

Eighteen Questions for the Better Understanding of RADS

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Abstract

RADS are typically associated with a solitary inhalation exposure to a very high concentration of an irritant gas, vapor, aerosol or fume. Evolution of asthma-like symptoms and airway hyperresponsiveness are consequences. Prompt medical assistance is needed within the first 24 hours. The manuscript unveils suggested sequences of RADS' pathogenesis. The airway injury causes sloughing off of damaged and dead airway cells. Putatively, escaping intracellular molecules, from dead and damaged cells, enter the extracellular space as damage-associated molecular patterns (DAMPs); they are also known as "alarmins." The molecules promote an inflammatory response and orchestrate cellular repair and tissue healing. Different mediators and regulatory intermediaries, chemokines and cytokines, arachidonic acid products, soluble growth factors, prostaglandins, and matrix components take part in regenerative process. Lung macrophages provide clean-up and repair services: and, they impact airway hyperresponsiveness. Metalloproteinases and extracellular matrix improve the epithelial-to-mesenchymal matrix. Airway wall thickening, subepithelial fibrosis, mucus metaplasia, myofibroblast hyperplasia, muscle cells hyperplasia and hypertrophy, and epithelial hypertrophy become features of the airway remodeling response.

Keywords: *Reactive Airways Dysfunction Syndrome (RADS); Chest X-ray; Bronchial biopsy; Adult respiratory distress syndrome (ARDS); Acute lung injury (ALI)*

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Case Example

This 39-year-old power plant utility worker experienced a heavy exposure to a 35% hydrazine solution while transporting a 55-gallon drum containing hydrazine solution at work. The drum accidentally overturned and a large quantity of the solution spilled on him. He was pinned down by the drum for about five minutes and could not call for help because of the pressure on his chest. The hydrazine solution flowed onto his face, mouth, neck, chest, arms, abdomen, and urogenital areas. He denied eye exposure, but stated he reflexively swallowed some of the solution. Eventually, a co-worker noted his dilemma and assisted with his removal. He was transported to the First Aid Station where he complained of a "prickly," pins and needles

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sensation over his face, neck, and anterior chest. A nurse recorded he had a reddish facial rash. About one-half hour later, he reported neck pain, respiratory symptoms with cough and wheezing, nausea, and abdominal cramping. He described wheezing and chest tightness. There was paroxysmal nonproductive coughing and muscle aching. A few hours later, he became dizzy, mentally confused, and confused about time and place. A motor vehicle transported him to a nearby Hospital Emergency Department (ED) for further evaluation and treatment. While in the ED, he complained of worsening respiratory symptoms. Chest X-ray was interpreted as being normal, and without parenchymal infiltrates. He received an injection of corticosteroids but was not admitted to the hospital but discharged from the ED with the diagnosis of “flu-like syndrome.” Over the next three weeks, he complained of persistent respiratory symptoms and musculoskeletal weakness. He was bothered by environmental cigarette smoke and aerosol cleaning agents. His Primary Care Physician treated him with repeated courses of tapering doses of prednisone, albuterol inhaler, and an oral theophylline preparation. There was an admission to a hospital for further evaluation. He was breathless on observation on admission. Vital signs were normal except for a pulse rate of 104 beats per minute. Auscultation of his chest disclosed inspiratory and expiratory wheezing. Interpretation of his chest radiograph was “normal.” Pulmonary function testing disclosed a moderated degree of airflow limitation. Methacholine challenge was positive with a PC₂₀ of 2.16 mg/ml methacholine dose. Bronchial biopsy revealed mild lymphocytic inflammation and edematous bronchial mucosa with loosely adherent mucous overlying a partially denuded epithelium.

Introduction

An exact and full understanding of the various aspects of (RADS) is currently not totally tenable. There remain lingering questions, which require further investigations. RADS are an intrathoracic asthma-like disorder [1]. The Adult Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI) affect more distal lung units (alveoli) causing marked hypoxemia and higher mortality rates. An intrathoracic disorder targeting the smallest sized airways, the bronchioles, leads to bronchiolitis obliterans [2]. Reactive Airways Dysfunction Syndrome (RADS) tend to affect larger sized bronchi rather than bronchioles.

The following discussion presents an assembly of important questions and responses regarding RADS. The contents of this manuscript will address information and topics for gaining a better understanding of the condition.

