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Sujana S. Chandrasekhar

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Devyani Lal, Angela M. Donaldson, and David W. Jang

Unified Airway Disease: A Contemporary Review and Introduction 1

Wytske Fokkens and Sietze Reitsma

Upper and lower airways diseases are very common, with population prevalence of 10% to 40%. The conditions are usually interlinked and referred to as “unified airway disease” or “the united airways.” Especially in phenotypes with more severe disease, type 2 immunologic endotype is often noted. Comorbid upper and lower airway diseases are usually caused by similar underlying immunologic response. Any patient with rhinitis or rhinosinusitis should have their lower respiratory tract evaluated. A multidisciplinary approach in the diagnosis and treatment of airway disease is advised, especially, for more severe phenotypes.

Unified Airway Disease: Diagnosis and Subtyping 11

Amar Miglani, Devyani Lal, and Rohit D. Divekar

The concept of a unified airway posits that pathology affects the respiratory tract in a continuum and that disease in one part of the respiratory tract may be associated with or directly or indirectly affect the function of a different part. Transcriptomic analysis has shown 91% homology between the genes expressed in the upper and the lower airway. Approaching inflammatory airway disorders using the unified airway hypothesis allows for a better clarification of disease process and provides a detailed and a high-level overview of dysfunction. There are several tools available to the clinician to use to subtype and diagnose accurately the abnormal pathways operating in inflammatory airway disorders. These tools include clinical history, physical examination findings, imaging (computed tomography and MRI), allergy and laboratory testing, pulmonary function testing (PFT), and tissue histopathology. Tests can be categorized based on platform, by specimen, or the marker being studied.

Unified Airway Disease: Genetics and Epigenetics 23

Tripti Brar, Michael J. Marino, and Devyani Lal

Although unified airway disease (UAD) may have heritable components, genetic changes involving coexistent chronic rhinosinusitis (CRS) are not well understood. Genetic predisposition is stronger in patients with CRS with nasal polyps compared with those without nasal polyps (CRSsNP). Genetic factors account for 25% to 80% of asthma risk and 90% of allergic rhinitis risk but risk contributions are not well described for CRS.

Susceptibility genes identified in coexistent CRS-asthma relate to innate and adaptive immunity, cytokine signaling, tissue remodeling, arachidonic acid metabolism, and other proinflammatory pathways. Non-type 2 UAD such as CRS-bronchitis/bronchiectasis and CRSsNP are currently inadequately characterized.

Unified Airway Disease: Environmental Factors

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Jesse Siegel, Navroop Gill, Murugappan Ramanathan Jr, and Monica Patadia

The unified airway is in constant exposure to environmental factors that promote inflammation and disease. Environmental allergens, including house dust mites, pets, pollens, and molds, are strongly linked with development and exacerbation of upper airway disease with nonlinear dose-dependent relationships. Occupational triggers, including combat exposures and construction workers, are associated with the development of both upper and lower airway disease resulting in a “healthy worker effect” where many people leave jobs due to significant morbidity.

Sex Differences in Airway Diseases

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Mackenzie Latour, Devyani Lal, and Michael T. Yim

It is evident that sex and gender differences impact pathophysiology, disease burden, and treatment outcomes for a variety of systems and major illnesses including those affecting the unified airway. Important male-female differences in unified airway disease are driven by various intrinsic and extrinsic mechanisms including anatomic, morphometric, hormonal, genetic (and epigenetic), environmental, psycho-social, and comorbidity-related factors. This review highlights current knowledge of how patient sex influences epidemiology, diagnosis, treatment, and outcomes for diseases affecting the unified airway.

Unified Airway Disease: Examining Prevalence and Treatment of Upper Airway Eosinophilic Disease with Comorbid Asthma

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Mitesh P. Mehta and Sarah K. Wise

The “unified airway” describes the concept that inflammation affects upper and lower airways by similar mechanisms; this often manifests as rhinitis, rhinosinusitis, and/or nasal polyposis in the upper airway with associated asthma or bronchial inflammation in the lower airways. The relationships between eosinophilic diseases of the upper and lower airways are highlighted by examining their prevalence and treatment regimens along with the synergistic effects of treatment on upper and lower airway symptoms. It is important to recognize the interrelatedness of upper and lower airway eosinophilic disease to assess and manage patients accurately and holistically.

Non-Eosinophilic Granulomatous Disease and the Unified Airway

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Joanne Rimmer and Valerie J. Lund

Granulomatous and vasculitic diseases of the airway may be part of more widespread systemic disease but can occur in isolation. They may present to the ear, nose, and throat (ENT) surgeon initially with vague symptoms that mimic more common chronic inflammatory unified airway conditions, such as rhinitis, chronic rhinosinusitis, and asthma. Early diagnosis is

associated with better long-term outcomes, so a high index of suspicion is required. Bloody nasal discharge and crusting are highly suspicious for granulomatous disease, which should also be considered in atypical or recalcitrant disease. A combination of clinical findings, serologic tests, imaging, and histology may be required to confirm the diagnosis.

