Abstracts, Posters, & Publications…Oh MY!

Intro to Scholarship for the Busy Internal Medicine Resident

Avital O'Glasser, MD, FACP, FHM

Noon Conference

11/30/2018

INTRO TO SCHOLARSHIP

- Goals:
  - Explore the value of scholarship as an internal medicine resident…including mentorship
  - Discuss options for submission types beyond RCTs and systematic reviews
  - Discuss practical tips to facilitate research, writing, and submitting…including mentorship
  - Share #OHSUscholarship real-life examples!

- Disclaimers:
  - I have no disclosures
  - I like “Hamilton the Musical”
  - I really really like “Hamilton the Musical”
  - I like goofy memes
  - You may tweet any content from this talk (@aoglasser)

- Acknowledgements:
  - Drs. Joe Chiovaro and Chris Sankey (Yale) who have previously given noon conferences on this subject

WHY SCHOLARSHIP & MEDICAL WRITING?

Pick up a pen, start writing

I wanna talk about what I have learned

The hard-won wisdom I have earned

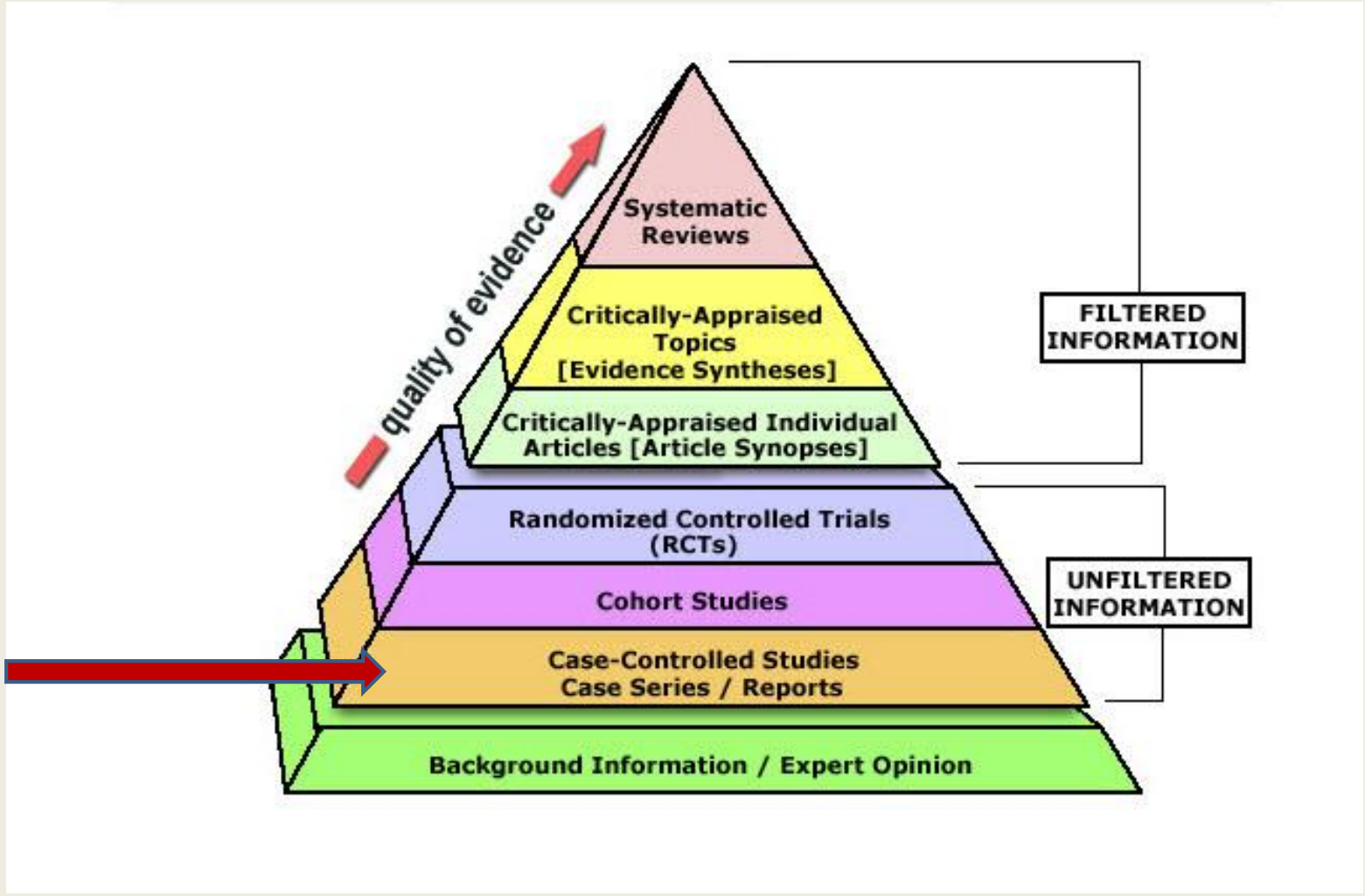
As far as the people are concerned

- *George Washington*
- *In the Broadway Musical "Hamilton"*

WHY SCHOLARSHIP & MEDICAL WRITING?

- Don't we document and write ENOUGH?
  - H&Ps, progress notes, DC summaries, clinic notes…
- A different type of writing:
  - Mentorship and colleague relationships, collaborative skills
  - Enhance learning—your own and the medical profession's
  - Cognitive skills
    - Editorial
    - Critical
    - Speculative
    - Imaginative and creative
    - *Ala ~ Clifford Packer, MD, SGIM Forum 2014, "Case Reports: Good for Evidence, Good for Teaching"*

WHAT KIND OF MEDICAL WRITING??



WHY SCHOLARSHIP & MEDICAL WRITING?

"Publish it…place it on permanent record as a short, concise note…such communications are always of value."

- *Sir William Osler*

SCHOLARSHIP VENUES

PEER-REVIEWED

- "Cream of the crop"
- Indexed in Medline
- More rigorous process to be considered for submission

NON-PEER REVIEWED

- Historically "discredited"
- Not indexed in Medline…
- …but still counts!!
- "FOAMed" and social media shaking up traditional citation metrics and dissemination

SCHOLARSHIP VENUES

- Peer-reviewed options
  - NEJM
  - BMJ
  - Lancet
  - American Journal of Medicine
  - JGIM
  - JHM
  - Annals of Internal Medicine
  - Etc…
  - Etc…
  - Etc…
- Non-peer-reviewed options
  - Many Society publications
    - SGIM FORUM
    - ACP Hospitalist
  - Lay press
  - Editorials
  - Online venues including blogs

“WE SHOULD WRITE THIS UP!”

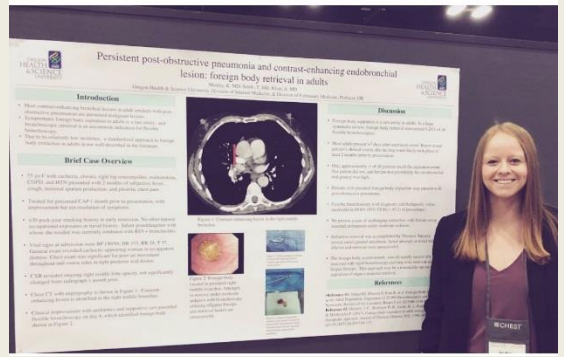
WHAT MAKES A "GOOD" CASE?

- "WE SHOULD WRITE THIS UP!"
  - New diagnosis (probably the hardest)
  - Rare diagnosis
  - Unusual manifestation of something relatively common
  - Unique/powerful images/visuals
  - Complex management
  - Complications of therapy
  - Novel therapeutic approach

POSTERS

SELLING POINT: does NOT preclude submission of a case for publication, often STRENGTHENS selection of cases for publications and then the formal write-up itself

- **General Medicine:**
  - Oregon ACP
  - National ACP
  - NW SGIM
  - SGIM
  - SHM
  - Oregon Geriatrics/AGS
  - Periop Summit
- **Subspecialty**
  - CHEST
  - ATS
  - AHA
  - Liver Meeting
  - And the list goes on!



Might get accepted as an ORAL presentation!!

CLINICAL IMAGES

Image driven case with accompanying description and/or learning points

- Why an image over a “full” case write-up?
  - Rare pathology
  - Striking histopathology
  - Radiology images
  - Physical exam findings
  - Other specimens
- Potential Submission Venues:
  - NEJM
  - JGIM
  - AJM
  - (Annals)
  - BMJ Case Reports

CLINICAL PRACTICE

Clinical Images

"If You Prick Us, Do We Not Bleed?": An Uncommon Cause of Xanthochromia

Avital Y. O'Glasser, MD, FACP and André M. Mansoor, MD

Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, Portland, OR, USA.

KEY WORDS: xanthochromia; hyperbilirubinemia; lumbar puncture; CSF analysis; subarachnoid hemorrhage; drug-induced liver injury.
J Gen Intern Med 30(6):853-4
DOI: 10.1007/s11606-015-3210-0

A 50-year-old man presented with amoxicillin-induced cholestatic liver injury with resultant dialysis-dependent acute kidney injury. Total bilirubin ranged from 30 to 33 mg/dL, AST/ALT 200 to 400 U/L, and alkaline phosphatase from 3,000 to 4,000 U/L.

Because of fever and delirium, lumbar puncture (LP) was performed on hospital day 30 after normal head imaging. Moderate xanthochromia was immediately visualized after a non-traumatic tap. Analysis revealed RBC 1/cu mm, WBC 1/cu mm, minimally elevated protein (50 mg/dL), and normal glucose (82 mg/dL).

Xanthochromia, "blond color" in Greek,[1] is caused by pigment in the cerebral spinal fluid (CSF). Xanthochromia is classically associated with subarachnoid hemorrhage (SAH): red blood cells lyse within hours and are metabolized from oxyhemoglobin (pink) to bilirubin (yellow). Xanthochromia is present in >90 % of patients with a SAH within 12 h of onset,[1–3] but can also occur with increased CSF protein (≥150 mg/dL) due to bilirubin binding, traumatic LP with delayed analysis, and serum hyperbilirubinemia (>10–15 mg/dL), which was the most likely cause in this case.[1,2,4] Literature suggests an association between CSF and serum bilirubin levels but not the duration of hyperbilirubinemia.[5] Spectrophotometry can be used to identify bilirubin with or

Fig. 1 CSF vials after lumbar puncture, with the hallmark blond color of xanthochromia.

CLINICAL PRACTICE

Clinical Images

Recurrent Melanoma Presenting as a Very Large Cardiac Mass with Concurrent Pancreatic Involvement

Avital Y. O'Glasser, MD[1] and Rebecca R. Sauerwein, BS[2,3]

[1]Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, Portland, OR, USA; [2]School of Medicine, Oregon Health & Science University, Portland, USA; [3]Department of Pathology, Oregon Health & Science University, Portland, USA.

KEY WORDS: melanoma; cardiac mass; cardiac tumor; metastatic melanoma.
J Gen Intern Med 29(11):1557–8
DOI: 10.1007/s11606-014-2853-6

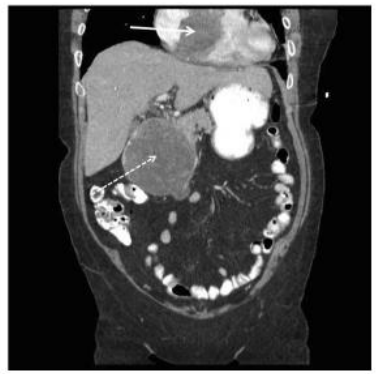


Figure 1. Abdominal CT demonstrating a large, heterogenous soft tissue mass of the pancreatic head (dashed arrow) and a large, hypodense cardiac mass (solid arrow).

A 59-year-old Caucasian woman was diagnosed with a right shoulder 2.0 mm deep, Clark's Level IV melanoma (stage T2aN0/IB), 2.5 years prior. She underwent wide-excision and surgical staging with negative lymph nodes. She did not receive whole-body imaging or adjuvant therapy.

She returned with two weeks of episodic syncope, exertional dyspnea, and epigastric pain. Abdominal computed tomography (CT) revealed a large pancreatic head mass and a right-sided cardiac mass (Fig. 1). She soon developed right heart failure and acute cardiogenic shock, which ultimately led to death.

Received December 17, 2013
Revised February 24, 2014
Accepted March 19, 2014
Published online May 10, 2014

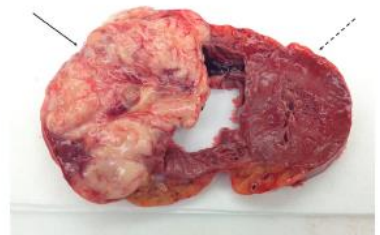


Figure 2. Cross-section of the heart at autopsy, with transmural involvement of the right ventricle free wall by the large mass (solid arrow). Concentric left ventricular hypertrophy (LVH) is also seen (dashed arrow).

Autopsy revealed a 10.8×8×7 cm tan, focally necrotic transmural right ventricular (RV) mass (Fig. 2) and a 13×8×6 cm pancreatic head mass. Immunohistochemistry staining was negative for typical melanoma markers, but eventually stained positive for SOX-10.

Melanoma has one of the highest rates of cardiac metastasis; autopsy series identify cardiac metastases in 50–70 % of patients with metastatic melanoma.[1] The majority are small and disseminated, although discrete masses up to 7–8 cm are reported.[2–4] Because cardiac melanoma usually occurs in the setting of diffusely disseminated disease, treatment options are often limited.

This case highlights that cardiopulmonary symptoms in a patient with a history of melanoma should raise concern for recurrent disease involving the heart.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

Corresponding Author: *Avital Y. O'Glasser, MD; Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, BTE 119, Portland, OR 97239, (e-mail: oglasser@ohsu.edu).*

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Images in...

OPEN ACCESS

Mitral Stenosis

Andrew C Oehler, Peter D Sullivan, André Martin Mansoor

Department of Internal Medicine, Oregon Health & Science University, Portland, Oregon, USA

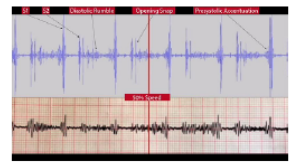
Correspondence to
Dr André Martin Mansoor, mansooan@ohsu.edu

Accepted 30 March 2017

DESCRIPTION

A previously healthy 29-year-old Mexican woman presented to an emergency department with transient hemiparaesthesias and dysarthria. There was no evidence of stroke on cross-sectional imaging of the head, and she was discharged without a clear diagnosis. Two days later, she returned with acute abdominal pain. Abdominal imaging revealed complete occlusion of the right renal artery, prompting emergency embolectomy. Following the procedure, she developed acute haemoptysis, dyspnoea and hypoxaemia. Chest imaging demonstrated evidence of pulmonary venous hypertension. Cardiac auscultation revealed an opening snap followed by a diastolic murmur with presystolic accentuation. These sounds were better appreciated in combination with phonocardiography, a technique supplanted by echocardiography in the 1970s[1] that visualised heart sounds (video 1). An echocardiogram confirmed the presence of mitral stenosis (MS), unifying the syndrome of embolic phenomena, haemoptysis and pulmonary hypertension. She underwent successful mitral valve replacement and has since returned to normal activities.

Despite the advances in developed countries, rheumatic heart disease remains the most common cause of MS worldwide. Early manifestations include dyspnoea and fatigue, but occasionally embolic phenomena are part of the initial presentation. Definitive diagnosis can be made with echocardiography, but careful cardiac auscultation remains an important step in the diagnostic pathway when any of the following four signs are present: (1) pronounced S1, (2) early diastolic opening snap, (3) rumbling diastolic murmur at the apex using the bell and (4) presystolic accentuation of the murmur.[2] In this case, phonocardiography was used to facilitate recognition of these signs.



Video 1 Audio of the heart sounds combined with phonocardiography (top phonocardiogram from a contemporary electronic stethoscope, bottom from a mid-20th century antique phonocardiograph), recorded over the apex of the heart demonstrating: (1) an abrupt, high amplitude S1, (2) an opening snap, (3) the low rumbling diastolic murmur of MS and (4) presystolic accentuation of the murmur.

Learning points

- Mitral stenosis due to rheumatic heart disease can present with embolic phenomena even in the absence of underlying atrial fibrillation.
- Diastolic murmurs can be difficult to detect, but in the adult population carry a relatively narrow differential diagnosis of primarily aortic insufficiency and mitral stenosis.
- Phonocardiography remains useful today as a learning tool to aid in the appreciation of heart sounds.

Contributors PDS captured the audio of the heart sounds. AMM captured the phonocardiogram using the antique phonocardiograph. ACO created the video combining the heart sounds audio with the phonocardiograms. ACO, PDS and AMM were involved in writing the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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To cite: Oehler AC, Sullivan PD, Mansoor AM. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220120

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JGIM

CLINICAL PRACTICE

Clinical Images

Urinothorax: A Rare Case of Pleural Effusion

Kathryn Wunderle, M.D.[1], Sull Kim, M.D., Ph.D.[1,2,3], and Joseph Chiovaro, M.D.[1,3]

[1]Department of General Internal Medicine, Oregon Health & Science University, Portland, OR, USA; [2]Section of Pulmonary and Critical Care Medicine, VA Portland Health Care System, Portland, OR, USA; [3]Division of Hospital and Subspecialty Medicine, VA Portland Health Care System, Portland, OR, USA.

KEY WORDS: clinical image; pulmonary diseases; urology.
J Gen Intern Med 32(9):1058–9
DOI: 10.1007/s11606-017-4032-z

A 71-year-old male presented with two weeks of nausea, vomiting, abdominal pain, and difficulty urinating. He denied shortness of breath or chest pain. Vital signs were normal. Laboratory tests were notable for a potassium of 7 mmol/l, BUN 176 mg/dl, and creatinine 17.6 mg/dl. A CT scan of his abdomen demonstrated a profoundly distended bladder with bilateral hydronephrosis and left calyceal rupture (Fig. 1). A chest x-ray revealed a large left-sided pleural effusion (Fig. 2). A Foley catheter was placed and drained 3.7 liters of urine, after which the patient's laboratory tests rapidly normalized. Urinothorax was suspected, and follow-up imaging was arranged. On repeat CT 6 weeks later, the effusion had resolved.

Urinothorax, or urine in the pleural space, is a rarely reported complication of bilateral urinary obstruction or trauma to the urinary tract. There are fewer than 100 reported cases in the literature, although it may be underdiagnosed because of low clinical suspicion.[1] Patients typically have only minor respiratory symptoms and are often diagnosed clinically, with an effusion that improves after the obstruction or urinary tract injury has resolved.[1] If performed, thoracentesis reveals a transudative fluid that smells of urine with a low pH (<7.3) and a fluid/serum creatinine ratio >1.

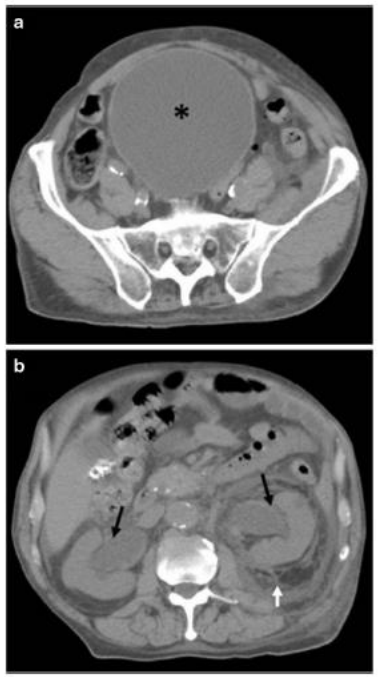


Figure 1 Markedly distended bladder (*asterisk*, panel a), bilateral hydronephrosis (*black arrows*, panel b), and fat stranding consistent with left calyceal rupture (*white arrow*, panel b)

A Couple's Colitis

David Phillip Serota, MD, Stephanie Halvorson, MD, and Sima Desai, MD

Department of Medicine, Oregon Health and Science University, Portland, OR, USA.

KEY WORDS: Infectious disease; Gastroenterology; Public health; Infectious diarrhea; Colitis.
J Gen Intern Med 30(12):1889–90
DOI: 10.1007/s11606-015-3292-8

A 32-year-old woman was admitted with 4 days of bloody diarrhea, abdominal pain, leukocytosis, and fever following fast food consumption and use of methamphetamine. An abdominal CT scan revealed continuous colonic mural thickening from the cecum to the splenic flexure (Fig. 1). Stool cultures for bacteria, ova and parasites, and fecal leukocytes were negative. Her symptoms resolved with supportive care, and on the day of discharge, her partner presented with identical symptoms (Fig. 2). His stool cultures grew shiga toxin 2-producing *E. coli*, serogroup O157:H7 (STEC). Based on his positive stool culture and the presence of diffuse colitis on both scans, a final diagnosis of STEC was given to both patients.

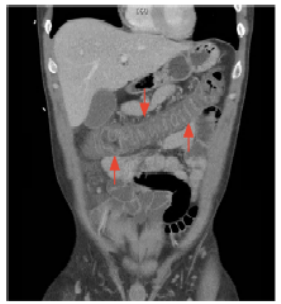


Fig. 2 Coronal section of abdominal CT scan of the man (first patient's partner), with arrows demonstrating colonic mucosal thickening with fat stranding at the transverse colon, consistent with colitis.

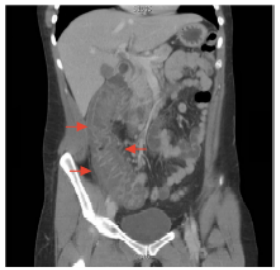


Fig. 1 Coronal section of abdominal CT scan of the woman (first patient), with arrows demonstrating colonic mucosal thickening with fat stranding at the ascending colon, consistent with colitis.

STEC is a common cause of hemorrhagic colitis, usually occurring in food-borne outbreaks. Among patients diagnosed with STEC, 6 % subsequently develop hemolytic uremic syndrome.[1] Microbiologic detection of STEC is highly dependent on obtaining stool cultures within 6 days of symptom onset, and the presence of fecal leukocytes indicates a higher yield sample.[2] The gold standard for diagnosis is stool culture on sorbitol MacConkey agar, followed by latex agglutination. ELISA, direct toxin assays, and toxin PCR methods all provide rapid diagnosis, with comparable sensitivity and specificity (77–96 % sensitivity, 98–99 % specificity).[3]

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

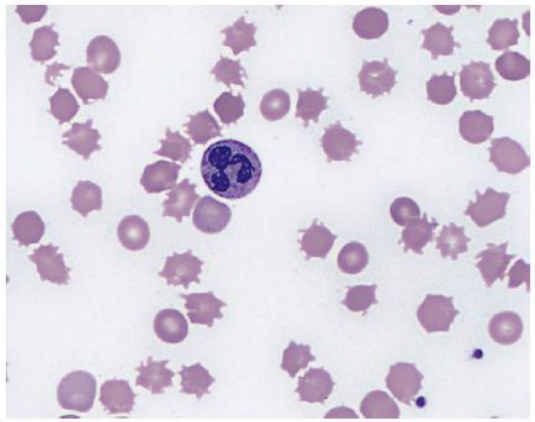
Corresponding Author: *David Phillip Serota, MD; Department of Medicine, Oregon Health and Science University, Portland, OR, USA (e-mail: serota@ohsu.edu).*

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Chana A. Sacks, M.D., *Editor*

Spur-Cell Anemia



Kaleb Keyserling, M.D.
Steven Koprowski, M.D.

Oregon Health and Science University
Portland, OR
keyserli@ohsu.edu

A 31-YEAR-OLD MAN WITH A HISTORY OF CIRRHOSIS, RECURRENT HEPATIC encephalopathy, and anemia presented to the emergency department with confusion. He was found to be encephalopathic, and his hemoglobin level was 6.7 g per deciliter (previous measurement, 9.0 g per deciliter). Additional laboratory tests revealed an elevated indirect bilirubin level of 11.4 mg per deciliter (194 μmol per liter), an elevated lactate dehydrogenase level, and an undetectable haptoglobin level. An evaluation for infection was unrevealing, and no evidence of bleeding was found. A peripheral-blood smear showed numerous acanthocytes (or spur cells), a finding consistent with spur-cell anemia, a form of hemolytic anemia that can occur in patients with decompensated cirrhosis. Spur cells acquire spiny projections on their surfaces as a result of altered lipid metabolism and an excess of cholesterol in patients with cirrhosis; these changes make the erythrocytes inflexible and prone to hemolysis. Acanthocytes are often confused with echinocytes (or burr cells), which have more regularly spaced spicules. Spur-cell anemia is associated with a poor prognosis and is definitively treated by liver transplantation; however, this patient was not considered to be a candidate for liver transplantation because of his ongoing use of alcohol. He remained encephalopathic, and his anemia did not resolve despite blood transfusions. The patient was ultimately discharged home, where he received hospice care; he died 2 weeks later.

DOI: 10.1056/NEJMicm1714572

Received: 26 March 2018 | Revised: 11 June 2018 | Accepted: 26 June 2018
DOI: 10.1002/ccr3.1723

CLINICAL IMAGE

WILEY Clinical Case Reports

Exaggerated arthropod assault: Eosinophilic dermatosis in a patient with small lymphocytic lymphoma

Curtis Lachowiez[1] | **Kevin White**[2] | **Stephen Spurgeon**[3]

[1]Department of Internal Medicine, Oregon Health and Science University, Portland, Oregon
[2]Department of Dermatology, Oregon Health and Science University, Portland, Oregon
[3]Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon

Correspondence: Curtis Lachowiez, Department of Internal Medicine, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (lachowie@ohsu.edu).

Key Clinical Message

Dermatologic reactions are commonly encountered in clinical practice. Providers must be aware of both the common and uncommon etiologies leading to these eruptions, particularly in patients with underlying malignancies. Establishing the appropriate etiology directs treatment of these conditions, which may be therapy directed at the malignancy itself.

KEYWORDS

arthropod bite, chronic lymphocytic leukemia, eosinophilic dermatosis, leukemia, skin eruption

1 | INTRODUCTION

Cutaneous manifestations of systemic disease are common and provide valuable clinical information to aid clinicians in the diagnosis of the underlying etiology. A subset of these eruptions known as eosinophilic dermatoses are often seen in patients with underlying hematological malignancies. Here, we present a case of a patient with an eosinophilic dermatosis and discuss the differential diagnosis, clinical course, histological findings, and approach to treatment.

2 | CASE PRESENTA

A 66-year-old man from rural Ore
intermediate-risk untreated small ly
(SLL) presented with an erythematou
of his right hand and progressive, pru
ules over his neck and arms (Figure 1
gression of cervical and axillary ader
there was no evidence of disease pr
SLL-directed therapy. The patient de
to topical agents, detergents, or medi

recent travel but spent much of his time outdoors in wooded areas. He denied any history of insect bites or exposures. His complete blood count revealed normal lymphocyte numbers although reactive lymphocytes were noted (1.15 K/cu mm). There was no eosinophilia. Erythrocyte sedimentation rate (ESR) was mildly prolonged at 40 mm/h. A comprehensive metabolic panel was normal.

His history of spending prolonged periods of time spent outside raised the suspicion of a type IV hypersensitivity dermatitis to an arthropod exposure, and he was empirically prescribed doxycycline, antihistamines, a short course of oral prednisone (1 mg/kg × 5 days), and intermediate strength

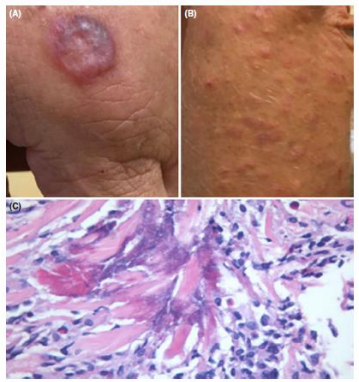


FIGURE 1 Gross (Panel A, B) and histologic (Panel C) findings in this patient with a malignancy associated with eosinophilic dermatosis due to arthropod exposure. Panel C demonstrates flame figures resulting from eosinophilic degranulation

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Anemia in Scurvy

Jeffrey Y. Bien, MD[1], *Richie Hegarty, MD*[1], *and Brian Chan, MD, MPH*[2]

[1]Department of Medicine , Oregon Health & Science University, Portland, OR, USA; [2]Division of General Internal Medicine & Geriatrics, Oregon Health & Science University, Portland, OR, USA.

KEY WORDS: scurvy; anemia; disparity; deficiency.

J Gen Intern Med
DOI: 10.1007/s11606-018-4597-1

ANEMIA IN SCURVY

A 60-year-old man from rural Oregon was admitted with symptomatic anemia, progressive, bilateral, dependent-leg ecchymoses (Fig. 1), and knee arthropathy. Physical exam revealed "corkscrew hairs," most distinctively on his shoulder (Fig. 2). A social history was notable for limited financial resources and a longstanding diet consisting solely of toast, boxed macaroni and cheese, and canned tuna.

Following administration of vitamin C, the patient's hematocrit stabilized. The serum vitamin C level from admission returned undetectable, confirming a diagnosis of scurvy. Upon discharge, he received dietary counseling and a multivitamin prescription.

Scurvy is caused by dietary deficiency of vitamin C, a key cofactor for collagen enzymes. It is the only known acquired connective-tissue disorder that is not immune-mediated. Anemia in scurvy can result from vascular fragility and subsequent subcutaneous hemorrhage and hemarthrosis.[1] Other features include gingivitis, myalgias, mood changes, perifollicular hemorrhage, occult gastrointestinal hemorrhage, and delayed wound healing. First described in 1753, scurvy is now rarely diagnosed in developed countries.[2] However, even in developed countries, associations between scurvy and low-income status persist.[3, 4] As in our case, the acute presentation of scurvy can mimic an acquired coagulopathy. A careful history and physical exam may preclude a costly workup and expedite treatment.

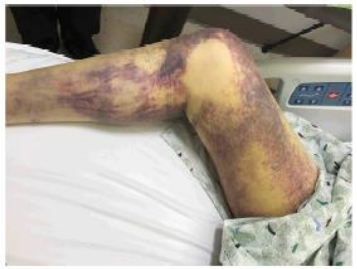


Figure 1 Painful, dependent ecchymoses and arthropathy of bilateral lower extremities from hemorrhage tracking along fascial planes.

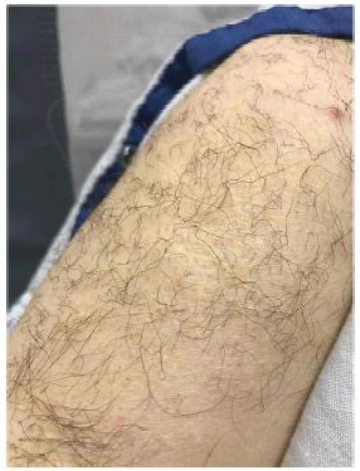


Figure 2 Patient's body hair (shown: right shoulder) growing in a distinctive "corkscrew" or "kinked" pattern.

Received March 9, 2018
Revised May 22, 2018
Accepted July 13, 2018

Corresponding Author: *Jeffrey Y. Bien, MD; Department of Medicine Oregon Health & Science University, Portland, OR, USA (e-mail: bien@ohsu.edu).*

Images in...

OPEN ACCESS

Friedreich's sign

Brook Pittenger, Peter D Sullivan, André Martin Mansoor

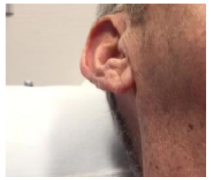
Department of Internal Medicine, Oregon Health and Science University, Portland, Oregon, USA

Correspondence to
Dr André Martin Mansoor, mansooan@ohsu.edu

Accepted 25 September 2018

DESCRIPTION

An 82-year-old man with chronic atrial fibrillation treated with anticoagulation was admitted to the hospital for subacute progressive exertional dyspnoea. On examination, the jugular venous waveform was elevated to the mandibular angle with the patient sitting upright. Heart sounds were muffled. Transthoracic echocardiography (TTE) revealed a large circumferential pericardial effusion with early tamponade physiology. Pericardiocentesis yielded a large volume of sanguineous fluid. Following the procedure, there was improvement in jugular venous pressure to 14 cm H_2O. The height of the waveform increased with inspiration (Kussmaul's sign) and there was a prominent y descent, known as Friedreich's sign (see video 1). Repeat TTE revealed thickened pericardium, early diastolic septal bounce and respirophasic changes in early diastolic filling consistent with constrictive pericardial physiology. Friedreich's sign is a physical finding of constrictive pericarditis. The normal jugular venous waveform contains two descents, x and y. The x descent, which corresponds to the combination of right atrial relaxation and depression of the atrial floor during ventricular contraction, is normally dominant. The y descent occurs as a result of passive ventricular filling during early diastole and is usually absent in patients with tamponade. In constrictive pericarditis, the characteristic sharp and deep y descent reflects rapid filling in early diastole which occurs when the unyielding pericardium elevates atrial pressure and limits ventricular filling to the early diastolic period. This patient was managed with diuretics, and the constrictive physiology resolved over a period of weeks. The aetiology of transient pericardial disease in this case was not definitively determined. Virtually any cause of acute pericarditis can lead to constriction which usually develops months to years later as a result of irreversible pericardial fibrosis. In some cases, particularly in association with tamponade, transient acute constriction may ensue for days to weeks following the initial pericardial insult as a result of reversible inflammation and oedema.[1–3]



Learning points

- Friedreich's sign, originally coined *Friedreich's diastolic collapse of the cervical veins*, describes a sharp and deep y descent of the jugular venous waveform. It can be a clue to the diagnosis of constrictive pericarditis.
- Preservation of both the x and y descents of the jugular venous waveform in patients with constrictive pericarditis is a distinguishing feature from cardiac tamponade, in which the y descent is typically absent.
- Transient constrictive pericarditis is characterised by an acute decrease in pericardial compliance due to inflammation and oedema, in contrast to the irreversible chronic fibrocalcific changes of classic constrictive pericarditis.

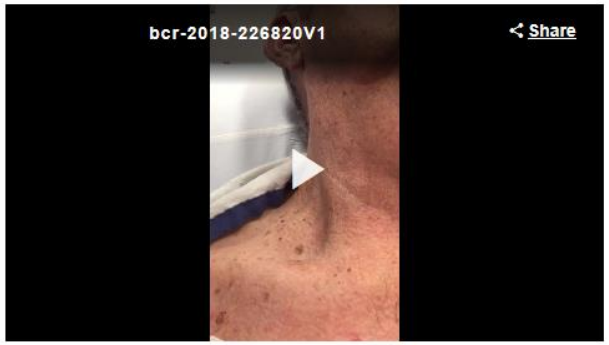
Contributors AMM recorded the clinical video. BP, PDS and AMM were involved in writing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Check for updates

To cite: Pittenger B, Sullivan PD, Mansoor AM. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-226820

BMJ



Video 1

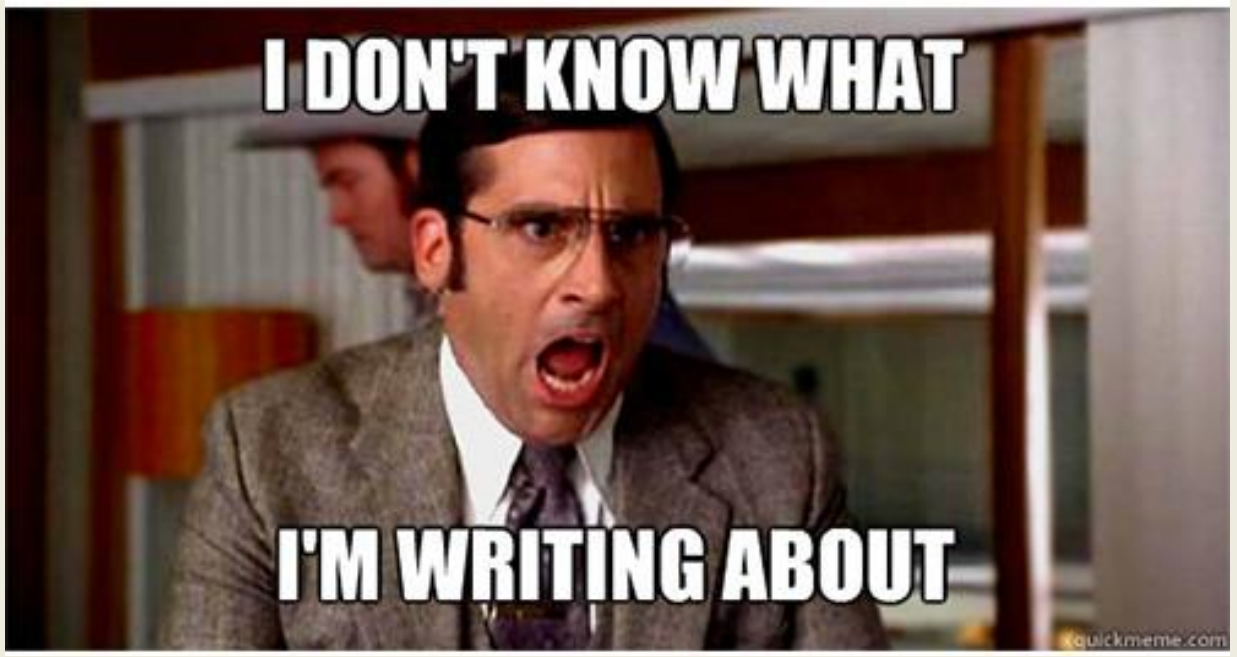
Friedreich's sign: the prominent y descent of the jugular venous waveform seen with constrictive pericarditis.

CLINICAL CASES/CASE REPORTS

- What it is?
  - Longer case presentation
  - May include a “review of the literature” of other cases reports
  - Involves some level of discussion (literature review) about the diagnosis
  - Clear teaching points
  - Do you have available images/visuals?
- Potential Submission Venues:
  - NEJM
  - JGIM
  - AJM
  - BMJ Case Reports
  - Subspecialty journals
  - Outline “only” journals?

APPROPRIATE CASE SELECTION

- Rare? Rare and "neat"?
- Rare but important?
  - Confabulation NOT causes by Wernicke's
- Common but atypical presentation?
  - Cdiff presenting with WBC > 100K concerning for tumor lysis syndrome
- Rare but mimics something common?
  - Beta-blocker rebound Takotsubo's looking like afib/tachycardia mediated CMP
- Not rare but mistaken for something else common (HEURISTICS)?
  - Postpartum "anxiety" → pheochromocytoma
- Intersection of diagnoses?
  - Thyrotoxicosis and methamphetamine use
- Management (including ethical) challenges or complications?
  - Surgical candidacy in recurrent endocarditis with active fungemia



- *Is it a completely NEW diagnosis???*

Respiratory Medicine Case Reports 21 (2017) 27–29

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Invasive aspergillosis related to ibrutinib therapy for chronic lymphocytic leukemia

Benjamin Arthurs, MD [a, b, *], Kathy Wunderle, MD [b], Maylee Hsu, MD [c], Suil Kim, MD, PhD [a, b]

[a] Division of Pulmonary & Critical Care Medicine, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States
[b] Department of Medicine, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States
[c] Department of Pathology, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States

ARTICLE INFO

Article history:
Received 2 January 2017
Received in revised form
15 March 2017
Accepted 19 March 2017

Keywords:
Aspergillus
Invasive aspergillosis
Ibrutinib
Bruton's tyrosine kinase
Chronic lymphocytic leukemia

ABSTRACT

We report a case of invasive pulmonary aspergillosis in a patient taking ibrutinib, a Bruton's tyrosine kinase inhibitor used to treat refractory chronic lymphocytic leukemia. We hypothesize that ibrutinib promoted this infection by suppressing innate immune responses against *Aspergillus*. Clinicians should be aware of potential *Aspergillus* infections in patients treated with this drug.

1. Introduction

Ibrutinib is a novel anti-cancer drug recently approved for the treatment of refractory chronic lymphocytic leukemia (CLL) [1] and other B-cell cancers [2,3]. Ibrutinib selectively inhibits Bruton's tyrosine kinase (BTK), a key enzyme that promotes the survival and proliferation of normal B cells and CLL cells downstream of B-cell receptor activation [4]. Treatment with ibrutinib has not been previously reported to promote invasive *Aspergillus* infections in non-neutropenic patients.

2. Case report

A 62-year-old man was admitted to our hospital with three weeks of non-productive cough, dyspnea, fatigue, and anorexia. He had started ibrutinib six weeks prior to admission for relapsed CLL. He was retired and lived in western Oregon. He reported no exposure to tobacco, dust, birds, or other animals. His tuberculin skin test was negative prior to initiation of ibrutinib. On examination, the patient was afebrile (36.7 C); pulse was 66/min; BP was 82/52 mm Hg; respiratory rate 16/min; and oxygen saturation 96% on room air. Cardiopulmonary examination was normal. Laboratory investigations revealed anemia (Hgb 5.0 g/dL), leukocytosis (21.2 × 10^3/μl), decreased platelets (140 × 10^3/μl), and a normal neutrophil count (1.91 × 10^3/μl). Serum chemistries were notable for a sodium of 129 mmol/L, chloride of 97 mmol/L, bicarbonate of 17 mmol/L, urea nitrogen of 26 mg/dL, and creatinine of 1.2 mg/dL.

Computed tomography scan of the lung showed multifocal upper lobe centrilobular nodules, patchy consolidations with air bronchograms, and small areas of cavitation (Fig. 1A), findings that were not present prior to ibrutinib initiation. Bronchoscopy revealed endobronchial masses in the lingula and right upper lobe (Fig. 1B). Biopsy of the masses showed necrotic mucosa containing septate fungal hyphae with acute angle branching.

Abbreviations list: BAL, Bronchoalveolar lavage; BTK, Bruton's tyrosine kinase; CLL, Chronic lymphocytic leukemia; TLR, Toll-like receptor.

* Corresponding author. 3181 SW Sam Jackson Park Rd, Mail Code UHN67, Portland, OR 97239, United States.
E-mail address: arthurs@ohsu.edu (B. Arthurs).

DIAGNOSTIC DILEMMA
Thomas J. Marrie, MD, Section Editor

THE AMERICAN JOURNAL of MEDICINE

A Greener Oregon: Acute Inpatient Delirium

Christopher Fine, MD,[a] Brittany Kishel, MD,[a] Avital Y. O'Glasser, MD,[b] Sima S. Desai, MD[b]
[a]Department of Medicine, [b]Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, Portland.

PRESENTATION

A visitor brought an innovative gift to a hospitalized 49-year-old man and thus helped complicate his recovery. The patient presented with acute-on-chronic left hip pain in the setting of known osteomyelitis. His medical history also included coronary artery disease, type 2 diabetes mellitus, and chronic hepatitis C without cirrhosis. Intravenous antibiotics were started, and he was taken to the operating room for debridement and arthroplasty on hospital day 2. He remained an inpatient for long-term intravenous antibiotic therapy and initially had an uneventful postoperative course.

However, on hospital day 13, the patient was found to be somnolent during late morning teaching rounds. This change in mental status was initially attributed to an overnight increase in his zolpidem dosage, the only recent significant medication change. Because he remained easily arousable and responsive to questions, we allowed him to sleep and reassessed him after rounds were complete. By the afternoon, however, he became unresponsive, prompting further evaluation.

ASSESSMENT

On examination, the patient's temperature was 97.5°F (36.4°C), his heart rate was 79 beats per minute, his blood pressure was 94/55 mm Hg, his respiratory rate was 6 breaths per minute with apneic episodes lasting up to 30 seconds, and his oxygen saturation was 95% on room air (Figure 1). Though the patient was initially unresponsive to verbal stimuli and sternal rub, he became more alert after several minutes and was oriented to self and place but not to time or situation. His responses were slow with slurred speech.

The patient's pupils measured 4 mm bilaterally and were minimally reactive to light. Although his tone was normal, his reflexes were sluggish, without asterixis or nuchal rigidity. Results from the remainder of the neurologic examination were normal. Inspection of the surgical incision site was reassuring: there was no erythema, tenderness, fluctuance, or drainage. A capillary blood glucose level was gauged at 347 mg/dL. Testing was repeated a few minutes later after more thorough cleansing of the patient's fingertips. The second attempt yielded a result of 110 mg/dL.

A venous blood gas level was significant for respiratory acidosis with a pH of 7.35, partial pressure of carbon dioxide of 53 mm Hg, and bicarbonate of 28 mEq/L. Laboratory data revealed a creatinine level of 1.88 mg/dL; 12 hours earlier, it had been 0.81 mg/dL. Plasma creatine phosphokinase was documented at 45 U/L, and a new mild leukocytosis (12.4 × 10^3 cells/mm^3) was recorded without a change in hematocrit. A bladder scan showed >1000 mL of retained urine. Despite the patient's initial refusal to attempt to urinate or be catheterized, a sample was obtained, and the results of a urinalysis were normal. Noncontrast computed tomography of the head was negative for an acute intracranial process.

DIAGNOSIS

While we contemplated the next diagnostic steps, a packet of aluminum foil containing partially consumed brownies was noted on the patient's bedside table. Concern was raised for the possibility that he had ingested a toxin: particularly marijuana. Although his admission urine drug screen was negative, a repeat assay was ordered based on our suspicions. The test was positive for cannabinoids. Given the likelihood of cannabis-induced acute delirium, additional testing was not pursued, and supportive care was implemented.

Acute delirium is a common problem encountered in the hospital. The differential diagnosis includes sleep—wake cycle disturbances, metabolic disorders, systemic illness, and a response to hospital-administered medications (Figure 2). Artificial hyperglycemia, dispelled after cleansing the patient's finger of residue from his illicit

Funding: None.
Conflict of Interest: None.
Authorship: All authors had access to the presented data and a role in this manuscript.

Requests for reprints should be addressed to Avital Y. O'Glasser, MD, Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code BTE 119, Portland, OR 97239.
E-mail address: oglassea@ohsu.edu

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2016.11.012

CLINICAL PRACTICE
Clinical Vignettes

Cotton Fever: Does the Patient Know Best?

Yingda Xie, MD[1], Bailey A. Pope, MD[2], and Alan J. Hunter, MD, FACP[2]
[1]National Institutes of Health, Bethesda, MD, USA; [2]Department of Medicine, Oregon Health & Science University, Portland, OR, USA.

Fever and leukocytosis have many possible etiologies in injection drug users. We present a case of a 22-year-old woman with fever and leukocytosis that were presumed secondary to cotton fever, a rarely recognized complication of injection drug use, after an extensive workup. Cotton fever is a benign, self-limited febrile syndrome characterized by fevers, leukocytosis, myalgias, nausea and vomiting, occurring in injection drug users who filter their drug suspensions through cotton balls. While this syndrome is commonly recognized amongst the injection drug user population, there is a paucity of data in the medical literature. We review the case presentation and available literature related to cotton fever.

KEY WORDS: cotton fever; drug abuse; case report; intravenous drug abuse.
J Gen Intern Med 31(4):442–4
DOI: 10.1007/s11606-015-3424-1

Injection drug use is associated with many infectious and non-infectious complications. The most common associated complications faced by managing physicians are soft-tissue infections, overdose, intoxication, and withdrawal.[1] A frequent and challenging triage dilemma in this population is that of fever with active injection drug use. Despite numerous unsuccessful attempts to develop discriminating decision rules to guide ambulatory triage in these cases, clinicians are still unable to reliably exclude occult infections such as endocarditis and osteomyelitis.[2,3] This often results in short-term hospitalization of these patients, with accrual of health care expenditures.[4] An infrequently recognized cause of fever in injection drug users is cotton fever, a poorly characterized systemic febrile inflammatory syndrome seen in this population. Ironically, while there is a paucity of literature and awareness in the medical community, cotton fever is a well-recognized syndrome amongst injection drug users. Originally coined in 1975, cotton fever was described as a benign self-limited febrile syndrome occurring in injection drug users who filtered their drug suspensions through cotton balls.[5] We present a case of presumed cotton fever in an active injection heroin user, in whom the diagnosis was only considered upon hearing the patient reference the syndrome after substantial workup had been completed. Additionally, a review of the medical literature and a discussion of the current theories about the pathophysiology of cotton fever are presented.

Key Points
- *Cotton fever is a benign febrile illness characterized by acute onset fever and leukocytosis, occurring immediately following intravenous drug injection.*
- *In addition to fever and leukocytosis, patients with cotton fever can exhibit shortness of breath, chills, headache, myalgia, abdominal pain, nausea, vomiting and tachycardia.*
- *Cotton fever is a diagnosis of exclusion, and likely has a higher prevalence than previously thought.*

Received May 7, 2014
Revised November 12, 2014
Accepted April 30, 2015
Published online June 24, 2015

CASE REPORT

A 22-year-old woman presented to an outside hospital 4 hours after developing acute onset of fevers, headache, abdominal pain and radiating back pain, which began 20 minutes after injecting heroin. She did not endorse any visual symptoms, chest pain, dyspnea, or rashes. Initial vital signs were notable for a temperature of 39°C and heart rate of 102 beats per minute. At the time, the remainder of her exam was reported as normal except for diffuse abdominal tenderness. In the setting of acute back pain, a lumbar spine MRI was obtained and interpreted as consistent with an L3-S2 epidural abscess. Blood cultures were drawn, and the patient was started on vancomycin and ceftriaxone. Twelve hours after initiation of symptoms, the patient was transferred to our institution for consideration of neurosurgical intervention for presumed epidural abscess. By the time of arrival, the patient's fever had resolved and her abdominal pain had improved. On examination, her heart rate was 101 beats per minute, blood pressure was 106/64 mmHg, and temperature was 37.6 °C. Her cardiac exam revealed a II/VI systolic crescendo-decrescendo murmur best heard at the left lower sternal border. Her abdomen was diffusely tender without peritoneal signs, and she exhibited lower back allodynia. She had numerous new and old injection tracks on her arms, but no other rashes or stigmata of endocarditis. Her fundus exam revealed a clear vitreous without hemorrhages or Roth spots. Her neck was supple and her pulmonary and neurologic examinations were unremarkable.

On transfer, the patient had a white blood cell count of 22.6×10^9/L without a left shift; the remainder of her laboratory values; including chemistries, urinalysis and cerebrospinal fluid, were all normal. Blood cultures were redrawn and she was continued on broad-spectrum antibiotics. A transthoracic echocardiogram showed no evidence of vegetations and only trace tricuspid insufficiency. Her original MRI was

MODERN RHEUMATOLOGY CASE REPORTS, 2018
VOL. 2, NO. 1, 33–38
https://doi.org/10.1080/24725625.2017.1351049

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CASE REPORT

Catastrophic antiphospholipid syndrome in a patient with systemic sclerosis and hereditary angioedema: case report and literature review

Jean Liew[a], Marcia Friedman[b], Sima Desai[a], Lindsay Taute[c], Nastaran Neishaboori[c], Peter Stenzel[c] and Ajay Wanchu[b]

[a]Department of Medicine, Oregon Health and Science University, Portland, OR, USA; [b]Division of Arthritis and Rheumatic Disease, Oregon Health and Science University, Portland, OR, USA; [c]Department of Pathology, Oregon Health and Science University, Portland, OR, USA

ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) is a rare form of the antiphospholipid syndrome (APS) in which microvascular thrombotic events cause rapidly progressive multiorgan dysfunction. We describe a case of CAPS presenting in a patient with suspected systemic sclerosis (SSc) and hereditary angioedema (HAE), and conduct a literature review to examine the reported cases of CAPS in individuals with SSc. Two reported cases of APS occurring with HAE were also found. In CAPS, there may be multiple thrombi in the microvasculature of any organ, most commonly in the intra-abdominal viscera. Patients rapidly develop multiorgan dysfunction or failure. Diagnosis is partly based upon the presence of positive antiphospholipid antibodies. The recommended therapy is systemic anticoagulation, high-dose corticosteroids, and plasma exchange with or without the addition of intravenous immunoglobulin. Given the high mortality rate of CAPS, urgent diagnosis and treatment are necessary to attempt to halt the progression of multiorgan failure.

ARTICLE HISTORY
Received 22 May 2017
Accepted 22 June 2017

KEYWORDS
Scleroderma; systemic sclerosis; antiphospholipid antibody syndrome; catastrophic antiphospholipid antibody syndrome; hereditary angioedema

Introduction

The antiphospholipid syndrome (APS) refers to the development of venous and/or arterial thromboses and pregnancy complications in the presence of positive antiphospholipid antibodies (APLAs) [1,2]. Catastrophic antiphospholipid syndrome (CAPS) is a rare form in which microvascular thrombotic events cause rapidly progressive multiorgan dysfunction, leading to mortality rates of around 50% [3]. Systemic sclerosis (SSc) is a connective tissue disorder characterised by autoantibody development, vasculopathy, and fibrosis. Overlap syndromes between SSc and other connective tissue or autoimmune diseases have been described, although that of CAPS and SSc is rarely reported [4,5]. Hereditary angioedema (HAE) has also been shown to be associated with autoimmune conditions [6]. We describe a case of CAPS in a patient with suspected SSc and HAE, and perform a literature review identifying the reported cases of CAPS in individuals with SSc or HAE.

Case report

A 37-year-old Native American woman was admitted with acute abdominal pain, vomiting, and diarrhoea. She had no known exposure to potentially infectious foods or animals, nor had she recently travelled, been hospitalised, or received antibiotics. Her past medical history was significant for HAE, suspected diffuse cutaneous systemic sclerosis (dcSSc), and hypertension. She had been diagnosed with HAE as a child, and had had multiple gastrointestinal exacerbations of angioedema. Recent laboratory evaluation, with decreased serum C1 esterase inhibitor activity and function, and decreased serum C4 level, was consistent with type 1 HAE. She reported a diagnosis of SSc six years prior by her primary care provider for symptoms of skin thickening and Raynaud's phenomenon, though she had not been previously treated, citing a neglect of her own health while caring for her ill mother. She received initial evaluation by rheumatology a month prior to admission, with nailfold capillaroscopy demonstrating periungual capillary dilatation. Labs were significant for positive antinuclear antibody (ANA) with a 1:10240 titre and a speckled pattern, positive rheumatoid factor (RF), positive antibodies for anti-U1 RNP, SS-A, and anticitrullinated peptide, but negative antibodies for anticentromere and anti-Scl-70. Serologies were negative for HIV and hepatitis B. There was reactivity to the hepatitis C antibody, but hepatitis C RNA was not detected. Further investigations for interstitial lung

CONTACT Jean Liew liew.jw@gmail.com Department of Medicine, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA

American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 516-519
DOI: 10.12659/AJCR.903747

Received: 2017.02.12
Accepted: 2017.02.27
Published: 2017.05.10

Obinutuzumab is Effective in Chronic Lymphocytic Leukemia and Rheumatoid Arthritis After Rituximab Failure: A Case Report

Author's Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BDEF 1 Curtis Lachowiez
BE 2 Atul Deodhar
B 3 Eliana Kozin
BDE 3 Stephen Spurgeon

1 Department of Medicine, Oregon Health and Science University, Portland, OR, U.S.A.
2 Department of Medicine, Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University, Portland, OR, U.S.A.
3 Department of Hematology and Medical Oncology, Oregon Health and Science University, Knight Cancer Institute, Portland, OR, U.S.A.

Corresponding Author: Curtis Lachowiez, e-mail: lachowie@ohsu.edu
Conflict of interest: None declared

Patient: Male, 68
Final Diagnosis: Chronic lymphocytic leukemia
Symptoms: Arthritis
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia affecting older adults. As such, many of these patients suffer from co-existing disease states, and the provider must take these comorbidities into account when determining a treatment regimen. The widespread use of monoclonal antibodies (mAbs) has drastically changed the treatment landscape of multiple diseases, ranging from leukemia to autoimmune conditions such as rheumatoid arthritis.

Case Report: We present the case of a patient who had progression of his CLL and rheumatoid symptoms on rituximab therapy, and was subsequently treated with the second-generation anti-CD20 antibody obinutuzumab. Obinutuzumab therapy was associated with simultaneous sustained remission of both disease states, allowing for discontinuation of all other disease-modifying anti-rheumatic drugs (DMARDs), and prolonged remission of his CLL.

Conclusions: While anti-CD20 antibodies have a clear role in the treatment of leukemia and inflammatory conditions, the success of obinutuzumab in RA has not been fully evaluated. We present this case as further evidence of the strong role of anti-CD 20 therapy in multiple conditions, and the unique opportunity for control of simultaneous disease states through targeted inhibition of shared common pathways.

MeSH Keywords: Arthritis, Rheumatoid • Leukemia, Lymphocytic, Chronic, B-Cell • Medical Oncology

Abbreviations: **CLL** – Chronic lymphocytic leukemia; **RA** – rheumatoid arthritis; **RAPID3** – routine assessment of patient index data 3; **ALC** – absolute lymphocyte count

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903747

Case Report

iMedPub Journals
http://www.imedpub.com/

ARCHIVES OF MEDICINE
ISSN 1989-5216

2017
Vol.9 No.5:5

DOI: 10.21767/1989-5216.1000241

Digoxin Toxicity Awareness: When Fatigue isn't what You Think

Melissa Rae LeBlanc*, Emma Pieris and Michelle Thompson

Oregon Health and Science University, Portland, Oregon, United States

*Corresponding author: Melissa Rae LeBlanc, Oregon Health and Science University, Portland, Oregon, United States, Tel: (503) 494-8311; E-mail: leblanme@ohsu.edu

Received date: October 07, 2017; Accepted date: October 12, 2017; Published date: October 16, 2017

Citation: LeBlanc MR, Pieris E, Thompson M (2017) Digoxin Toxicity Awareness: When Fatigue isn't what You Think. Arch Med Vol No:9 Iss No:5:5

Abstract

Use of digoxin, a cardiac glycoside, has reduced over the last two decades, as have rates of hospitalization for digoxin toxicity. Decreased use of digoxin and concurrent decrease in the incidence of toxicity has led to decreased awareness and recognition of this toxicity which may delay treatment with digoxin immune fab, increasing morbidity and mortality. We present a case of an elderly gentleman with digoxin toxicity who presented with fatigue, diffuse weakness, AKI, hyperkalemia, atrial tachycardia with intermittent AV nodal block, ventricular ectopy and slow ventricular response to atrial fibrillation, who responded to treatment with digoxin immune fab with resolution of symptoms.

Keywords: Digoxin; Toxicity; Digoxin immune fab; Digibind

Introduction

Use of digoxin, a cardiac glycoside, treating atrial fibrillation and heart failure has reduced over the last two decades, as have rates of hospitalization for digoxin toxicity [1] though the therapeutic window remains narrow as ever. Toxicity may be acute or chronic and symptoms include lethargy, somnolence, confusion, anorexia, nausea, vomiting, diarrhea, visual disturbances and a wide variety of cardiac arrhythmias which can occur simultaneously [2,3].

Toxicity more often occurs at higher serum concentrations, but can occur in some populations at lower serum concentrations, particularly the elderly or those with renal disease [3-6]. Decreased use of digoxin and concurrent decrease in the incidence of toxicity has led to decreased awareness and recognition of this toxicity, which may delay treatment with digoxin immune fab, increasing morbidity and mortality [5,6].

Case Presentation

An elderly man with history of atrial fibrillation on metoprolol, digoxin and warfarin; also with diabetes, chronic kidney disease and ulcerative colitis status post colectomy presents with three weeks of progressive fatigue, malaise, muscle weakness, anorexia, confusion, nausea and vomiting and worsening of baseline diarrhea after experiencing viral upper respiratory symptoms one month prior, which had since resolved. Physical exam revealed episodes of intermittent symptomatic bradycardia (heart rate in the thirties) alternating with tachycardia with persistent atrial fibrillation. Labs revealed hyperkalemia (5.7), acute kidney injury (AKI) with a creatinine of 3.1 from baseline of 1.8, mild leukocytosis without left shift (12.7) and digoxin level of 1.8 ng/ml (reference range 0.5-2.0 ng/ml).

Computed Tomography (CT) of the head without contrast was unremarkable and initial EKG showed prominent T waves in precordial leads. He was admitted to the medical intensive care unit (ICU) for altered mental status, hyperkalemia and AKI. While in the medical ICU he was placed on telemetry, treated with intravenous fluid resuscitation, and his furosemide, aldactone and digoxin were held due to AKI and hyperkalemia, as was metoprolol given bradycardia.

He had improvement in his hyperkalemia (4.6) and mild improvement in his creatinine (2.9). He was subsequently transferred to the general medical floor on the second day of his admission where he continued to have notable muscle weakness, confusion, nausea, vomiting and poor appetite. Review of telemetry showed atrial tachycardia with intermittent AV nodal block, ventricular ectopy evidence by frequent premature ventricular contractions (PVCs) as well as slow ventricular response to atrial fibrillation (Figure 1).

The confluence of his symptoms, telemetry and risk factors made this case clinically concerning for digoxin toxicity. He was treated with 2 vials of Digoxin immune fab. He responded well with improvement in creatinine from 2.9 to 1.9 the same day, stable potassium, improved mental status, resolution of his nausea and vomiting, improved appetite and improvement in weakness. Telemetry also normalized with resolution of PVC's, bigeminy and AV blockade to his baseline atrial fibrillation with adequate rate control.

CLINICAL REASONING

- What it is?
  - Describes/interprets the *PROCESS* of arriving at the diagnosis rather than the diagnosis itself
  - Usually "applied for" or solicited before being written
  - May involve a third party "expert"
- Potential Submission Venues:
  - JHM
  - JGIM
  - NEJM
  - SGIM Forum "Morning Report"
  - JAMA Internal Medicine "Teachable Moment"

ONLINE FIRST SEPTEMBER 26, 2018—CLINICAL CARE CONUNDRUM

So Much More than Bald and Bloated

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similar to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

Briana Ketterer, MD[1]*, Anthony Montanaro, MD[2], Alan J. Hunter, MD[3]

[1]Department of Medicine, Division of General Internal Medicine, Section of Palliative Care and Medical Ethics, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [2]Division of Allergy and Immunology, Department of Medicine, Oregon Health & Science University, Portland, Oregon; [3]Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, Portland, Oregon.

A 44-year-old previously healthy semiprofessional male athlete presented with five days of nausea, vomiting, and abdominal pain. He had also experienced several months of decreased energy and new episodes of constipation three weeks prior to presentation.

At this point, we do not have sufficient information to completely determine the cause of his abdominal symptoms. Common causes of abdominal pain and vomiting in adults of his age group include peptic ulcer disease, pancreatic or hepatobiliary track disorders, small or large bowel processes, appendicitis, or even renal pathology. Further characterization may be possible by describing the location and quality of pain and factors that might relieve or exacerbate his pain. Despite the ambiguity, multiple clues might allow us to narrow the broad differential diagnosis of abdominal pain. In a previously healthy, vigorous, middle-aged man with subacute abdominal pain associated with constipation, the differential diagnosis should include disease states that may cause a bowel obstruction; these states include inflammatory bowel disease (IBD), gastrointestinal malignancy, or peptic ulcer disease. Mechanical obstruction due to volvulus or intussusception would be less likely in his age group. Given his history of several months of fatigue and several weeks of constipation, he should be evaluated for metabolic causes of abdominal pain and constipation, such as hypothyroidism or hypercalcemia. In addition to basic laboratory and imaging studies, obtaining additional history regarding prior abdominal surgeries, medication use, alcohol intake, and family and travel history will be the key in directing the evaluation.

Six months prior to admission, the patient began to feel more fatigue and exercise intolerance, reduced sweating, increased cold intolerance, and increased presyncopal episodes. He was diagnosed with hypothyroidism (TSH 6.69 μIU/mL; free T4 not done) and initiated on levothyroxine. One month prior to presentation, he developed constipation, loss of taste, reduced appetite, and weight loss of 30 pounds. He developed blurry vision and photophobia. He also complained of erectile dysfunction, urinary hesitancy and straining, which were diagnosed as benign prostatic hypertrophy.

Given the addition of numerous historical features in a previously healthy man, it is important to strive for a parsimonious diagnosis to unify his seemingly disparate features. His fatigue, constipation, and cold intolerance are consistent with his diagnosis of hypothyroidism but are nonspecific. Whether the degree of hypothyroidism caused his symptoms or signs is doubtful. The constellation of symptoms and signs are more likely to be representative of a nonthyroidal illness. His abdominal pain, unexplained weight loss, and presyncopal episodes should raise consideration of adrenal insufficiency. The combination of hypothyroidism and adrenal insufficiency suggest the possibility of an autoimmune polyendocrine syndrome or other pituitary pathology. In this case, history of headache, dysgeusia, and visual disturbances might support the diagnosis of pituitary adenoma. A cosyntropin stimulation test could establish the diagnosis of adrenal insufficiency. A low ACTH level would establish a diagnosis of pituitary or hypothalamic hypofunction. If pituitary hypofunction is documented, then a brain MRI would be needed to confirm the diagnosis of pituitary adenoma.

His newly reported erectile dysfunction suggests the possibility of a psychiatric, neurologic, hormonal, or vascular process and should be explored further. Sexual dysfunction is also associated with adrenal insufficiency and hypopituitarism. However, the presence of suspected prostatic hypertrophy in a male competitive athlete in his forties also raises the question of exogenous androgen use.

His past medical history was notable for a two-year history of alopecia totalis, seasonal allergies, asthma, and a repaired congenital aortic web with known aortic insufficiency. He was married with two children, worked an office

*Address for correspondence: Briana Ketterer, MD, UPMC Montefiore Suite 933W, 200 Lothrop Street, Pittsburgh, PA 15213; Telephone: 412-692-4834; Fax: 412-692-4944; E-mail: briana.ketterer@gmail.com

Received: December 28, 2017; Revised: July 26, 2018; Accepted: August 3, 2018

 DOI 10.12788/jhm.3083

MORNING REPORT

OCCAM'S RAZOR VERSUS HICKAM'S DICTUM: HEADACHE IN AN IMMUNOCOMPROMISED PATIENT

Carlton D. Scharman, MD (presenter); André M. Mansoor, MD, Avital Y. O'Glasser, MD, FACP, FHM (discussants)

Dr. Scharman (cscharman@tuftsmedicalcenter.org) is a recent graduate of the OHSU Internal Medicine Residency Program and is now a Hematology/Oncology fellow at Tufts Medical Center. Dr. Mansoor (mansooan@ohsu.edu) is a hospitalist at OHSU. Dr. O'Glasser (oglassea@ohsu.edu; Twitter, @aoglasser) is also a hospitalist at OHSU and an assistant program director for the Internal Medicine Residency Program.

A 34-year-old man with a history of simultaneous pancreas-kidney transplant for Type I diabetes and associated nephropathy, requiring chronic immunosuppressive therapy with tacrolimus, prednisone, and mycophenolate, presented with acute onset headache and subjective confusion. Two weeks prior, he had been diagnosed with antibody-mediated kidney transplant rejection, undergoing first treatment of plasmapheresis and intravenous immunoglobulin (IVIG) several days prior to his acute presentation.

We have a medically complex patient whose headache differential starts out broadly. We should immediately be concerned about infection causing meningitis, encephalitis, or meningoencephalitis given his chronic immunosuppression as well as recent acute rejection treatment. Bacterial, viral, or fungal infections are concerning. Medication adverse effect and intracranial bleed should also be considered early.

On examination, his temperature was 37.8°C, and he was hypertensive to 183/107 mmHg with mild tachycardia. He was intermittently somnolent, agitated, and disoriented. Neck pain and stiffness were present.

Meningitis due to infection remains high on the differential given his nuchal rigidity. His normal temperature does not exclude the possibility. His hypertension and chronic tacrolimus also raise concern for posterior reversible encephalopathy syndrome (PRES). His recent IVIG therapy could also cause an aseptic meningitis.

He was started on empiric vancomycin and ceftriaxone for bacterial meningitis coverage; acyclovir was not empirically initiated. Urgent head CT was unremarkable. MRI was also subsequently unremarkable. Lumbar puncture (LP) was performed urgently as soon as the head CT showed no signs of impending herniation, although this was a difficult bedside procedure with multiple attempts needed to access the cerebrospinal fluid (CSF) space. The CSF initially appeared red in color. The intensity of the color did not lessen with subsequent sampling; vials one through four were identical in their dark red appearance.

The stable CSF appearance between vials one and four made trauma from needle insertion less likely, as this is typically associated with a bloody CSF appearance that lessens over time as fluid is collected. CSF appears cloudy with RBC concentrations between 500-6000 K/cu mm and begins to appear grossly bloody when the concentration exceeds 6,000 K/cu mm1 (K/cu mm or K/mm3 is equivalent to cells/μL.) The differential for grossly bloody CSF includes traumatic LP, subarachnoid haemorrhage, and hemorrhagic meningoencephalitis. SAH seems less likely here given negative imaging and absence of head trauma.

Because of the association between HSV encephalitis with CSF erythrocytosis in combination with his immunosuppressed status, he was immediately started on empiric intravenous acyclovir. Subsequent CSF analysis revealed WBC count of 2,106 K/cu mm (76% neutrophils), RBC count of 42,000 K/cu mm, protein 249 mg/dL, and normal glucose relative to serum levels (64 mg/dL).

In HSV encephalitis, CSF erythrocytosis occurs in approximately 80% of cases and is attributed to the necrotizing and hemorrhagic nature of the infection.[1] CSF HSV polymerase chain reaction (PCR) is associated with a sensitivity of 98% for detecting infection, but can be falsely negative in the setting of significant erythrocytosis due to presence of porphyrin (a heme-degradation product) which can interfere with the assay.[2] Therefore, in such a setting, negative PCR results should be interpreted with caution. Peripheral blood contamination of CSF after traumatic LP artificially increases WBC count. However, this CSF pleocytosis appears "real" as the pro-

continued on page 2

TEACHABLE MOMENT

When Medical Care Leads to Harm—Difficulty Finding Words

A Teachable Moment

Erin Chamberlain, MD Department of Medicine, Oregon Health and Science University, Portland.

Matt DiVeronica, MD Veterans Affairs Portland Health Care System, Portland, Oregon.

Renee Segura, MD Veterans Affairs Portland Health Care System, Portland, Oregon.

Story From the Front Lines

A 66-year-old man with diabetes, hypertension, and peripheral vascular disease presented with complaint of fevers, rigors, and malaise along with a mild frontal headache of 7 days' duration. He was febrile and hypotensive though alert and oriented. Examination findings were consistent with cellulitis in his right lower extremity. Blood cultures grew group G *Streptococcus*, with cellulitis as the presumed source for sepsis. Infectious disease specialists were consulted.

Given the indolent time course of symptoms, and a grade I/VI diastolic murmur not auscultated at presentation, endocarditis was considered, and a transthoracic echocardiogram was recommended. Despite a lack of documented abnormalities on neurologic examination, a computed tomographic (CT) angiogram of his head and neck was also recommended to evaluate for mycotic aneurysm out of concern for the history of headache. Findings of the echocardiogram were negative for valvular regurgitation or vegetation. The CT angiogram revealed stenosis of various segments of the intracerebral arteries and a 4-mm aneurysm of the left posterior cerebral artery without evidence of infectious cause.

After recovery and discharge, a neurosurgery consult was obtained regarding management of the incidental discovery of cerebral aneurysm. The neurosurgeon believed that because the aneurysm was asymptomatic, it did not require intervention; however, further evaluation of the stenotic intracerebral arteries with cerebral angiography was recommended to better understand the pattern of blood flow in these areas. Cerebral angiography did not show an aneurysm.

Three days following cerebral angiography, the patient presented with acute-onset confusion, word-finding difficulty, and short-term memory defects. Magnetic resonance imaging of the brain revealed multiple foci of acute ischemic lesions in different vascular territories consistent with embolic stroke. Further evaluation determined the source to be iatrogenic due to cerebral angiography. At last follow-up, patient was undergoing physical and speech therapy to aid his recovery.

Teachable Moment

The patient described herein experienced harm as a result of overutilization of available health care services, specifically unnecessary diagnostic imaging modalities. His initial testing with head CT angiography led to a cascade of further unnecessary imaging studies, most notably the cerebral angiography that resulted in significant patient harm in the form of iatrogenic stroke. With a more judicious approach to testing, this patient's stroke may have been prevented.

The modified Duke criteria[1] used to assist in the diagnosis of infective endocarditis require presence of 2 major, 1 major and 3 minor, or 5 minor criteria. They incorporate consideration of the offending microorganism as well as evidence of endocardial involvement on echocardiogram.[1] This patient's blood cultures grew an atypical organism that cleared after 1 day, and the echocardiogram findings were negative for intracardiac involvement. He met only 1 major criterion (auscultation of a regurgitant murmur) and 2 minor criteria (fever and bacteremia with an atypical microorganism). Despite his lacking evidence for endocarditis, the patient underwent CT angiography to rule out one of its neurologic complications. This revealed both incidental and asymptomatic segmental cerebral artery stenosis and aneurysm, which by size carried less than a 1% chance of enlargement or bleeding per year and should not have merited further evaluation by cerebral angiography.[2] This patient experienced the unfortunate 2.6% risk of neurologic complication from this procedure, which led to a further cascade of preventable diagnostic imaging to confirm its iatrogenic source.[3]

The physicians involved in this case demonstrated concern for the potential outcome of a ruptured mycotic aneurysm resulting in stroke. However, the available clinical data that ruled out endocarditis and its complications were overlooked, ultimately resulting in the very same feared complication but caused iatrogenically.

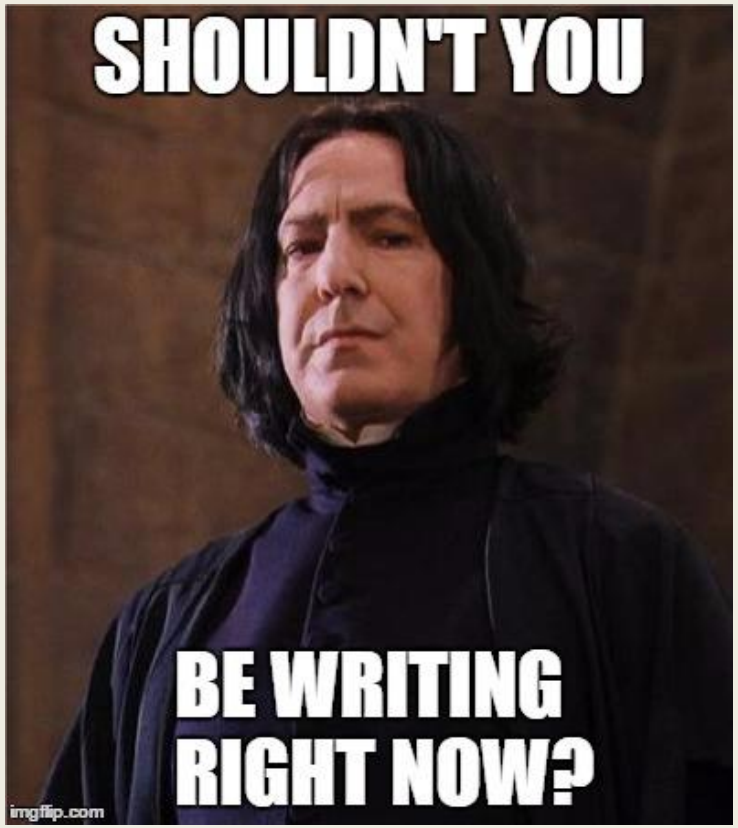
An alternative approach would have been to first rule in or out the diagnosis of endocarditis using the modified Duke criteria.[1] If endocarditis was ruled in, the next step would have been to consider potential complications. Intracranial mycotic aneurysms are relatively rare, comprising less than 10% of all neurologic complications of endocarditis.[4] In a study of patients with infective endocarditis, the negative predictive value of absent focal neurologic deficits for the presence of mycotic aneurysm was 99%. Notably, the absence of altered mental status alone conferred a negative predictive value for mycotic aneurysm of 94%.[5] In patients not meeting criteria for endocarditis, such absent examination findings should be especially reassuring. This evidence suggests that CT angiography should be used only when focal neurologic deficits are present.

We work in a medical system that allows us to provide excellent care of patients, though when advanced diagnostic tools or treatments are overused, they can result in grave harm. With evidence-guided care, we will not be left struggling to find words to explain how an unnecessary procedure cost a patient his own words.

Corresponding Author: Erin Chamberlain, MD, Department of Medicine, Oregon Health and Science University, Mail Code VA P-3-GP1, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (chambeer@ohsu.edu).

“It is an ancient need to be told stories. But the story needs a great storyteller.”

- *Alan Rickman*



EXPERIENCES OF CARE

- What it is?
  - Humanities
  - Narrative medicine
  - Reflection piece
  - Patient reflection
  - Physician reflection
  - Prose or poetry?

- Potential Submission Venues:
  - Annals
    - On Being a Doctor
    - On Being a Patient
  - JGIM "Materia Medica"
  - SGIM Forum
  - AJM "Personomics" (6/2017):
    - *"how knowing the patient as a person helped solve a diagnostic enigma, designed a treatment plan for a given individual, fortified the patient's dignity, illustrated the hazards of making assumptions about people, or added awe and wonder to the daily work of a doctor."*

ESSAY

The Unknown Unknowns

Avital Y. O'Glasser, MD, FACP

Dr. O'Glasser is assistant professor of medicine in the Division of Hospital Medicine and assistant medical director of the Pre-Operative Medicine Clinic at Oregon Health & Sciences University in Portland, OR.

> "…There are known knowns; there are things we know that we know. There are known unknowns; that is to say, there are things that we now know we don't know. But there are also unknown unknowns—there are things we do not know we don't know."
>
> —Donald Rumsfeld, United States Secretary of Defense, February 12, 2002

These astute words were delivered during a news briefing with regard to the absence of evidence going into the Iraq wars. Nearly 12 years later, I listened to an infectious disease specialist reiterate these words regarding our struggles with super-bugs and antibacterial resistance—and nearly 12 years and thirty seconds later, I realized how perfectly these words captured the essence of my clinical practice.

I started practicing peri-operative medicine serendipitously almost five years ago. A clinical opportunity presented itself. The solo hospitalist in our Pre-Operative Medicine Clinic (PMC) needed a back up and a colleague. I threw myself in, hopped along for the ride, and hoped for the best.

I was hooked. The hospital had transitioned from an anesthesiologist-led to a hospitalist-led perioperative clinic just a few years prior. Here it was—internal medicine in its purest form! Every organ system to be considered, with the cardiac system on its golden pedestal. Here was the Revised Cardiac Risk Index and the 2007 American College of Cardiology/American Heart Association algorithm nobly helping us ford the great river of "pre-op clearance." Here was the pulmonary system on its ever-so-slightly-shorter silver pedestal, buttressed by the Arozullah Respiratory Failure Index. But there was so much more! Here was diabetes, chronic liver disease, substance abuse, and poorly controlled skin and dental infections. Here was chronic anticoagulation, bleeding diatheses, chronic kidney disease, immunosuppressants, and chronic steroid therapy masking underlying secondary adrenal insufficiency. And then there is rheumatology and rheumatoid arthritis, with the risk of cervical spine instability and subluxation with intubation.

Here was systems-based practice and multidisciplinary care. Patient education. Communication skills. Good old-fashioned bread-and-butter history-taking and physical diagnosis skills combined with sophisticated testing modalities. I was board-certified in internal medicine but learning tomes about anesthesiology and surgery by the day.

It was invigorating to meet patients at such an excitedly vulnerable and vulnerably exciting juncture in their lives. I have been able to look a patient in the eye and say, "Your last A1C was 6.4, which is excellent in general and certainly reassuring going into a major surgery." To another I have said, "I hear your concerns that your father died of a post-op MI, but you've never smoked, you exercise regularly without concerning symptoms, and your EKG is normal. I don't have any indications to perform a stress test." But I am also comfortable saying, "I know that your aortic valve area is 0.6 cm^2 and you've been feeling more short of breath climbing stairs lately. I know that surgery will be very risky for you, and it is something that I need to advise against."

The known knowns.

There have been countless opportunities to use my brain and my diagnostic skills to drive patient care forward. There have been chances to engage with a patient and say, "You've been on insulin for 40 years with an A1C never less than 8. I hear abnormal blood flow when I listen to the carotid arteries in your neck. I am very concerned that you have significant blockage, but I can't tell you how bad it might be, which is why I'm ordering more tests for you." I may also say, "You appeared floridly winded walking into clinic, you can't lie flat, and your last CXR showed an enlarged heart and fluid on your lungs. I am very concerned that you have some degree of heart failure, but I don't know how extensive or what type." When a good, juicy, sink-your-teeth-into-it history raises my pre-test probability of underlying disease, it makes my decision to test immediate.

The known unknowns.

I like to think that I am a cost-conscious, less-is-more physician. I like the known unknowns. They make it easier to decide to test and justify my recommendations to delay or cancel surgery.

But even the known unknowns can be stress-inducing and grueling. The frantic 11th hour search for the long-forgotten coronary angiogram. Where was it done? Why? What clinical concerns might have prompted a catheterization, let alone non-invasive cardiac testing? What did it show? What do you mean, "It was fine"? Do you mean fine as in "diffuse multivessel disease not amenable to revascularization" or fine as in "normal coronaries"? Both results seem to get transmitted

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HEALING ARTS
Materia Medica
"Heart"

Elizabeth Lahti, MD

Department of Internal Medicine, Division of Hospital Medicine, Oregon Health & Sciences University, Portland, OR, USA.

Delores Hailey* is a patient on the heart transplant wait list. Her case is unique in that she received a transplant 12 years ago. Despite impeccable self care and adherence to her medical regimen, her transplanted heart is failing. It was from a young donor, but like our own organs, has a genetic predisposition all its own.

I visit with Delores on rounds each morning. She greets me wearing brightly colored pajamas, her husband Winston by her side. Her breath is sometimes short. Her jugular vein quivers just above her clavicle. After I examine her and ask the official questions, the ones whose answers will appear in my chart note, I pull up a chair and ask the questions that connect us. She tells me about her family. She tells stories of her granddaughter, her friends and her faith. She tells me how hard it is being so far from home.

One day Delores tells a story about a group of people who have the same last name, but are not related. They meet once a year for a two-day picnic. There are over a thousand like-named people who come together and, according to Delores, have become a family of sorts. She tells me she would like to find all the other Haileys and do the same thing.

"You are the Delores of the thousand Haileys," I say.

When we hear the words, we agree they sound like the first line of a poem. We decide to each write a poem using that first line. It is a small challenge to pass the unknown stretch of time while she waits for her new heart.

That night, I begin my poem. I write the first words that come to mind. I do not edit or think too much. When complete, I think to myself, I cannot show this to Delores. It is about death. Someone has to die for Delores to live. And although death dances around much of what we do as physicians, to confront the human complexities of someone else's life ending so Delores can live seems like a Pandora's Box I don't want to open. I put the poem away and hope she will forget.

The next day, Delores tells me about getting a letter from the mother of the man whose heart beats in her chest now.

"He was young." She pauses. "Driving his wife and new baby."

Her voice breaks and then becomes whole again. "They survived."

Delores watches my eyes fill with tears.

"I live my life for him too, you know," she says. "I'm sorry to lose this heart. It's been with me a lot of years."

I am both afraid and hopeful Delores will remember the poem assignment. Part of me wants to share more closely in this complicated journey with her.

The following morning, I bring a copy of the poem I wrote for Delores, folded in my white coat pocket, just in case. I did not change it or replace the difficult lines with easy ones. To do so would seem dishonest. Delores tells me she has written her poem, too.

"I almost didn't bring mine," I say.

"It was hard to write," she says.

"Sometimes I don't know where it will take me." The writing, I mean.

"To the truth," she says.

My heart beats fast and I am nervous to show her my words, my thoughts, my humanity. I feel like I have shed my white coat and stand naked before her. What kind of doctor writes poetry with her patient? What kind of doctor imagines a person, full of life, before he or she becomes a cadaver donor? And what kind of doctor shares those thoughts with the patient waiting for a heart? We hand each other our folded pieces of paper and put them aside to read later, alone.

When I read Delores's poem I am struck by both the similarities to and differences from my own. We choose many of the same words, but ultimately we write from our own perspectives. I write of someone else dying. Delores writes of someone dying, but not knowing if it will be her. When I compare the poems, side by side, I see that through talking to Delores, I have learned bits of who she is: the grandmother, the wife, the friend, the patient. But writing together we have shared what we were unable to with spoken words. Our connection deepens as our daily visits are enhanced by conversations sparked by the poems.

Perhaps the poems are prescient. A few weeks later, while evaluating ongoing shortness of breath, a CT scan reveals a slow-growing adenocarcinoma in Delores's lung. Just like that, she is off the list. I'm not the attending anymore, but I find her.

"We knew it might happen," she says. Her eyes are bright, her grip strong on my hand. She smiles, despite the news.

KEY WORDS: narrative medicine; patient-centered care; medical humanities
J Gen Intern Med 30(3):374-5
DOI: 10.1007/s11606-014-3052-1

Published online October 21, 2014

intima
a journal of narrative medicine

POETRY | SPRING 2018

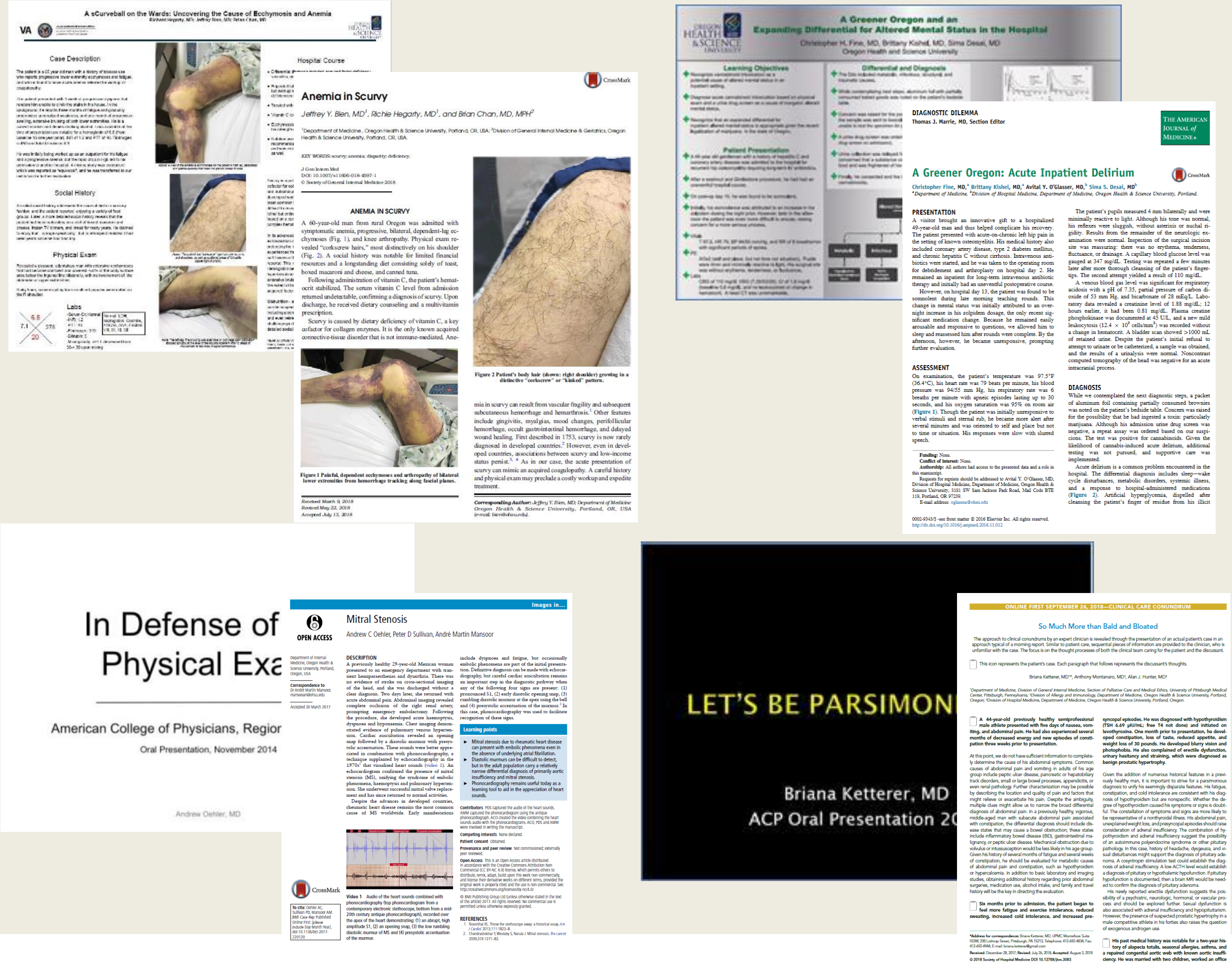
Disheartening News

By Alina Plavsky

We had to know your pressure
look right, look left
we thought we could find
the main one
or several to open
to then get you
net, even
but now
your right
you're right
your left
you're left
with a clear corollary
with a weak pump
maybe weeks? maybe months?
just a fraction
it's hard to tell
your heart
this disheartening news

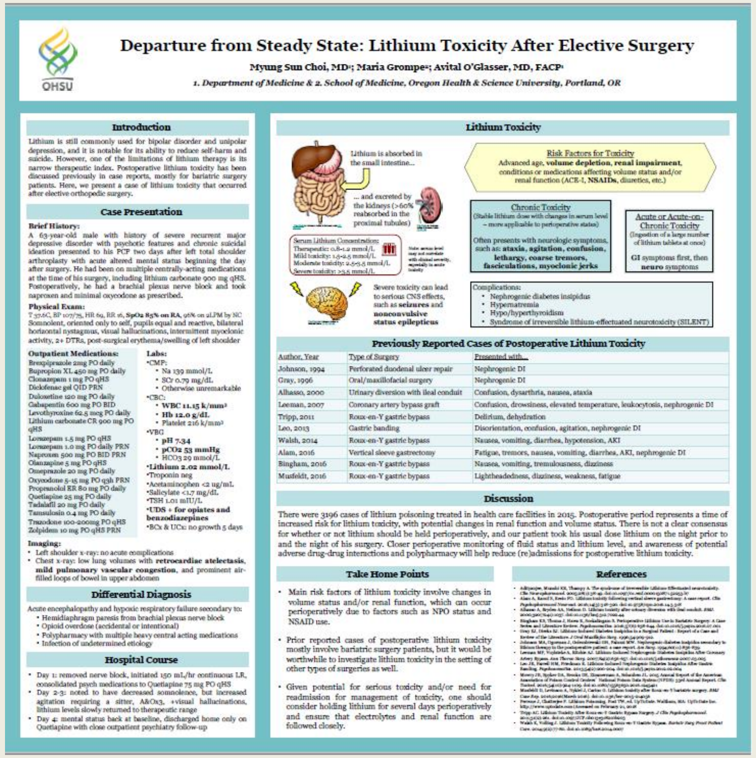
MILEAGE & MOMENTUM

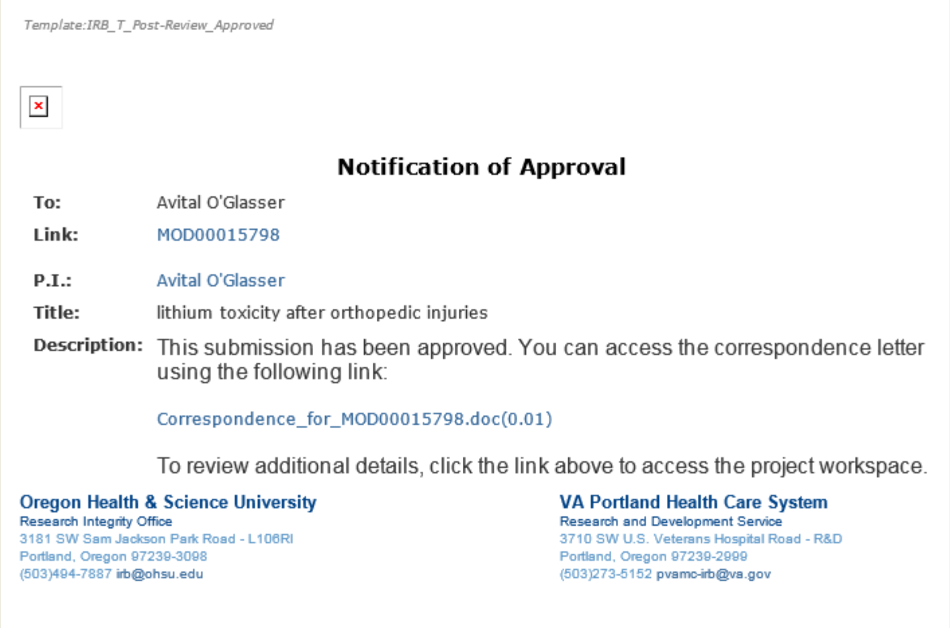
Abstract to poster to publication!



MILEAGE & MOMENTUM

- Clinical vignette abstract to poster to RESEARCH project and/or publication





Template:IRB_T_Post-Review_Approved

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Title: lithium toxicity after orthopedic injuries

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Oregon Health & Science University
Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, Oregon 97239-3098
(503)494-7887 irb@ohsu.edu

VA Portland Health Care System
Research and Development Service
3710 SW U.S. Veterans Hospital Road - R&D
Portland, Oregon 97239-2999
(503)273-5152 pvamc-irb@va.gov

PROFESSIONALISM IN SCHOLARSHIP

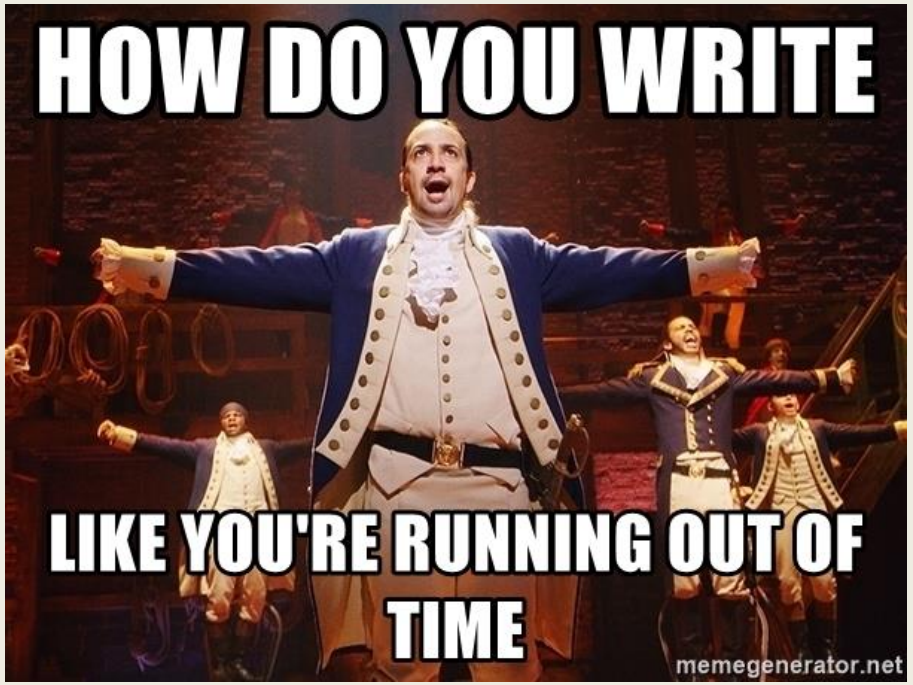
"I want to be in the room where it happens"

- Consent:
  - Signed patient consent?
  - Verbal consent?
  - How do you ASK a patient?
  - Local rules (ex. Photos/media)
  - VA approval process
- Confidentiality:
  - Collect, store, share case information and drafts
  - De-identify all images
  - Protect anonymity with "journalistic liberties"
- "Ownership"/authorship

RESEARCH

- Abstracts and posters
  - *Published meeting abstracts*
- Oral presentations
- Publications
- Type
  - Basic research
  - Clinical research
    - