September 24, 2019

CTS INSPIRATIONS

CTS NEWS

President's Message

Dear members and friends of the California Thoracic Society,

There is still time to register for our Southern California CTS Educational Conference on October 4-5, 2019 at the Hotel Irvine! Here is the link to registration: https://calthoracic.org/events/2019-southern-annual-educational-conference/. If you have not yet reviewed the program, let me bring to your attention the Saturday afternoon Hands-On session in Pleural Procedures. We will have experts from many institutions sharing their expertise on topics including ultrasound guided thoracentesis, pleural manometry, placement of tunneled indwelling pleural catheters, and thoracostomy tube insertion. So if you need a refresher or if these are new procedures for you, please join these amazing experts for their tips and tricks. Special thanks to these experts (including Laren Tan, MD; Jason Lee, MD; Shazia Jamil, MD; Ara Chrissian, MD; Steve Escobar, MD; and Yaron Gesthalter, MD) who have spent countless hours organizing this session and arranging for the necessary equipment for these sessions.

Also please remember, anyone who attends the Southern California CTS conference will also receive a discount on the registration for the Northern California CTS Conference on January 17-18 in Monterey. Look for information soon about how trainees can submit abstracts for the poster competition and for our first California Thoracic Society Women in Pulmonary, Critical Care and Sleep Medicine Conference to be held in coordination with the Northern California Conference.

I am looking forward to seeing many of you in Irvine!

Best regards

Lorriana Leard, MD
President, California Thoracic Society

Editor's Note

We conclude our mini Asthma series that began last month with Dr. Tan's review of bronchial thermoplasty with two superb articles by Dr. Praveen Akuthota (UCSD) and Drs. Michael Peters (UCSF) and Amir Zeki (UCSD). Dr. Akuthota's piece highlights the exciting developments in biologic therapies for TH2-high asthma, while Drs. Peters and Zeki remind us that a significant group of patients suffer from TH2-low asthma and the promise of ongoing research into therapies for these patients through the PrecISE network trials being launched this year. California is fortunate to have three clinical research centers at U.C. Davis, U.C. San Diego, and U.C. San Francisco that will be enrolling patients into the NHLBI-sponsored Precision Interventions for Severe Asthma (PrecISE) Network. More information can be found at **preciseasthma.org**.

Also, page 9 features the Disaster Guidance: 10 Tips for Staying Healthy During Wildfires document published by CTS and ATS last year. As we enter into peak wildfire season, it may help people to prepare ahead of time. Please share it with your patients, colleagues and friends.

New Asthma Therapies

Praveen Akuthota, MD
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Associate Clinical Professor

Disclosures relevant to this article: Dr. Akuthota has acted as a consultant and received research funding from AstraZeneca and GlaxoSmithKline.

- While the anti-IgE monoclonal antibody omalizumab has been FDA-approved for use since 2003, we have definitively entered an era of biologic therapies for asthma with the approval since 2015 of four additional asthma biologics and the ongoing development of multiple new agents.

- Two monoclonal antibodies against IL-5, mepolizumab and reslizumab, and one monoclonal antibody against the IL-5 receptor, benralizumab, have recently been approved for the treatment of eosinophilic asthma.

- IL-5 is critical for the development, survival, and trafficking of eosinophils; therefore, targeting IL-5 or its receptor is a strategy for targeting eosinophils in asthma.

- Patients with peripheral eosinophilia and refractory asthma are good potential candidates for anti-IL5 therapies.

- Dupilumab is a monoclonal antibody against the IL-4 receptor alpha subunit that blocks the signaling of both IL-4 and IL-13, two major components of “Th2” inflammation.

- Therapies in late stage development include therapies that target more upstream targets in Th2 inflammation, such as IL-33 and Thymic stromal lymphopoietin (TSLP).

- We still will need to refine our understanding of which therapy will best fit an individual patient. The upcoming NHLBI PrecISE Network is tasked with testing novel interventions in biomarker-driven, precision medicine approach and will have multiple sites in California.

In 2003, the anti-IgE monoclonal antibody, omalizumab (Xolair, Genentech/Novartis), was approved for use in the treatment of asthma. It has taken several years since this early preview of the potential use of biologic agents to specifically target components of allergic inflammation in asthma, but we can finally say that we have definitively entered the era of biologic therapy in asthma. Over the last four years, two monoclonal antibodies against **IL-5 (FIGURE 1)**, mepolizumab and reslizumab, and one against the receptor for IL-5, benralizumab, have been approved by the FDA for severe eosinophilic asthma and are being used regularly by clinicians. Dupilumab targets IL-4 and IL-13, two major components of “Th2” inflammation, and was recently FDA-approved in late 2018 for the treatment of moderate to severe eosinophilic or steroid-dependent asthma.

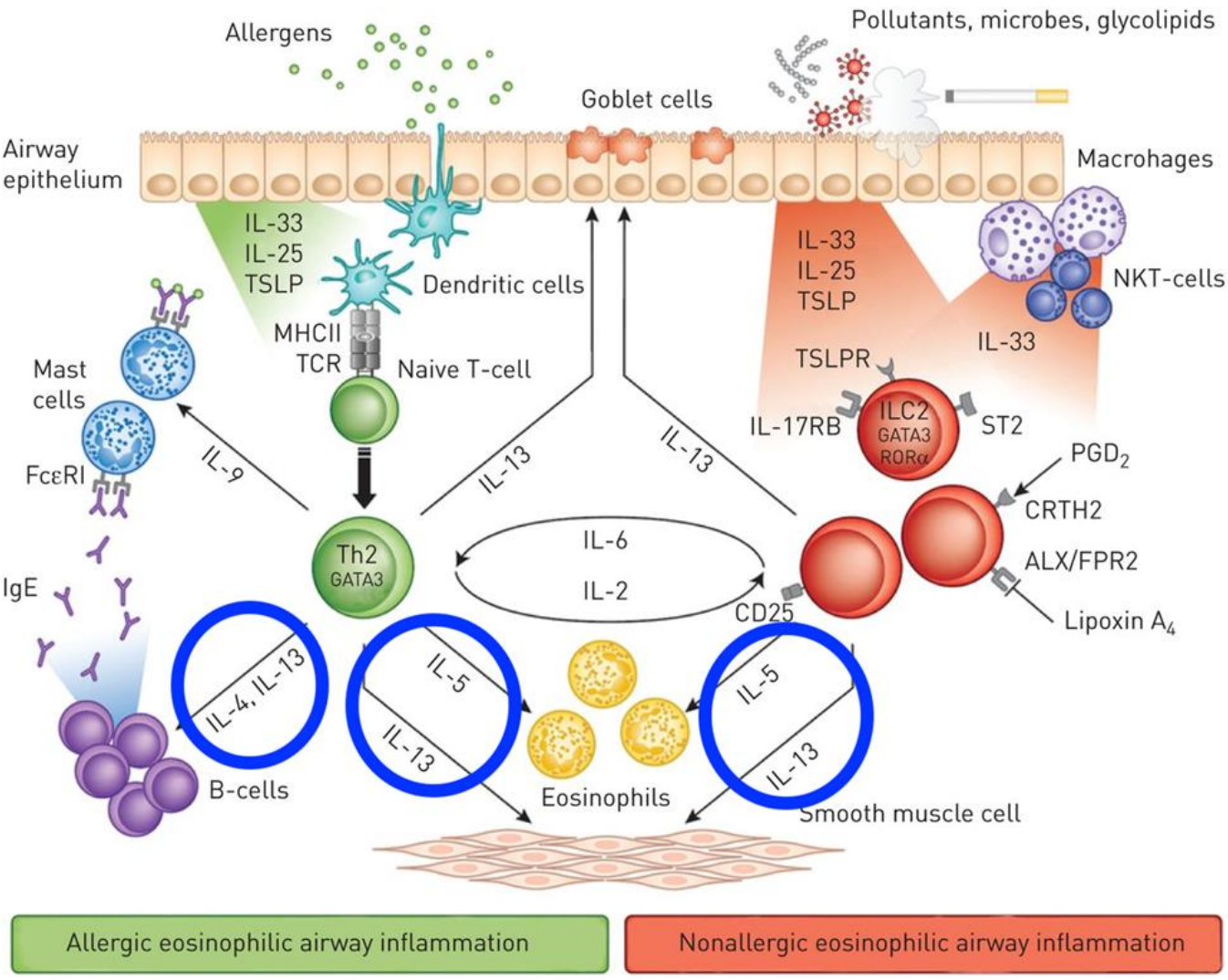


FIGURE 1
Jantina C. de Groot, Anneke ten Brinke, Elisabeth H.D. Bel
ERJ Open Research 2015 1: 00024-2015