What is RADS?

Reactive Airways Dysfunction Syndrome (RADS) is first described in 1985 [1]. Almost all RADS cases are accidental and usually occur without warning [3]. Typical causative agents for RADS are irritating gases, vapors, aerosols and/or fumes including solvent vapors, metallic fumes, and acid mists [4,5]. The foremost clinical characteristics are asthma-like complaints and airway hyperresponsiveness that may persist for a prolonged period. There is need for prompt medical assistance within the first 24 hours after the inhalation exposure [6]. Airflow obstruction may be mild, non-existent, or more persistent [7]. The prognosis is variable. Table 1 presents the diagnostic criteria of RADS [1]. An inhalational exposure first passes through the nose and mouth and contacts the skin and eyes. The eyes, nose, throat (ENT) and/or upper airways sites are not spared. It is biologically unlikely there is absence of accompanying physical signs of injury affecting the eyes, nose, throat (ENT) and/or cornea, conjunctivitis, possibly swelling of the tongue, nasal burning/inflammation, unrelenting rhinitis, redness of the facial skin, and/or inflammation of the larynx [8]. Stethoscope auscultatory findings may reveal wheezing. There is a sound basis for identifying the exposure’s chemical makeup. Knowing what constitutes the exposure is imperative. Perusal of the appropriate Material Safety Data Sheets (MSDS) provides valuable information, such as the chemical’s actual identity and its physical properties (i.e., vapor pressure, pH and irritancy). A chemical with a low vapor pressure is less likely to be airborne

compared to a chemical having a high vapor pressure. Chemicals displaying very high or very low pH values are typically extremely irritating agents. The diagnosis of RADS necessitates recording the onset of asthma-type symptoms within 24 hours after the exposure. A delay of passage of days or weeks between the onset of symptoms and medical care is inconsistent with RADS diagnostic criteria. There is suspicion when the time span is greater than 24 hours.

1. Absence of pre-existing respiratory disorder, asthma symptomatology or a history of asthma in remission and exclusion of conditions that can simulate asthma such as VCD.
2. Onset of asthma symptoms after a single exposure or accident.
3. Exposure is to an irritant vapor, gas, fumes or smoke in very high concentrations.
4. Onset of complaints occurs within minutes to hours and always less than 24 hours after the exposure.
5. Finding of a positive methacholine challenge test (<8 mg/ml) following the exposure documents nonspecific airway hyperresponsiveness.
6. Possible airflow obstruction on pulmonary function testing.
7. Another pulmonary disorder (such as VCD) to explain the symptoms and findings exclude RADS.

Table 1: Diagnostic Criteria for RADS.

Causes of RADS

Many types of irritants cause RADS. The condition evolves after an individual inhales a solitary high-level irritant gas, vapor, or fume exposure [6,8,9]. Dangerous inhalation events occur in the workplace, the home surroundings, and in various community environmental situations [10]. The originally reported causative agents of RADS were uranium hexafluoride gas, floor sealant, spray paint containing significant concentrations of ammonia, heated acid, 35% hydrazine, fumigating fog, metal coating remover, and smoke [1]. There may be unanticipated explosions or situations where there is the accidental release of irritant(s) held under pressure. RADS symptoms may ensue following an unforeseen explosion or unexpected environmental chemical release. Performing activities while working within a confined space having a reduced air exchange ventilation rate and/or a space with reduced fresh air make-up are potentially unsafe situations. Elevated emissions of irritating airborne smoke and associated irritant gases accompanying a fire are worrisome [11]. Workers engaged in repairing damaged workplace structures or malfunctioning machines are in danger. Cleaning activities are risky when a worker is not properly equipped, trained, or aware of potential hazardous risks while performing a job [12]. Adverse pulmonary consequences may ensue after an accident involving trains or trucks transporting chemicals. The Bhopal disaster, involving methyl isocyanate, caused serious lung consequences to workers and surrounding residents [13-15]. Intentional inhalational casualties result from chemical warfare attacks during World War I and the Iran-Iraq War. A RADS-like condition affected rescue workers involved with the collapse of New York’s World Trade Center on September 11, 2001 [16]. Table 2 lists specific causes of RADS.

