Making the Case for a New Disease Entity: Bactrim Associated ARDS

A Call Away Telephone Triage

Jenna Miller, MD FAAP

Pediatric Critical Care Physician

Children's mercy Kansas city

Disclosures and Disclaimers

- I encourage Tweeting @JennaMillerKC
  - #tmpsmxards
- All patients in the images used have provided written consent to be identified
- I may reference Bactrim throughout the presentation for ease but I am referring to all forms of Trimethroprim-Sulfamethaxozole
- I have paid consulting with Ocugen, INC.

Objectives

- Describe the clinical presentation of rare lung toxicity associated with trimethoprim-sulfamethoxazole
- Describe the pathologic finds of rare lung toxicity associated with trimethoprim-sulfamethoxazole
- Recognize challenges in identifying rare adverse drug reactions

Kansas City's Own

Zei Uwadia

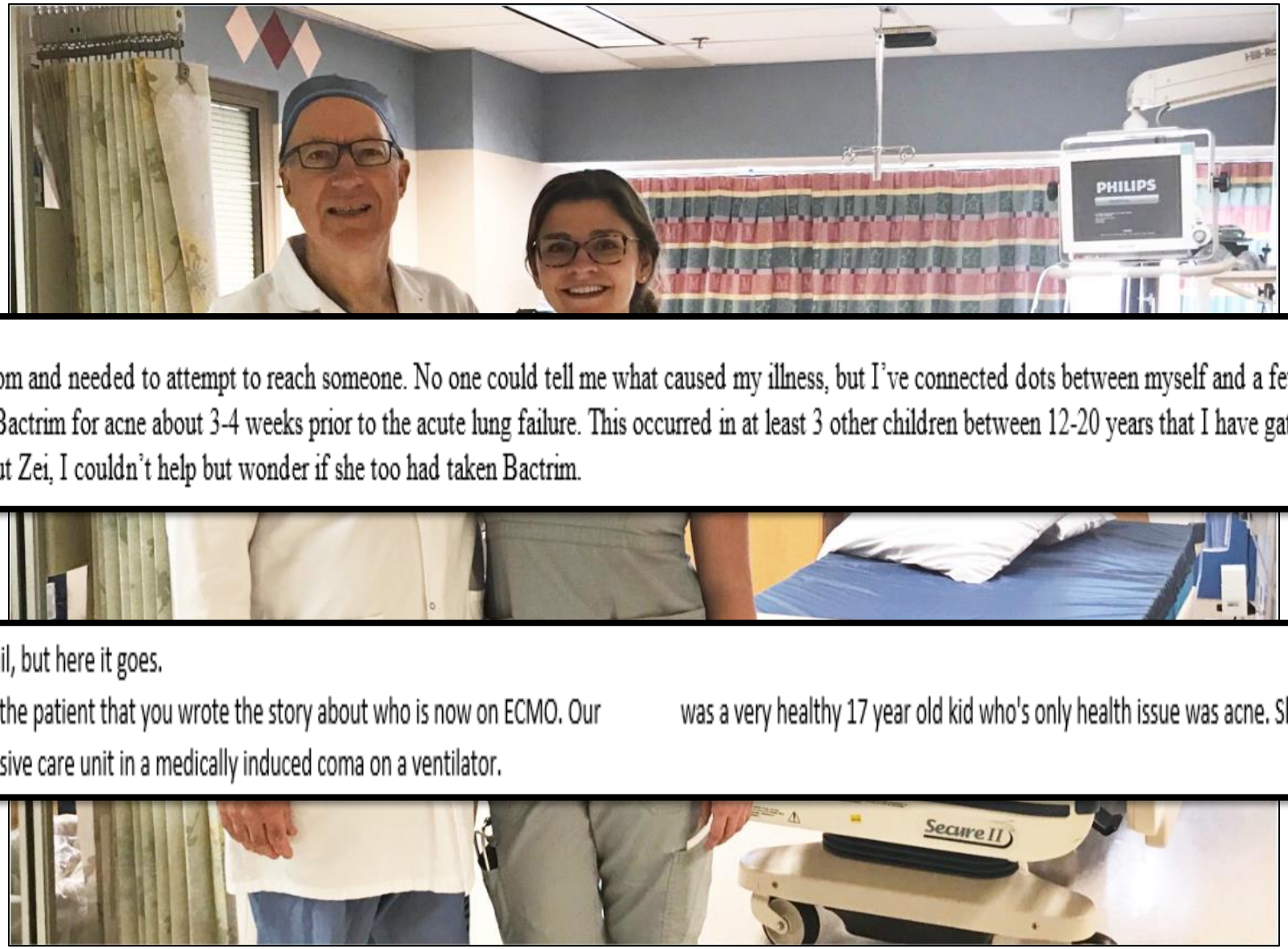
CNN health Food Fitness Wellness Parenting Vital Signs Edition

The 16-year-old girl who walks and eats tacos while on life support

By Jacqueline Howard, CNN

Updated 10:34 AM ET, Wed March 21, 2018

How it Began
March 2018



I saw the article about Zei on CNN.com and needed to attempt to reach someone. No one could tell me what caused my illness, but I've connected dots between myself and a few other young adults who became ill in a very similar way. I began taking Bactrim for acne about 3-4 weeks prior to the acute lung failure. This occurred in at least 3 other children between 12-20 years that I have gathered. The similarity between our cases are uncanny. When I heard about Zei, I couldn't help but wonder if she too had taken Bactrim.

I am not sure where to start with this email, but here it goes.

Our daughter was in a similar situation as the patient that you wrote the story about who is now on ECMO. Our was a very healthy 17 year old kid who's only health issue was acne. She was prescribed Bactrim to help with it.

A couple weeks later, she was in the intensive care unit in a medically induced coma on a ventilator.

Acta Med. Okayama, 2010
Vol. 64, No. 3, pp. 181–187

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Interstitial Lung Disease during Trimethoprim/Sulfamethoxazole Administration

Syota Yuzurio[a]*, Naokatsu Horita[a], Yutaro Shiota[a], Arihiko Kanehiro[b], and Mitsune Tanimoto[b]

[a]*Department of Respiratory Medicine, Kure-Kyosai Hospital, Kure, Hiroshima 737–8505, Japan,*
[b]*Department of Hematology, Oncology, Respiratory Medicine, and Allergology, Okayama University Medical School and Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan*

CASE REPORT

Acute fibrinous organising pneumonia: a manifestation of trimethoprim-sulfamethoxazole pulmonary toxicity

Fady Jamous,[1] Syed Zain Ayaz,[2] Jacquelyn Choate[3]

[1]Department of Pulmonary & Sleep Medicine, Avera Medical Group, Sioux Falls, South Dakota, USA
[2]Department of Internal Medicine, University of South Dakota, Sioux Falls, South Dakota, USA
[3]Department of Physicians Laboratory, Avera McKennan Hospital, Sioux Falls, South Dakota, USA

Correspondence to
Dr Fady Jamous,
fady.jamous@avera.org

Accepted 15 October 2014

SUMMARY
A 50-year-old man was treated with trimethoprim-sulfamethoxazole (TMP-SMX) for acute arthritis of his right big toe. Within a few days, he developed dyspnoea, hypoxaemia and diffuse pulmonary infiltrates. Symptoms improved with discontinuation of the antibiotic but worsened again with its reintroduction. An open lung biopsy was performed. We describe the workup performed and the factors that pointed to a final diagnosis of TMP-SMX-related pulmonary toxicity in the form of acute fibrinous organising pneumonia.