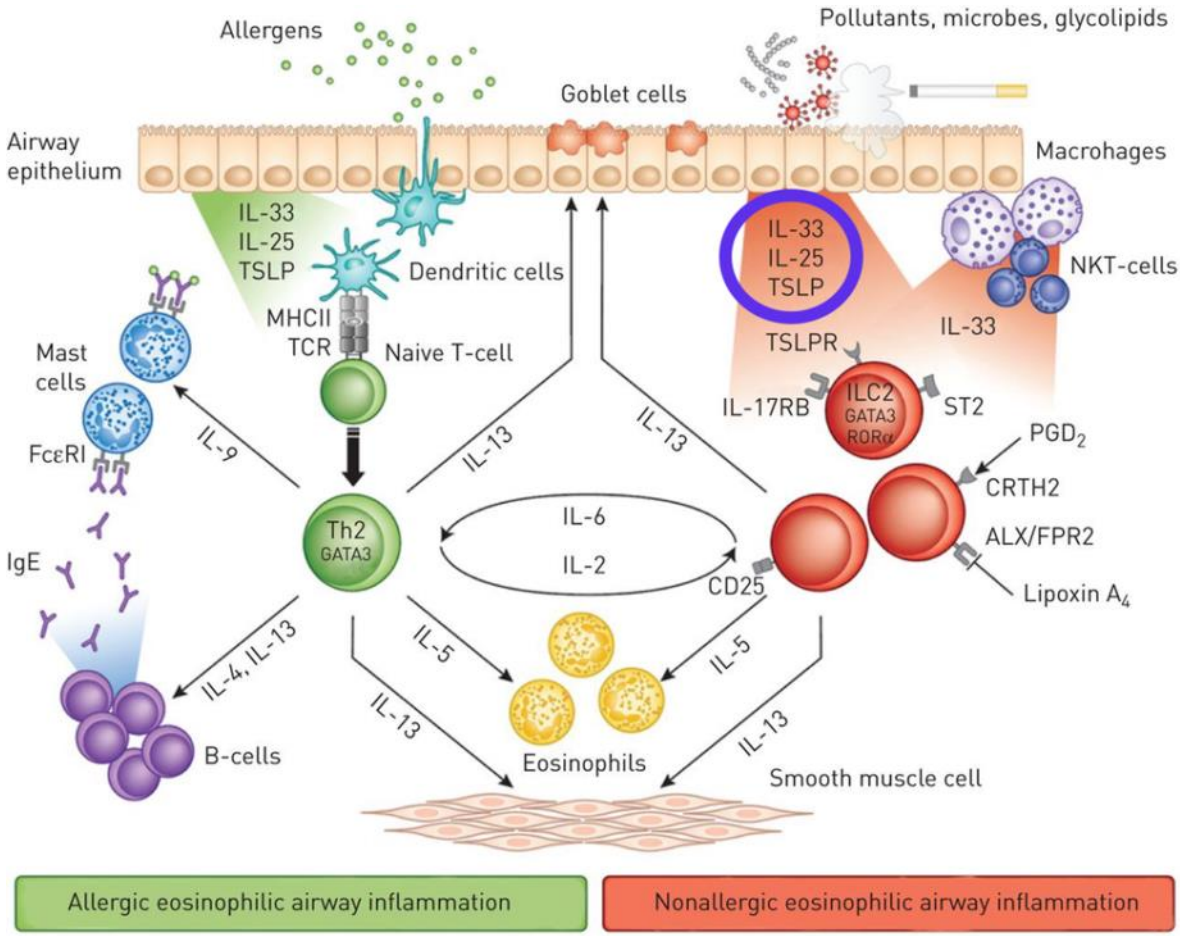
IL-5 represents an attractive therapeutic target given its central role in promoting eosinophil development, survival, and trafficking [1]. Though initial studies of mepolizumab in *unselected* patients with asthma did not show improvement in lung function, subsequent studies of mepolizumab, reslizumab, and benralizumab - selecting patients with eosinophilic asthma (by sputum or blood eosinophilia, depending on the study) and using exacerbations as the primary outcome measure – demonstrated the benefit of these drugs [2-4].