Exposure	Reported Agent or Process
Acids	Glacial acetic, Sulfuric, Hydrochloric, Hydrofluoric acid, Hydrozoic acid, Hydrobromic acid, Hydrofluoric acid
Alkali	Ammonia, Bleach, Sodium hydroxide, Calcium oxide, Sodium hydroxide, World Trade Center dust
Gases	Chlorine, Sulfur dioxide, Mustard, Ozone, Hydrogen sulfide, Phosgene, Nitrogen dioxide; Dinitrogen tetroxide, Sodium azide gas in automobile airbags
Spraying	Spraying using paints and coatings
Explosion	Irritant gas, Vapor or fume releases under pressure, Uranium hexafluoride explosion, World Trade Center disaster

Fire/pyrolysis	Combustion and pyrolysis products of fires, burning paint fumes, pyrolysis products of polyvinylchloride (PVC) meat wrapping film; smoke inhalation, urea vapors/fumes
Confined spaces	Epichlorhydrin, Acrolein, Floor sealant, Metal coating remover, Biocides, Fumigating aerosol, Cleaning aerosol sprays, Mixture of drain cleaning agents
Environment & Workplace	SO ₂ gas in pyrite mining dust explosion, isocyanates mixed with organic solvent, silicon tetrachloride, aerosols of metalworking fluid, aluminum smelter workers exposed to pot-room fumes, bleachery workers with ozone and chlorine dioxide/SO ₂ gassing, anhydrous sodium sulfate release, inorganic salts used as oxidizing agents in hair bleaches & hair-coloring preparation, workers exposed to SO ₂ from apricot sulfurization, cleaning and disinfecting workers in the food industry, chili pepper pickers, dust exposure in Norwegian smelters; 2-hydroxyethyl methacrylate and methyl methacrylate in dentists; synthetic leather workers exposed to organic solvents (toluene, xylene and methyl ethyl ketone); eucalyptus oil, gases from liquid manure, irritant gas containing chromate at a chrome pellet manufacturing plant

Table 2: Causes of RADS.

How Fast Does RADS Develop?

There is usually a need for prompt medical assistance, within the first 24 hours after the inhalation exposure [6].

Does RADS' Exposure have to be High?

The definition of RADS requires there be a single high-level irritant gas, vapor, or fume exposure [1,8]. The toxicological features and the concentration of the airborne irritant(s) are critical [17]. More than 500 years ago, Paracelsus, the Swiss physician, alchemist, and one of the earliest toxicologists, expounded on the concept of dose-response as he declared in Latin: "sola dosis facit venenum" [18]. In other words: "only the dose makes the poison". RADS transpires when the dose/concentration of the exposure to the hazardous airborne irritant is sufficiently great.

Duration of RADS

RADS' duration may be short, transient, or prolonged. Approximately 25% of subjects show a disappearance of bronchial hyperresponsiveness two years after the inhalational accident with a plateau afterwards [19]. In one study, transient respiratory complaints linked to RADS resolved within 12 weeks or less [14]. In other cases, asthma-type symptoms and nonspecific airway hyperresponsiveness persists for years following the inciting irritant exposure [20]. One publication on RADS reports a median duration of symptoms lasting 13 months [5]. The reason for the differences in RADS duration is unknown.

Medical Acknowledgement of RADS

RADS are now an entity acknowledged by treating physicians and nurse practitioners. Decades ago, allergic occupational asthma is in the forefront of international interest [21-23]. "Experts" are reluctant to fully accept irritants as being capable of causing asthma [24]. Authorities are dubious about the likelihood of nonspecific airway hyperresponsiveness being consequential of a solitary high-level irritant exposure [25]. No published medical report quantifies the intensity of RADS' exposure, mainly because the majorities are accidental in occurrence. There is little documentation that an individual has documented normal bronchial responsiveness prior to the irritant exposure causing RADS. The strict diagnostic criteria for RADS are considered restrictive and circumstantial. Of the latter, practitioners cautiously account a history claiming an absence of preceding symptoms. They must accept there is normal prior lung function, and acknowledge there is no preceding bronchial hyperresponsiveness. Some ask the question as to whether RADS is simply a coincidental incident where the onset of asthma transpires after an irritant exposure. In such a scenario, RADS development is likened to a temporary upper respiratory tract infection preceding a case of asthma. It is not causally proven [24]. Some researchers prefer calling RADS

"occupational chemical bronchitis." RADS is deemed an "occupational injury" rather than an occupational disease [24]. Some observers question whether RADS is sufficiently unique to be distinguished from the term "inflammatory bronchoconstriction" [26]. Now, in the 21st century, RADS is internationally accepted as a distinct medical entity. The American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), the Canadian Thoracic Society (CTS), the European Thoracic Society (ETS), occupational medical physicians, pulmonologists, and allergists recognize RADS [27].