Immunoglobulin Deficiency and the Unified Airway 97

Chadi A. Makary, David W. Jang, and Patricia Lugar

Primary Ig deficiencies are a heterogeneous group of disorders with widespread implications for the unified airway. Manifestations can vary greatly, with some patients being asymptomatic, whereas others suffering from acute and chronic life-threatening pathologic conditions of the upper and lower airways. Although the diagnosis of PIDs can be complex, the onus of early diagnosis and initiation of treatment will often fall on the shoulders of the otolaryngologist.

Aspirin-Exacerbated Respiratory Disease and the Unified Airway: A Contemporary Review 107

Benjamin K. Walters, John B. Hagan, Rohit D. Divekar, Thomas J. Willson, Janalee K. Stokken, Carlos D. Pinheiro-Neto, Erin K. O'Brien, and Garret Choby

Aspirin-exacerbated respiratory disease (AERD) is characterized by abnormal arachidonic acid metabolism leading to chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma, and upper and/or lower respiratory symptoms after ingestion of cyclooxygenase-1 inhibiting nonsteroidal antiinflammatory drugs. Diagnosis is clinical and may involve an aspirin challenge. Inflammatory biomarkers may be useful for diagnosis and treatment monitoring. Conventional medical management for asthma and CRSwNP is often inadequate. Endoscopic sinus surgery followed by continued medical management with or without aspirin desensitization frequently improves symptoms and objective disease measures. Biological agents targeting eosinophilic inflammation are promising alternatives to conventional management.

Unified Airway—Cystic Fibrosis 125

Do-Yeon Cho, Jessica W. Grayson, and Bradford A. Woodworth

Cystic fibrosis (CF) is a genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR channel is responsible for the transport of the anions (chloride and bicarbonate) across airway epithelia. Patients with CF have thick mucus, disrupted mucociliary transport, and chronic bacterial infections in the upper and lower airways. In this article, the pathophysiology of CFTR dysfunction and its impact on the united airway are reviewed as well as the treatment strategies for patients with chronic rhinosinusitis-related CF and acquired CFTR dysfunction.

Pediatric Unified Airway: Chronic Rhinosinusitis and Lower-Airway Disease 137

Carly Mulinda, Nathan Yang, and David A. Gudis

The unified airway concept is a framework for the understanding and management of the upper and lower airways as one integrated physiologic

unit. The sinonasal and bronchopulmonary systems have an interdependent physiologic function, and inflammatory conditions that impact one system tend to impact the other similarly. The application of the unified airway concept in the pediatric population is not well described. This study identifies and characterizes the common manifestations of the pediatric unified airway, including pediatric chronic rhinosinusitis, adenoid disease, asthma, cystic fibrosis, and primary ciliary dyskinesia.

Upper Airway Cough Syndrome

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Angela M. Donaldson

Upper airway cough syndrome (UACS), formerly known as postnasal drip syndrome, is one of the most common causes of chronic cough. UACS, asthma, and gastroesophageal reflux make up 90% of the cause of chronic cough. UACS is a clinical diagnosis of exclusion with no diagnostic testing or objective findings. UACS can be present with or without associated rhinitis and chronic rhinosinusitis. Treatment includes dual therapy with H1 receptor antihistamines and decongestants. Diagnosis is confirmed when therapeutic intervention results in symptom resolution.

Unified Airway Disease: Medical Management

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Eamon Shamil and Claire Hopkins

Concurrent chronic rhinosinusitis with nasal polyps (CRSwNP) in the upper airway, and asthma in the lower airway, often have a shared underlying pathophysiology, namely type 2 inflammation; hence, the term “unified airway disease.” The combination of CRSwNP and asthma is associated with uncontrolled disease. The range of treatment of CRSwNP includes intranasal corticosteroids, nasal saline irrigation, oral corticosteroids, antibiotics, and biologics. A combined clinical algorithm for the management of the upper and lower airways in type 2 inflammation will be beneficial, especially for patients with uncontrolled disease who may benefit from biologics.

Unified Airway Disease: Surgical Management

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Amar Miglani, Tripti K. Brar, and Devyani Lal

Support for the unified airway hypothesis is embedded in similarities in upper and lower airway structure, function, and cellular/extracellular compositions. The impact of endoscopic sinus surgery (ESS) on the unified airway is influenced by multiple factors including the underlying upper and lower airway condition(s) present and severity of pathology. Beyond improvements in subjective and objective CRS outcomes, ESS also improves clinical asthma outcomes and measures of asthma control. Emerging evidence suggests that early ESS may mitigate the risk of developing asthma in CRS patients without asthma. Comprehensive management of upper and lower airways is paramount to optimize patient outcomes.

Unified Airway Disease: Future Directions

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Jumah G. Ahmad, Michael J. Marino, and Amber U. Luong

Unified airway disease describes the shared epidemiologic and pathophysiologic relationship among the chronic inflammatory diseases of the

upper and lower airways including allergic rhinitis, chronic rhinosinusitis, asthma, and chronic otitis media. This concept proposes that these diseases are manifestations of a single inflammatory process and require an integrated diagnostic and therapeutic approach to achieve global disease control. Future directions to further establish this entity should focus on pathophysiology, diagnostic markers, flora microbes with particular emphasis on fungi, the role of type 3 inflammation, and targeted therapeutics including biologics, JAK inhibitors, and synthetic peptides.