IL-4 and IL-13 are produced by Th2 CD4+ lymphocytes and are integral components of allergic airways inflammation (FIG 1) . Dupilumab is a monoclonal antibody against the IL-4 receptor alpha subunit that blocks the signaling of both IL-4 and IL-13 and has been demonstrated to decrease exacerbation rate in patients with moderate to severe asthma, with greater benefit seen in patients with increased blood eosinophils [5].

Mepolizumab (Nucala, GlaxoSmithKline) is approved for asthma at a single dose of 100 mg given every 4 weeks by subcutaneous injection. Mepolizumab also is approved for the treatment for eosinophilic granulomatosis with polyangiitis at a higher dose of 300 mg every 4 weeks. Earlier this year, an autoinjector version approved for home use became available. Reslizumab (Cinqair, Teva) is approved as an intravenous infusion dosed by weight at 3 mg/kg given every 4 weeks. Benralizumab (Fasenra, AstraZeneca) is given as a subcutaneous injection at a dose of 30 mg every 4 weeks for the first three doses and then every 8 weeks. Dupilumab is dosed for moderate to severe asthma at 400 mg by subcutaneous injection for the first dose, followed by 200 mg every 2 weeks for subsequent doses. For patients with steroid-dependent disease, 600 mg followed by 300 mg every 2 weeks may be given. Dupilumab is approved for self-administration with proper training and also has on-label indications for the treatment of atopic dermatitis and chronic rhinosinusitis with nasal polyposis.

All of these agents are generally well tolerated, though precautions should be taken for the possibility of anaphylaxis. Reslizumab carries a 0.3% risk of anaphylaxis and carries a black box warning for this observation. The potential side effect profiles of all asthma biologics (including omalizumab) should be reviewed prior to prescribing. Conjunctivitis occurs approximately in 10% of patients receiving dupilumab.

Other biologics agents targeting more upstream components of the Th2 inflammation characteristic of allergic endotypes of asthma are under investigation and include monoclonal antibodies against IL-33 and TSLP (FIGURE 2). SEVERAL CHALLENGES REMAIN. There continues to be a paucity of available therapies for patients with non-eosinophilic uncontrolled severe asthma. Matching the right patient with the right therapy continues to be a challenge, even with the use of blood eosinophils and exhaled nitric oxide as biomarkers.



For over 30 years we have known that inflammation driven by the type-2 cytokines IL-4, IL-5, and IL-13 is a key immunopathologic mechanism in asthma(1). This increase in airway type-2 inflammation leads to airway and blood eosinophilia, airway mucus production, and bronchial hyperresponsiveness. Based upon this scientific knowledge, a new class of asthma biologics has emerged that inhibit these type-2 cytokines. These drugs are FDA-approved and very effective at preventing asthma exacerbations and decreasing oral corticosteroid use in patients with eosinophilic or T2-high asthma(2–4). However, in the course of developing these medications another new clinical obstacle has been uncovered. Namely, that a large sub-group of asthma patients do not demonstrate evidence of airway type-2 inflammation, and these patients with T2 low disease fail to respond to both ICS and this new class of T2 biologic agents
(4–6). Thus, in T2-low asthma there remains a significant and unmet clinical need.

A study from the NIH AsthmaNet investigators found that up to 70% of mild to moderate asthma subjects demonstrated low levels of sputum eosinophilia on repeat measurements(7). These shocking findings suggest that T2-low asthma is not as rare as previously suspected. Furthermore, the authors found that patients with non-eosinophilic asthma showed no differential response to either mometasone, tiotropium, or placebo over 42 weeks of study follow-up. These results question the conventional wisdom of mandatory inhaled corticosteroid (ICS) treatment in the sub-group of patients with T2-low asthma.

Further work has found that T2-low asthma is not simply restricted to mild or moderate asthma. In the Severe Asthma Research Program (SARP), up to 50% of severe asthma subjects also lack evidence of airway T2 inflammation(8). These T2-low severe asthma subjects suffer asthma exacerbations at high rates and demonstrate significant impairments in lung function despite aggressive treatment with inhaled and systemic corticosteroids. Thus, T2-low asthma is prevalent in asthma patients with mild, moderate, or severe asthma.