Legal Acknowledgement of RADS

RADS cases are compensated. At first, RADS cases are legally rejected because the plaintiffs cannot meet the traditional toxicological exposure-dose criteria for proving causation [28]. The legal unacceptance is eventually reversed as Courts allow a physician's differential diagnosis as proven causation. The United States Court of Appeals for the Seventh Circuit (Illinois) recognizes a different legal proof of causation, referred to as "differential etiology." The United States District Court for the Northern District of Illinois rules that "differential etiology" is a Daubert-compliant proof of RADS. The Court excludes hard and fast "rules" requiring toxicological analysis [28]. Legally, RADS is accepted as a type of sudden onset asthma caused by an exposure to irritant chemicals. It often arises in the work environment and can cause a permanent respiratory injury [28].

A Lower-Level Irritant-Induced Asthma?

The answer to this question remains controversial. There are numerous pulmonologist who believe it occurs. Possibly, irritant-induced asthma is underreported [29]. Irritant-induced asthma is reported after repeated irritants inhalational exposures taking place over a period of time [30,31]. Other investigators describe similar actualities [32-34]). Chan-Yeung et al. report on three pulp mill workers who develop "irritant-induced asthma" following multiple episodes of gassing [35]. Tarlo and Broder report several cases of irritant-induced asthma developing after repeated irritant inhalation exposures described as "spills;" they are exposures concentrations exceeding threshold limit values [36]. A retrospective investigation of 86 asthmatic subjects with clinical features of irritant-induced asthma is undertaken [37]. A collection of subjects experience brief repeated irritant exposures transpiring over weeks or months. In these cases, the initiation of asthma takes longer to evolve. The group with this clinical scenario is referred to as "not-so-sudden" irritant-induced asthma. Eighty-eight percent of individuals with not-so-sudden irritant-induced asthma display a statistically significant history suggestive of an atopic disposition. An allergic diathesis may be important in these types of cases. Some of the subjects in this group experience childhood asthma. Their childhood asthmatic condition resolves and remains quiescent for at least one year before the exacerbating irritant exposure occurs. Preexisting atopy and/or preexisting asthma appear as contributors to the pathogenesis of some not-so-sudden irritant-induced asthma cases. This contention is challenged by others [38]. There are also cases depicted as "low dose" RADS where asthma onset is after an irritant exposure that is less intense or acute in nature [39].

Allergy in Relation to RADS?

The answer to the question is maybe but not yet proven. RADS are considered a type of non-allergic airway disease. Asthma is divided into two distinct variants: (1) the extrinsic, allergic asthma variant occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels; and, (2) a non-allergic/intrinsic asthma variant, with no detectable sensitization; it shows low serum IgE levels [40]. Non-allergic asthma is considered to be a distinct pathogenetic variant [41]. The most important inducers of the increase serum IgE in patients with allergic asthma are the cytokines IL-4 and IL-13 [42]. Their role in RADS is unknown. The inflammatory processes in both allergic and nonallergic asthma types show similarities but also differences [40]. A qualitative difference between the mucosal tissue of patients with

allergic and nonallergic asthma is the concentration of the chemokine RANTES, which are formed by certain macrophage subtypes [41]. The amount of RANTES in the bronchoalveolar lavage fluid of patients with nonallergic asthma is higher than in patients with allergic asthma [40]. It seems that allergy is not a direct mechanism for RADS, but perhaps, may represent a predisposition for enhanced irritant responsiveness [37]. An asymptomatic individual with roots in childhood asthma may have their asthma exacerbated by accidental repeated irritant exposures [43,44]. Many young individuals with allergic childhood asthma enter a complete remission or display a reduction in asthma symptoms between the ages of 10 and 20 years [45]. Never the less, while the severity of asthma symptoms fluctuates with time, the inherited tendency towards future respiratory symptoms never disappears [46,47]. Asymptomatic asthmatic subjects can still demonstrate substantial air flow limitation and show increases in bronchial hyperresponsiveness. The presence of airway hyperresponsiveness (AHR) is a cardinal feature of RADS. The relationship between AHR and inflammation of the airways is well established [48]. Interleukin-13 may play a unique role in the development of AHR in RADS [49]. ADAM33 has been reported to be susceptibility gene linked to AHR [50].

