

N

O

P

R

S

T

U

V

W

Y