The disease mechanisms of T2-low asthma remain poorly understood, but recent work has identified some promising new therapeutic targets. A recent randomized controlled trial demonstrated that inhibition of c-kit, a key mast cell growth factor was effective at reducing airway hyperresponsiveness in patients with non-eosinophilic asthma(9). Furthermore, multiple studies have now found that patients with obesity-associated systemic IL-6 inflammation have worse lung function and frequent asthma exacerbations(10,11). Targeting the IL-6 axis has been helpful in treating cardiovascular disease, rheumatoid arthritis, and at preventing the development of lung cancer(12,13). Therefore, it is reasonable to consider the benefits of inhibiting IL-6 inflammation in severe asthma.

California is fortunate to have three clinical research centers at U.C. Davis, U.C. San Diego, and U.C. San Francisco that are planning to enroll patients into the NHLBI-sponsored Precision Interventions for Severe Asthma (PrecISE) Network. The objective of this network is to test if these (or other) therapeutic interventions could be beneficial in subgroups of patients with severe asthma. In addition, the network will be testing both predictive and monitoring biomarkers to assist in matching patients to the most effective asthma medication.

Updates on the activities and specific interventions being studied in PrecISE can be found at the PrecISE website, **preciseasthma.org.**

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The National Heart, Lung & Blood Institute's Precision Interventions for Severe and/or Refractory Asthma (PrecISE) Network is developing a protocol to test multiple novel interventions in a biomarker-driven, precision medicine approach and is launching later in 2019. There will be multiple California sites for the PrecISE Network: UC San Francisco (Dr. John Fahy and Dr. Michael Peters), UC Davis (Dr. Nicholas Kenyon and Dr. Amir Zeki), UC San Diego (Dr. Praveen Akuthota), and Rady Children's Hospital (Dr. Julie Ryu). Find the PrecISE Network at preciseasthma.org.

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Asthma Treatments "Two Steps Forward, One Step Back"

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- Asthma is not simply a disease of type-2 (T2) inflammation and many asthma patients demonstrate type-2 low or non-eosinophilic disease.

- Patients with T2-low asthma do not respond to the new class of T2 biologic medications, and are also less responsive to traditional asthma medications such as inhaled corticosteroids (ICS).

- Up to 70% of mild to moderate asthma patients demonstrate T2-low disease suggesting that T2-low asthma is significantly more common than previously assumed. Furthermore, many severe asthma patients (up to 50%) also demonstrate T2-low disease indicating that a very significant percentage of patients with asthma have insufficient treatment options.

- New treatments are being tested for patients with T2-low asthma, and three clinical research sites in California will soon be enrolling patients into adaptive clinical trials in the Precise Clinical Research Network.

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CRSC CORNER

New CSRC CTS Liaison – Krystal Craddock

I am humbled and honored to be the new CTS Liaison for the CSRC. I hope to
fulfill my job duties and represent the respiratory care profession as well as my predecessor, Rick Ford, has done. I am very passionate about the field of respiratory care, and the services we provide for our patients with acute (inpatient) and chronic (outpatient) lung diseases. Currently I am the Adult Clinical Educator and QI Coordinator, as well as the COPD Case Management Coordinator at the UC Davis Medical Center.I have spent many years working in, and helping to build the COPD Case Management program at UC Davis, under the Reversible Obstructive Air-ways Disease (ROAD) program to assist in transitioning patients with COPD from hospital to home with the goal of reducing unnecessary readmissions. I am also passionate about elevating the education requirements for RCP's and work as adjunct faculty in the San Mateo Community College District, teaching in their Respiratory Care Bachelor's Degree program. I look forward to working with everyone and communicating what we are doing in the CSRC that may affect the great work that the CTS is doing, and vice versa. My passion for transition of care and outpatient care leads me to the topic our outgoing CTS Liaison, Rick Ford, has written for this month's news-letter, regarding the Breathe Act.

H.R. 2508, the Better Respiration through Expanding Access to Tele-Health Act, (the BREATHE Act) Rep. Thompson, Mike [D-CA-5] (Introduced 05/02/2019)

The Breathe Act is a 3-year pilot that allows respiratory therapists to furnish disease management services, such as self-management education and training, demonstration/evaluation of proper inhaler techniques, smoking cessation and remote patient monitoring to Medicare beneficiaries with Chronic Obstructive Pulmonary Disease (COPD). Its purpose is to demonstrate the value RTs bring to the health care system and their patients through improved health outcomes and lower costs and to identify RTs as telehealth practitioners in the Medicare statute. With more and more services provided in the outpatient setting, it expands the RT role and gives visibility to the that does not exist under the current law.