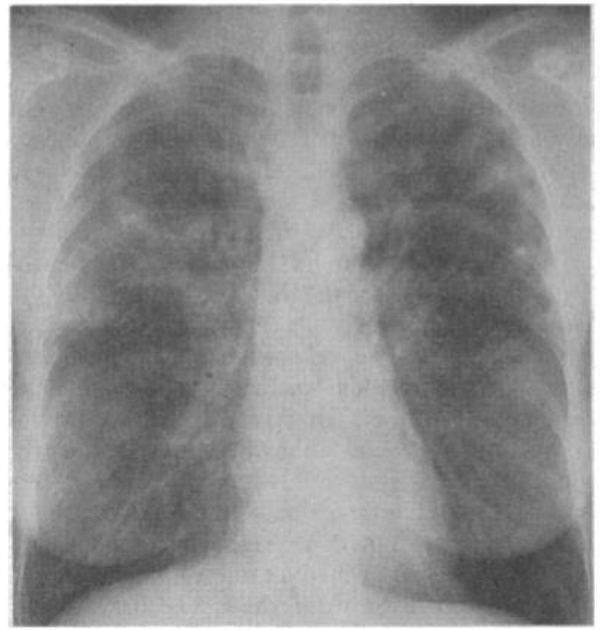
BACKGROUND
This is a case of an unusual manifestation of pulmonary drug toxicity in relation to a very commonly prescribed antibiotic.

CASE PRESENTATION
A 50-year-old man developed acute arthritis of the

Figure 1 Bibasilar infiltrates with interstitial changes on initial presentation.

Hypersensitivity pneumonitis induced by trimethoprim

Drs T HIGGINS (Department of Paediatrics) and P M NIKLASSON (Department of Infectious Diseases, Växjö County Hospital, S-385 17 Växjö, Sweden) write: We report on a patient who developed hypersensitivity pneumonitis induced by trimethoprim. A 43 year old woman with no history of allergy received a 25 day course of trimethoprim 100 mg/day in February 1989 for recurrent urinary tract infection. A new course was begun in September 1989. Four weeks later she presented with a two week history of a severe hacking cough and a five day history of fever, muscle pain, nausea, and headache. No other medications had been taken. The chest radiograph showed a nodular pattern of opacities (figure).



Chest radiograph showing nodular pattern of opacities

Cor Pulmonale in Children With Acute Respiratory Failure on Venovenous Extracorporeal Membrane Oxygenation

To the Editor:

We read the article by Dong *et al*.[1] with great inter
too have experienced cor pulmonale in children w
respiratory distress syndrome (ARDS) supported wi
venous extracorporeal membrane oxygenation (VV
Two previously healthy male children (7 and 8 year
on VV-ECMO via dual-lumen cannula were transferr
facility for evaluation for possible ECMO bridge to lu
plantation (LTx). The 7-year-old boy with a history of au
bone marrow transplant complicated by bronchiolitis o
syndrome developed ARDS in association with acu
plasma pneumoniae pneumonia. He was ventilated fo
before starting VV-ECMO and then transferred 6 days
second child was healthy until experiencing an immu
response to trimethoprim-sulfamethoxazole leading
and subsequent irreversible pulmonary fibrosis. He
tilated on high airway pressures for 6 days before sta
ECMO and then transferred to our center 49 days late

Lung (2014) 192:1005
DOI 10.1007/s00408-014-9642-1

LETTER TO THE EDITOR

Pediatric Ambulatory ECMO

Don Hayes Jr. · Eric A. Lloyd · Andrew R. Yates · Patrick I. McConnell · Mark Galantowicz · Thomas J. Preston

Received: 4 July 2014 / Accepted: 1 September 2014 / Published online: 10 September 2014

To the Editor,

The current literature provides a modest experience regarding ambulating adult patients on venovenous extracorporeal membrane oxygenation (VV-ECMO), with some older teens also reported. However, there is no previous report of ambulation in a younger child.

We report the ambulation of an 8-year-old child on VV-ECMO who developed acute respiratory distress syndrome due to a medication reaction to trimethoprim/sulfamethoxazole. At his initial presentation, he had developed fever, cough, and dyspnea soon after starting the antimicrobial coverage for osteomyelitis. With worsening respiratory status and facial swelling, he presented to a community pediatric facility where he was found to have a pneumothorax and was intubated. Due to refractory hypercapnia, he was transferred to a quaternary pediatric facility for implementation of VV-ECMO through cannulation of the internal jugular with a bicaval dual-lumen catheter. With a prolonged course in the intensive care unit, he underwent tracheostomy. To avoid complications from immobilization, he was ambulated on VV-ECMO and underwent active participation of physical therapy including riding a hand and foot-pedaled tricycle (Figure).

In a critical care setting especially with ECM
prolonged immobilization can result in skelet
atrophy and loss of muscle fibers, which can re
loss of muscle strength, decreased range of m

CHEST Annual Meeting 2017 | TORONTO CANADA October 28 - November 1

Diffuse Lung Disease

SESSION TITLE: Diffuse Lung Disease 2

SESSION TYPE: Original Investigation Poster

PRESENTED ON: Wednesday, November 1, 2017 at 01:30 PM - 02:30 PM

Sulfa-Induced Acute Eosinophilic Pneumonia in Adolescents

Faria Nasim[4] Jennifer Boland-Froemming and Mark Wylam Mayo Clinic, Rochester, MN

PURPOSE: In contrast to chronic eosinophilic pneumonia acute eosinophilic pneumonia (AEP) more commonly affects person's age 20-40 years old. AEP has been suggested to be an acute hypersensitivity reaction to an unidentified inhaled antigen in a previously healthy individual. Acute and organizing diffuse alveolar damage (DAD) is common, and in this age group AEP is responsive to corticosteroids, commonly with complete recovery.[1,2] Herein, we report 3 adolescents with severe AEP.

METHODS: Retrospectively, we identified 3 cases transferred to our institution that developed AEP in association with recent use of a sulfa medication. All patients presented with acute onset pulmonary infiltrates, fever and pneumomediastinum as well as marked peripheral eosinophilia. Referring hospitals did not perform BAL which was further delayed despite ECMO. In each case the onset was crescendo over 1 week duration, and occurred within 1 month of beginning a daily orally-administered sulfa-containing medication.

RESULTS: All 3 patients were female with a mean age of 15 years. 2 patients had received treatment with sulfamethoxazole for acne and 1 was treated with sulphasalazine for colitis. Patients were on Sulpha medication for 1-3 weeks prior to presentation. Mean eosinophil count was 2.21 X 10^9/L. 2 patients were treated with ECMO. 1 underwent heart-lung transplantation and 1 bilateral living-related lobar lung transplantation. In both cases lung biopsy and explants showed acute and organizing diffuse alveolar damage with increased interstitial and airspace eosinophils.

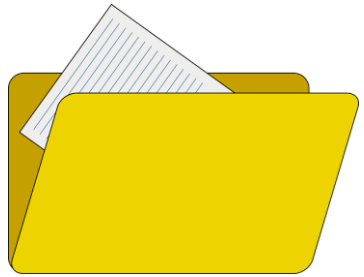
CONCLUSIONS: This is the first report to describe the clinical features of sulfa-induced severe AEP in a pediatric population. Compared to prior reports of AEP in young adults, sulfa-induced AEP in adolescents may follow brief use, elicit severe respiratory failure presenting with air leak and response to corticosteroids may be limited.

CLINICAL IMPLICATIONS: Sulfa-induced AEP is rare and manifests as severe acute respiratory failure that requires prompt recognition and management. References: 1. Philit F et al Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med. 2002 Nov 1; 166(9):1235-9. 2. Allen JN, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med. 1989;321(9):569.

DISCLOSURE: The following authors have nothing to disclose: Faria Nasim, Jennifer Boland-Froemming, Mark Wylam

No Product/Research Disclosure Information

Timeline



PEDIATRICS®

March 2018

Fall 2018

May 2019

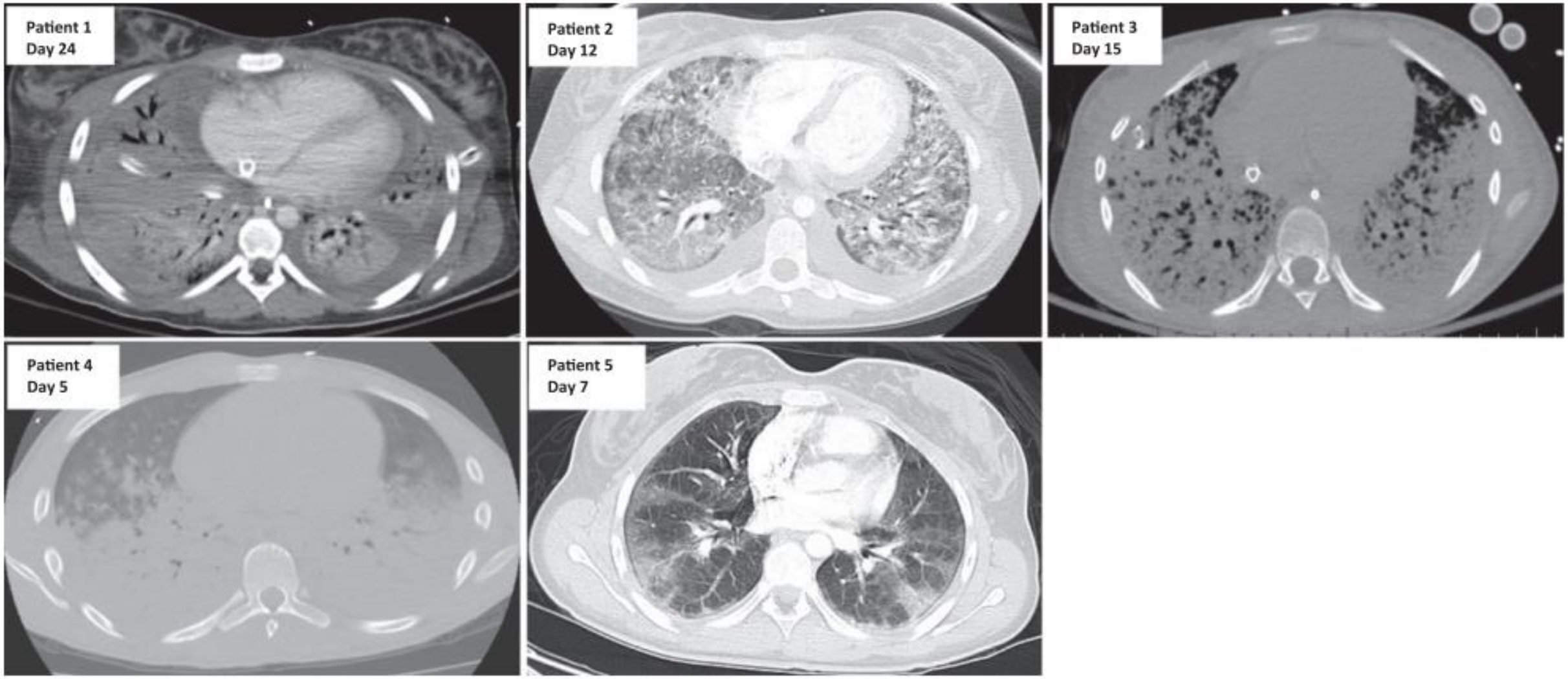
PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Severe Acute Respiratory Failure in Healthy Adolescents Exposed to Trimethoprim-Sulfamethoxazole

Jenna O. Miller, MD, FAAP,[a] Jane Taylor, MD, MS,[b] Jennifer L. Goldman, MD, MS[c,d]

TABLE 1 Characteristics of Adolescent Patients With Severe Respiratory Failure and Recent TMP-SMX Exposure

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	16	17	13	18	15
Sex	Female	Female	Female	Male	Female
Days of TMP-SMX exposure	24	17	25	23	10
Lung biopsy pathology	Not performed	Not performed	Diffuse alveolar damage, acute and organizing with increased eosinophils consistent with acute eosinophilic pneumonia	Not performed	Diffuse alveolar damage, acute and organizing with increased eosinophils consistent with acute eosinophilic pneumonia
Additional complications	Tracheostomy, pleural effusion pneumothorax, pneumomediastinum, renal failure	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, pulmonary emboli	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, internal jugular thrombosis	Tracheostomy, pleural effusion, pneumothorax, pneumomediastinum, bilateral pulmonary emboli
Immunosuppressive therapy	Mycophenolate mofetil	Steroids	Steroids, hydroxychloroquine	Steroids	Steroids, azathioprine, rituximab, cyclophosphamide, plasma exchange
ECMO duration, d	193	N/A	114	29	190
Organ transplant	Lung, heart, and kidney transplants considered; not performed	Transplant not considered	Lung and heart transplant performed	Lung transplant considered; not performed	Lung transplant considered; not performed
Disposition	Survived	Survived	Died	Survived	Died

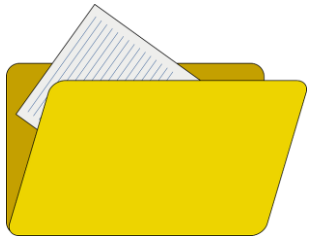

Patient 1
Day 24
Patient 2
Day 12
Patient 3
Day 15
Patient 4
Day 5
Patient 5
Day 7

Timeline

Hi Dr. Miller,

I saw the story of your patient Zei in the news and was struck by the potential similarity to two young patients we saw about two years ago with rapid and profound respiratory failure requiring ECMO. Yours is a particularly inspiring story and it's great that it raised so much attention and awareness.

CNN



MGH 1811

PEDIATRICS

March 2018

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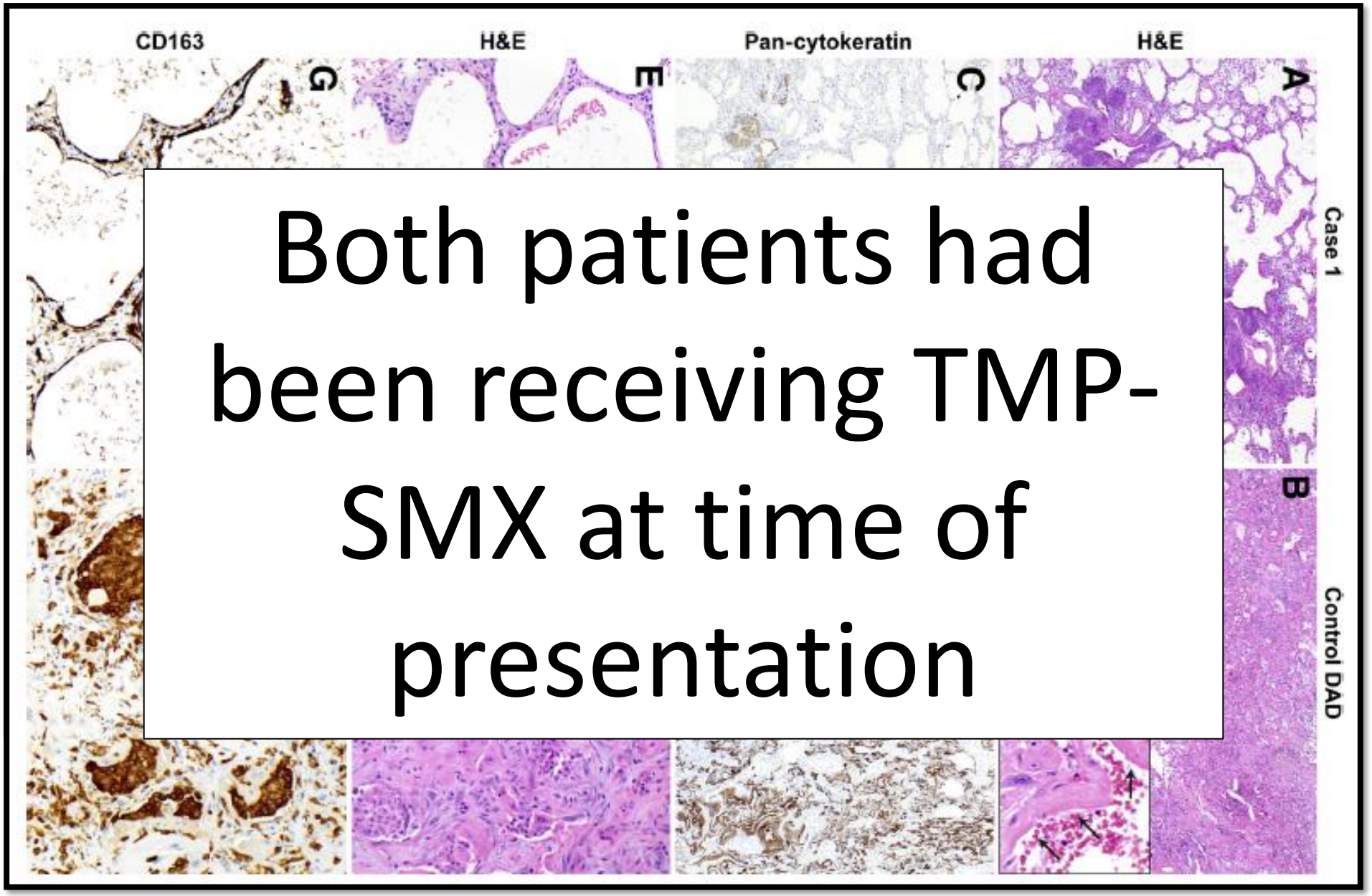
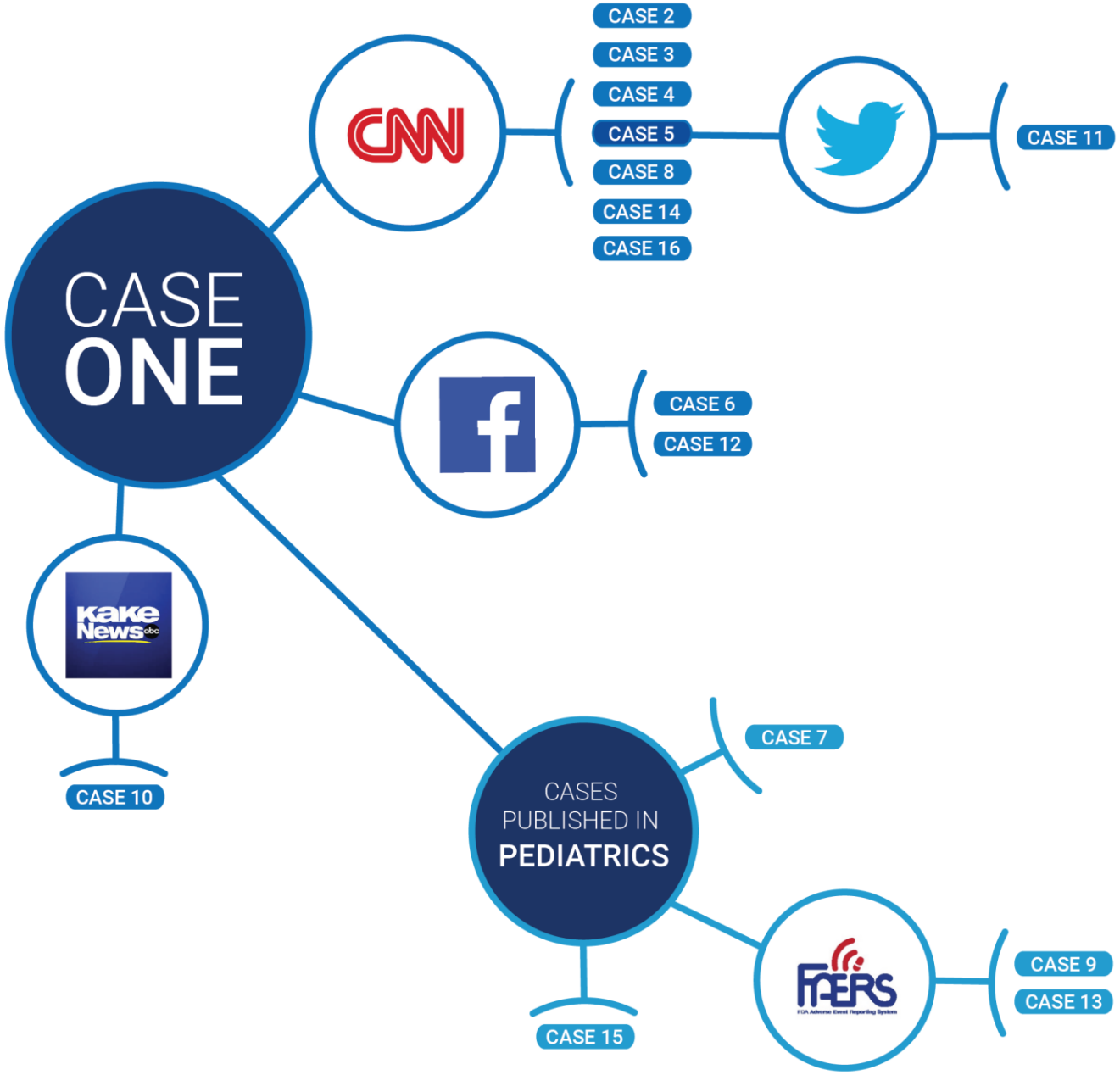
May 2019



Both patients had been receiving TMP-SMX at time of presentation

Media Finds a Way



Graphic by Ashley Saunders

Print Media

Reuters Administration

Product:
Medical
Pub date:
2019-05-31
Byline:
Marilynn Larkin
Headline:
Trimethoprim-su
Body Text:
By Marilynn Lar
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Children's Mercy KANSAS CITY

Kansas City, Nov

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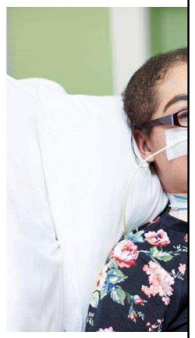

By Taylor Adam

For nearly a yea
following the st
died after spen
City hospital.

Now, a major b
made with the

Medscape

News > Medscape Medical News

Trimethoprim-Sulfamethoxazole Linked to ARDS

Nicola M. Parry, DVM

June 03, 2019

6

Trimethoprim-sulfameth
may be linked to the ons
respiratory distress sync
according to a recent ca
May 31 in *Pediatrics.*

"Although there is no av
causality between TMP-SMX and ARDS in these adolescents, the extensive negative workup, paired with recent TMP-SMX exposure and similarity among these cases, raises the possibility that the observed ARDS was TMP-SMX triggered," write Jenna O. Miller, MD, University of Missouri–Kansas City and Children's Mercy Hospital and Clinics, and colleagues.

CHILDREN'S HOSPITAL ASSOCIATION

ARTICLE | July 28, 2020

Researchers' Quest to Explain Popular Antibiotic Link to Respiratory Illness

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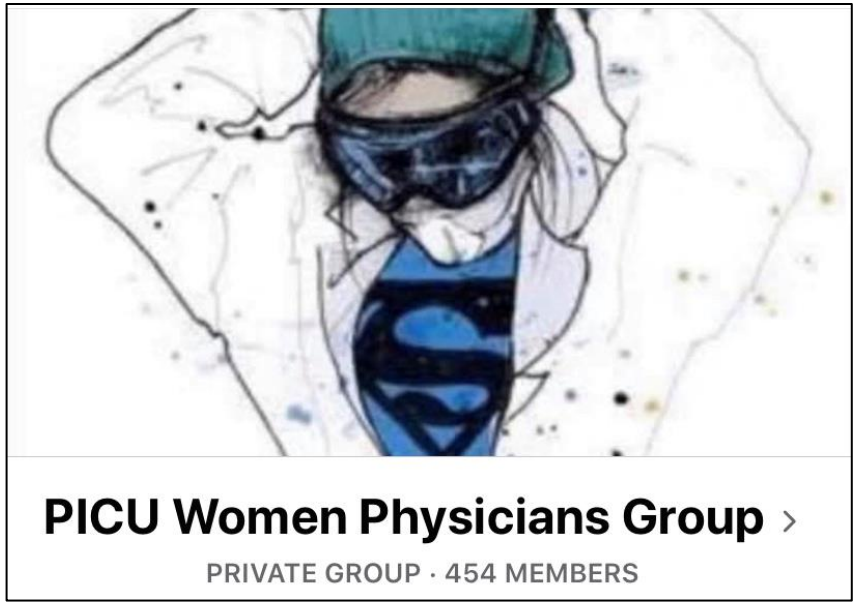
M.D./alert

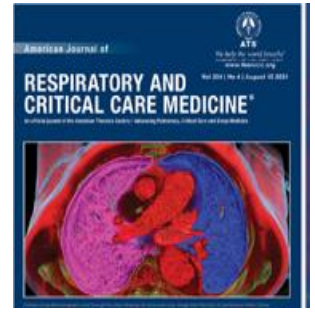
Trimethoprim-sulfamethoxazole implicated in respiratory failure in five teens

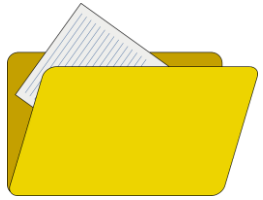
TV News Stories

Social Media



Timeline





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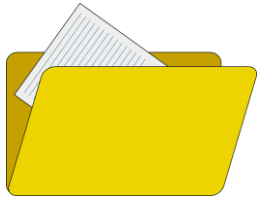


March 2018 | Fall 2018 | February 2019 | May 2019 | Summer 2019 | Fall 2019-2020 | Jan 2021

American Journal of Respiratory and Critical Care Medicine

Publishes the most innovative research, highest quality reviews, clinical trials, guidelines, and statements in pulmonary, critical care, and sleep-related fields

Am J Respir Crit Care Med. 2021 Apr 1;203(7):918-921. doi: 10.1164/rccm.202009-3421LE.

Trimethoprim–Sulfamethoxazole–associated Fulminant Respiratory Failure in Children and Young Adults

Jenna O Miller [1], Angela R Shih [2], Mari Mino-Kenudson [2], Martin S Taylor [2], Jennifer L Goldman [1]

Hot off the press

The Pharmacogenomics Journal

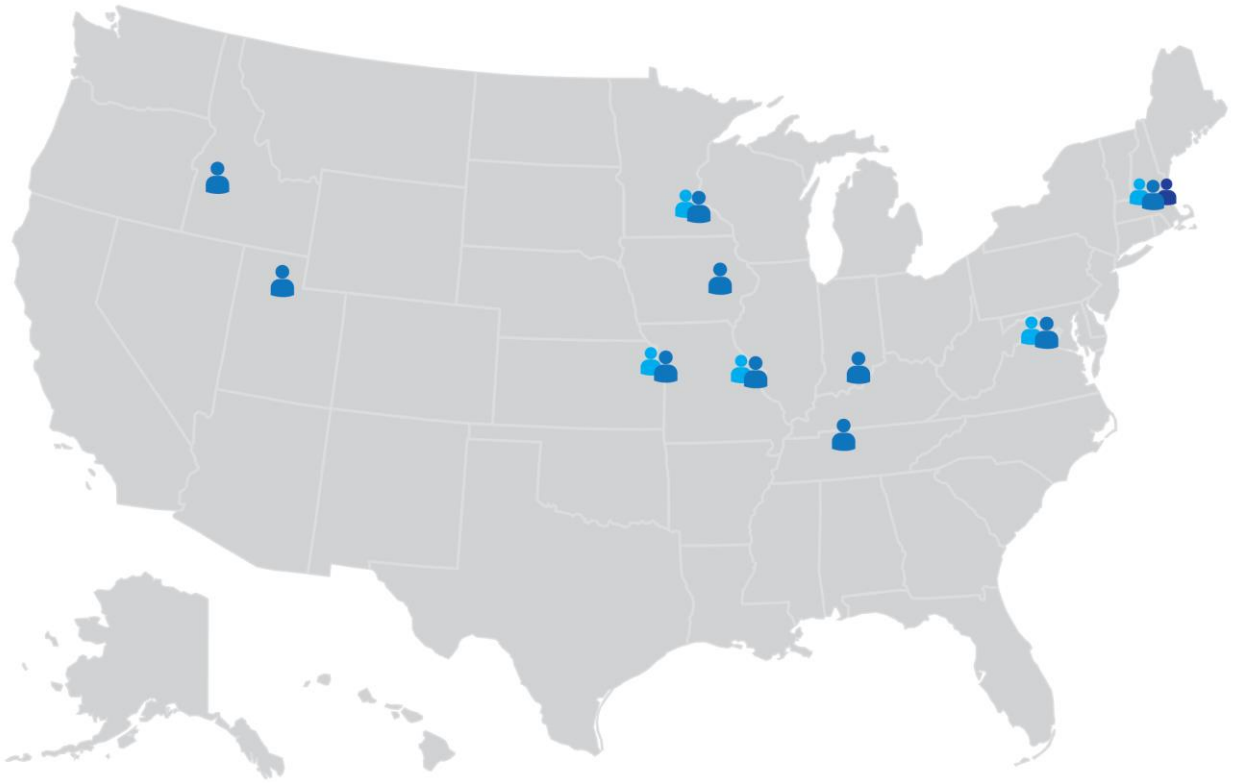
*HLA-B*07:02* and *HLA-C*07:02* are associated with trimethoprim-sulfamethoxazole respiratory failure

Jennifer L. Goldman ✉, Jenna O. Miller, Neil Miller, Robert Eveleigh, Andrew Gibson, Elizabeth J. Phillips & Tomi Pastinen

Inclusion Criteria

- No previous pulmonary disease
- No other cause for respiratory failure
- Documented TMP-SMX exposure ≥ 6 days
- All medical records available to verify history and TMP-SMX exposure
- Minimal to no vaping or smoking history

Geographical Distribution



Current Cohort of 19

13 females, 6 males

16 Caucasian, 2 Asian, 1 Mixed

Indications:

- 9 acne
- 6 SSTI
- 2 ENT procedure
- 1 UTI

Bactrim Exposure Profile

Treatment dosing, DS

NO prophylactic dosing cases

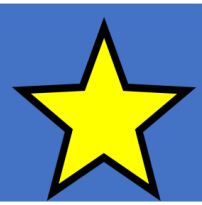
Range of time taking prior to onset of symptoms

- 6-28 days
- Mean 16 days

Initial Symptoms

Non specific symptoms can include: cough, fever, SOA, chest pain, sore throat, fatigue, headache, congestion, rash

Important question: Are these NEW since starting the antibiotic?



Most Common:

- Fever 80%
- Cough 80%
- Fatigue 55%
- Chest Pain 50%
- SOA 50%

Hospital Presentation Symptoms

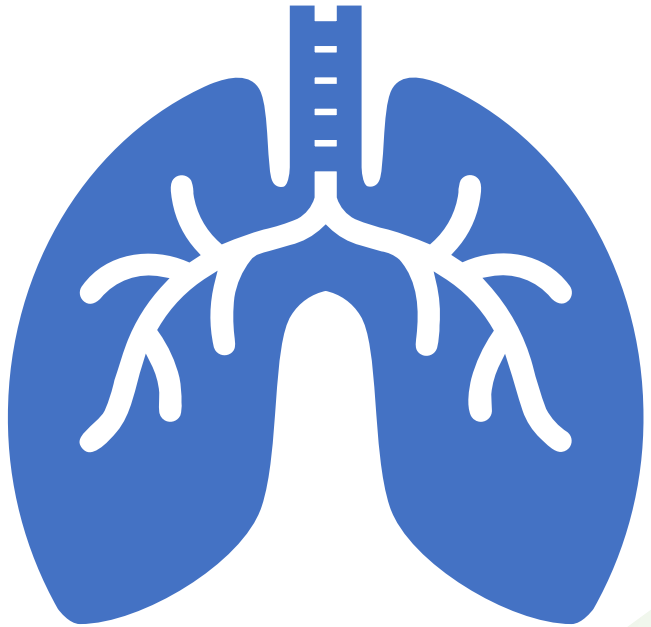
Symptoms can include: Hypoxemia, SOA, Chest pain, fever, cough, sore throat, fatigue

Most Common:

- SOA 100%
- Hypoxemia 80%
- Cough 66%
- Chest Pain 50%
- Fatigue 33%

Chest Pain in Kids?

- Seems uncommon compared to adults
- One finding specific to this disease could explain
- Half of these patients present with pneumomediastinum when admitted
  - This often causes chest pain
- Air leak, or pneumomediastinum/pneumothorax early is a hallmark of this disease

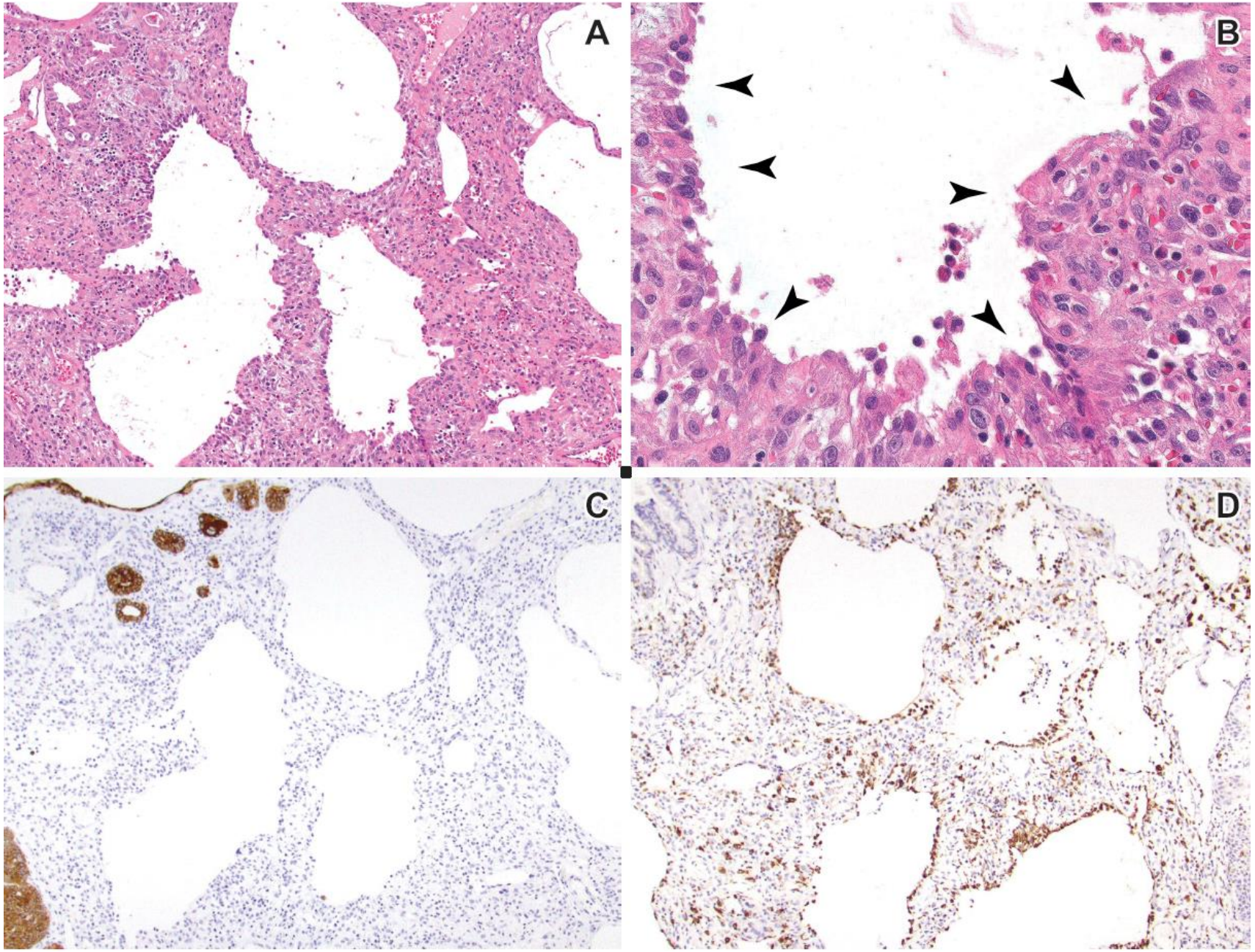


Pathology

Lung pathology - no./total no. (%)	9/14 (64)
Biopsy or autopsy consistent with DAIDE*	7/9 (78)

- 9 tissue samples available
  - Autopsy, explant or biopsy
- 7 samples consistent with **D**iffuse **A**lveolar **I**njury with **D**elayed **E**pithelialization (DAIDE)
  - 1 explant sample was 3 months into process
  - 1 biopsy sample was peripheral and small, thus inconclusive

Diffuse Alveolar Injury with Delayed Epithelialization



Cytokeratin lack of epithelial cells

CD68 highlighting macrophages

Courtesy of Pulmonary Pathology Department Massachusetts General Hospital

Outcomes

Prolonged hospital stays

16/19 needed ECMO

- 2 from the 90's before ECMO was utilized

7/19 died ~ 40% mortality

- 2 from disease
- 1 sepsis
- 2 post transplant complications
- 2 hemorrhagic complications

Is it Really TMP-SMX?

INCREASED USE OF ECMO

INCREASED SOCIAL MEDIA USE

DIFFERENT MANUFACTURERS

NO VAPING OR SMOKING HISTORY

Label change may 2021

Rx only

BACTRIM™
sulfamethoxazole and trimethoprim DS
(double strength) tablets and tablets USP

Other severe pulmonary adverse reactions occurring within days to week of BACTRIM initiation and resulting in prolonged respiratory failure requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), lung transplantation or death have also been reported in patients and otherwise healthy individuals treated with sulfamethoxazole and trimethoprim products.

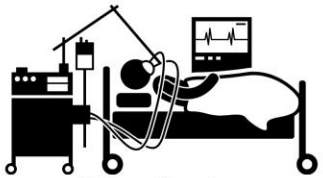
What advice can you give?

- If these symptoms are new and different from indication for which Bactrim was prescribed…
  - Stop the drug and be seen in an ER
  - Let prescribing clinician know of new symptoms
- Think about your advice if they call with new rash after Bactrim and Stevens Johnson is possible… that raises alert and concern
- Many of these patients were told this type of reaction to Bactrim doesn’t exist so we can now take their symptoms seriously
- This is RARE, but you may help someone by knowing about this reaction

Trimethoprim-Sulfamethoxazole Associated Fulminant Respiratory Failure in Children and Young Adults

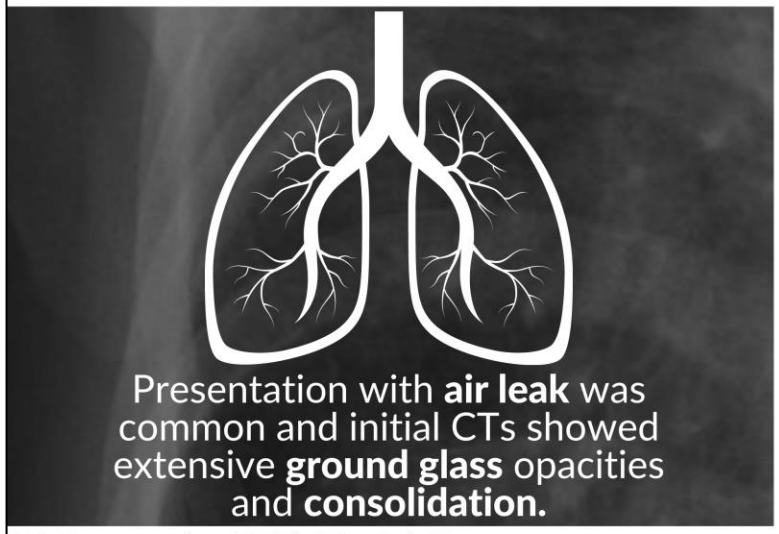
An underappreciated severe adverse drug reaction to a commonly prescribed antibiotic.

Fourteen healthy children and young adults exposed to **TMP-SMX (Bactrim®).**



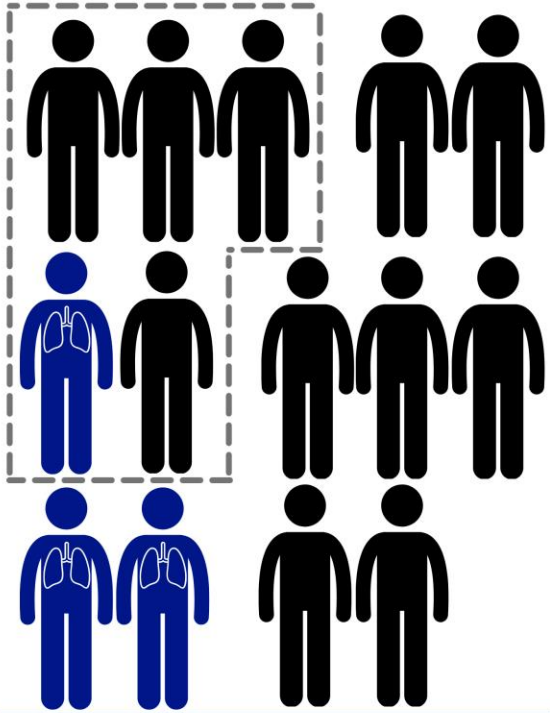
All patients presented with **shortness of breath**, required **intensive care admission,** and needed **mechanical ventilation**.

Key Outcome:
Twelve of the 14 patients in this study required Extracorporeal membrane oxygenation (ECMO).



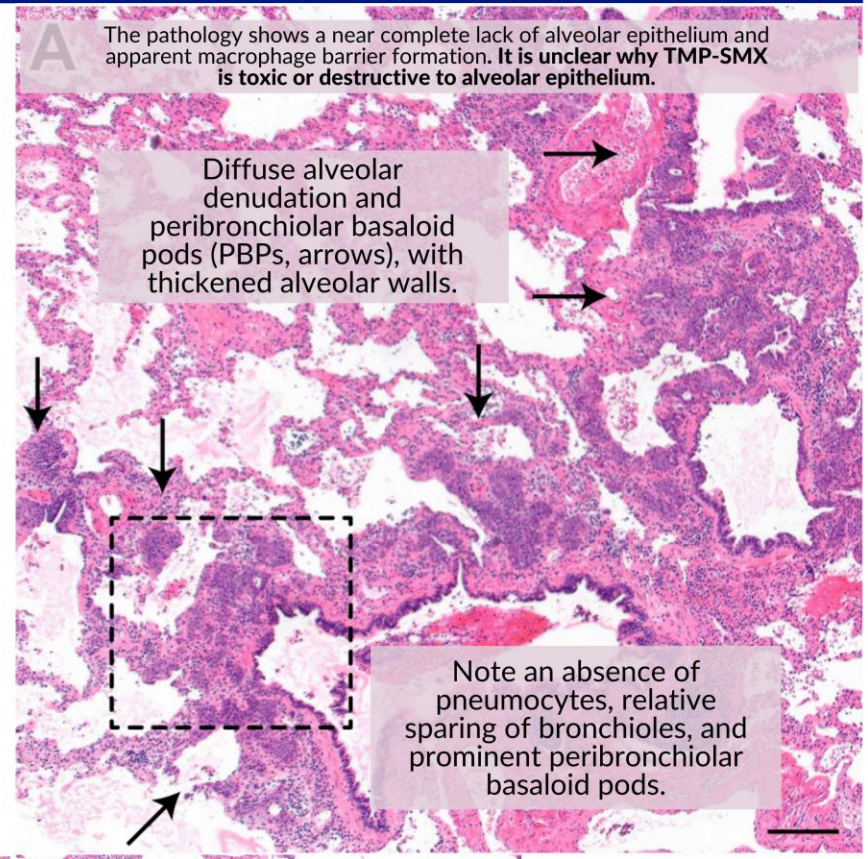
Presentation with **air leak** was common and initial CTs showed extensive **ground glass** opacities and **consolidation.**

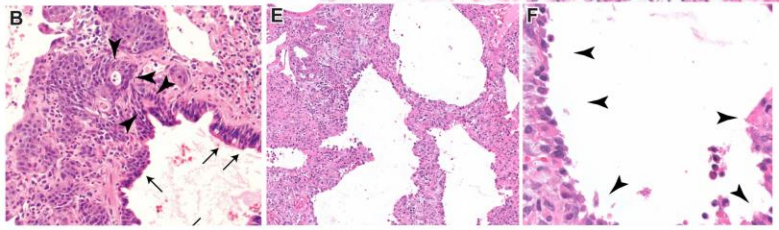
5 of 14 patients died, one of whom received a transplant before death.



3 of 14 patients underwent lung transplant, one of whom was a heart-lung transplant.

Seven of seven patients with appropriately-timed biopsies demonstrated a pattern of injury consistent with ***Diffuse Alveolar Injury with Delayed Epithelialization.***





Thickened alveolar walls lack hyaline membranes or pneumocytes (E) and are lined by macrophages (F).

Alveolar pneumocytes are replaced by CD68-positive macrophages.

Join the conversation: @ATSBlueEditor, #pulmCC
Connect with the authors on Twitter: @Jgmanpc, @JennaMillerKC, @MSTaylor_MDPhD, @AngelaRShih

Jenna O. Miller, MD, Angela R. Shih MD, Mari Mino-Kenudson MD, Martin S. Taylor MD, PhD, Jennifer L. Goldman MD
American Journal of Respiratory and Critical Care Medicine

Graphic Design by: Tricia Pendergrast @traependergrast

Continue to Follow The Developments

- remember me on Twitter @JennaMillerKC
- #tmpsmxards for stories or to follow

IN Summary-This is a thing

- Early recognition of this as an entity could possibly decrease severity if drug is stopped earlier
- Trimethoprim-Sulfamethoxazole can be associated with severe ARDS and prolonged ECMO need
- Trimethoprim-Sulfamethoxazole can be associated with a novel pathology finding called diffuse alveolar injury with delayed epithelialization

Thank you

To our patients and families who have been courageous in their quest to share knowledge and raise awareness

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