Mimic of RADS and Asthma

Vocal Cord Dysfunction (VCD) clinically imitates both RADS and bronchial asthma [51-53]. The Irritable Larynx Syndrome causes laryngeal hyperresponsiveness [54]. Vocal cords exist in the larynx, the throat, an extrathoracic site [55]. RADS location is in an intrathoracic site, the bronchial tree. Purportedly, a single odorous irritant exposure causes VCD [56]. A publication asserts that irritants cause VCD mimicking RADS [57]. The assertion is doubted by others [58].

Odors and VCD

Odorants can trigger VCD [59]. Suggestive tip-offs for suspecting odorant-related VCD instead of RADS are: (1) hoarseness and/or voice change; (2) heightened sensitivity to numerous odorants and scents; and, (3) unresponsiveness to aggressive asthma/RADS pulmonary treatment regimens [60,61]. There may be excessive worry, apprehension, repeated Emergency Department visits, and/or hospitalizations. Unlike asthmatics, VCD patients rarely awaken from sleep due to acute attacks. There may be constricting throat complaints. Patients with VCD (asserted as RADS) typically receive treatment with asthma-type medications such as aerosol bronchodilators and/or oral or parenteral corticosteroids. Be cognizant of VCD by observing for evidence of posterior nasal drainage and/or gastro-esophagus reflux disease (GERD), supposed contributors to vocal cord hyper reactivity. The physical examination is stereotypically “normal” between acute VCD attacks. The chest x-rays shows no lung abnormalities or hyperinflation. Measurement of residual volume is not increased, a finding typical of an asthmatic patient. Spirometry clinches the diagnosis during an acute VCD interlude. Imperatively, the spirometer used for testing must provide a visual flow-volume (FV) tracing for uncovering VCD [62]. Vocal cord closure may occur during both phases of respiration [63]. Change in the inspiratory loop of the FV curve is pathognomonic of VCD. The inspiratory loop of the flow-volume curve will be truncated or show flattening [64]. According to the American Thoracic Society, at least three spirometric tracings are necessary, with two of the three loops showing consistency [62]. Patients with pure VCD do not have a bronchodilator response and in many instances seem to have difficulty performing consistent spirometric tracings. Some clinicians consider endoscopic examination with direct visualization of the vocal folds via flexible, trans nasal fiber-optic laryngoscopy during an acute attack as the gold standard for diagnosis of VCD [51,55]. There is observation of adduction (closure) of the anterior two-thirds of the vocal cords with posterior chinking that creates a diamond shape [56]. The endoscopic examination of a patient with VCD tends to be normal when the patient is symptom-free. Vocal cord visualization via endoscopy is accomplished with the patient executing sniffing, phonating, rapid panting, and repetitive deep breathing

maneuvers [63,65]. Provocation testing utilizes administration of aerosolized methacholine or inhaled mannitol powder, strenuous exercise, and/or breathing in refrigerated cold air. Specialized centers test for VCD induction by inhaling odorants/irritants, such as perfume or cleaning agents containing chlorine or ammonia [66].

VCD Diagnosed and Treatment

Symptoms improve with interventional speech therapy in contrast to the treatment by a pulmonologist [56,64,67]. Diagnostic videostroboscopy involves insertion of a steel scope containing a tiny camera and strobe light placed inside the patient's mouth. The camera is angled to allow a clear view of the patient's interior throat enabling a videotape of vocal cord movement and vibration in slow motion. The camera projects a moving image of the vocal cords, frame by frame, onto the television monitor, instantly retrievable as a video recording or as a still photo.

Pathology of RADS?

The originally reported cases of RADS identify mononuclear cell inflammation, denuded epithelium, and edematous mucosa days to weeks after the exposure [1]. Mucosal squamous cell metaplasia, thickening of the basement membrane and reticulum, and collagen-associated bronchial wall fibrosis are other pathological findings [67,68]. In a human investigation, bronchial biopsies are obtained at three and 15 days after an accidental workplace inhalational of chlorine gas; later biopsies are taken at three and five months [69]. The earliest bronchial biopsy depicts mucosal cellular denudation with sloughing of epithelial cells and infiltration of a submucosal fibrinohemorrhagic exudate [69]. Cellular regeneration involves mucosal basal and parabasal cells proliferation and deposition of collagen. Another study involves inhalation of sodium hypochlorite and hydrochloric acid [67]. Biopsy samples, several months after the exposure, display persistence of cellular destruction, lymphocytic inflammation, and subepithelial fibrosis without thickening of the basement membrane. Sprague-Dawley rats sustain a single exposure to 1,500 parts per million of chlorine gas for 5 minutes, mirroring a human RADS scenario [70,71]. At 24 hours after the exposure, the rat's airway biopsy exhibits a severe injury to the bronchial mucosal with sloughing of damaged epithelial cells and their cellular detachment from the basement membrane. Bronchoalveolar lavage fluid identifies acute neutrophilic inflammation. Signs of epithelial regeneration show epithelial stratification by the third day after the exposure. Cellular regeneration changes persist for seven days. Increasing numbers of mucus-secreting cells reach maximal capacity by 14 days. Regeneration changes are observed up to 30 days after exposure. Pathological abnormalities clear approximately 90 days after the exposure.

Is There an Explanation for Rads Pathogenesis?

RADS employs mechanisms of innate immunity rather than adapted allergy/immunologic immunity following a non-microbiological inhalation exposure. An inhaled irritant exposure severely damages airways' epithelial cells and mucosal surfaces leading to the exodus of intracellular constituents into the extracellular space where they prompt an innate repair processes. Numerous bioactive molecules contribute to cellular and tissue repair processes (72-81). Soluble growth factors, cytokines, chemokines, interleukins, prostaglandins discharges, matrix constituents, fibroblasts actions, and endothelial cells endeavors work in concert for accomplishing airways repair (82-84). Lung macrophages migrate to assist in the repair and clean-up processes (85-89). It is not evident whether airway wall and basement membrane thickening, subepithelial fibrosis, goblet cell and submucosal gland enlargement, myofibroblast hyperplasia, increased smooth muscle mass, decreased cartilage integrity, and increased airway vascularity are characteristic for RADS as in typical bronchial asthma (90-91).

Is RADS a Unique Phenotype?

The answer is unknown. Phenotype differentiation has been applied to subtypes of asthma but not to RADS [92-95]. Possibly, repeated exposure-type irritant-induced asthma (e.g., not-so-sudden) exemplifies a distinct asthma phenotype.

How is RADS Treated?

The treatment of RADS is similar to the treatment afforded patients suffering from an acute inhalational injury. Aerosolized bronchodilators are helpful for treating bronchoconstriction (as measured by spirometry) or bronchospasm (as determined by auscultation finding of wheezing). The beneficial effect of parenteral steroids has been shown in an animal model of RADS in which dexamethasone was administered immediately before chlorine inhalation [96]. No human study shows oral corticosteroid efficacy in the treatment of RADS after the exposure. Inhaled steroids may reduce the degree of airway hyperresponsiveness [69].

Discussion

The American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), the Canadian Thoracic Society (CTS), the European Thoracic Society (ETS), occupational medical physicians, pulmonologists, and allergists recognize the role of irritancy in causing acute airway symptom and disorders such as RADS [3]. Newer information delving into molecular information learned about injury in bronchial asthma permits a better understanding of RADS.

Conclusion

Reactive Airways Dysfunction Syndrome (RADS) is an abrupt-onset asthmatic disorder of a non-allergy origin after inhalation of a single high-level irritant exposure. The inhaled exposure assaults the airways' epithelial cells and mucosal surface, a first line of airway defense. Implementation of innate immunity permits the airways to deal with non-microbiological constituents arising after a massive irritant inhalation exposure. The treatment of RADS is similar to the treatment afforded patients suffering from an acute inhalational injury.

Conflict of Interest

I certify that I (Stuart M. Brooks, MD) am the guarantor and the only corresponding author. I hold no potential conflicts of interest; no sources of funding and support; no information on statistical analyses; correct name/participation/degree/institution of the only author. I also certify that I did not accept compensation for inclusion of any of the statements contained in the manuscript.

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