If this bill is enacted, for the first time CMS will have the means to track claims data that can demonstrate how well RTs perform in terms of improving health outcomes and reducing costs. We expect the data to show the value RTs bring to the health care system and that's a huge win for the respiratory care profession, regardless of where you work. It gives us a starting point for bigger and better things in the future and, if shown to save money, can pave the way for RTs to become qualified telehealth professionals in expanded settings, including hospitals.

The CSRC is supportive of this legislation and ask for the support of CTS. Additional information can be found at:

https://www.congress.gov/bill/116th-congress/house-bill/2508/text?q=%7B%22search%22%3A%5B%22cartwright%22%5D%7D&r=52&s=1

The California Thoracic Society (CTS), and the American Thoracic Society, have prepared an educational document to be shared with the general public, healthcare professionals and patients affected by the catastrophe of wildfires.

Disaster Guidance: 10 Tips for Staying Healthy During Wildfires

Wildfire smoke can irritate the eyes, nose, throat, and lungs. It can cause coughing wheezing or difficulty in breathing. Inhaling smoke can be especially dangerous to those with lung disease (such as asthma, COPD/emphysema, pulmonary fibrosis, etc.), heart disease, pregnant women, the elderly and children. These high-risk populations need to take special care and consider consulting with their doctors regarding specific precautions.

The South Coast Air Quality Management District lists the following areas of direct smoke impacts:
http://www.aqmd.gov/docs/default-source/air-quality/advisories/advisory1.pdf

http://www.baaqmd.gov/about-air-quality/interactive-data-maps

Here are 10 basic steps to consider for patients and healthcare providers:

1. **Stay indoors** with windows and doors closed.
2. **Reduce physical activity.**
3. **Reduce other sources of indoor air pollution** such as smoking cigarettes, using a wood-burning stove or frying meat. Do not vacuum anywhere in the house.
4. **Use central air conditioner or filters**: A home's heater set to the fan mode may be able to filter out some of the particles by "re-circulating" the indoor air through the filter.
5. **Use air purifiers with HEPA filters.** Note: do not use filters that produce ozone such as "super oxygenators".
6. **When traveling in a vehicle,** keep windows closed, run the air conditioner and set air to re-circulate to reduce smoke.
7. An **N95 or greater mask** can help reduce inhalation of particulates if properly fitted. A surgical or simple dust mask **will not** protect against particulate exposure. **None** of these masks protect against hazardous gas inhalation. The following video demonstrates how to properly put on an N95 mask. https://m.youtube.com/watch?v=0d_RaKdqeck
8. **Consider evacuation** to areas with lower air quality index for individuals with lung disease (especially those with asthma, COPD / emphysema, pulmonary fibrosis).
9. **Create a clean room at home.** Use an interior room with fewer doors and windows and run an air conditioner and room air cleaner if available.
10. **Patients with asthma or COPD** should ensure that they continue to take their maintenance ("controller") medications or discuss an appropriate regimen with their physician.

Adapted from Fire Dangers, Air Quality and Safety for Pulmonary Clinicians and Their Patients from the California Thoracic Society by

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- http://wildfirerecovery.org/general-info/consumer-awareness/

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Volume 19, Issue 2							
Title (Click on title to open the manuscript, **CME in Bold**)	**Journal Section**	**First Author**	**Year**	**Vol**	**Issue**	**Pages**	**Date Posted**
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Pulmonary Disease Linked to Vaping	News	Robbins RA	2019	19	2	84	8/22/19
Severe Accidental Hypothermia in Phoenix? Active Rewarming Using Thoracic Lavage	Critical Care	Mozer M	2019	19	2	79-83	8/21/19
CEO Compensation-One Reason Healthcare Costs So Much (News)	News	Robbins RA	2019	19	2	76-8	8/19/19
Medical Image of the Month: Mounier-Kuhn Syndrome	Imaging	Ali A	2019	19	2	73-5	8/15/19
Left Ventricular Assist Devices: A Brief Overview	Critical Care	Gali B	2019	19	2	68-72	8/14/19
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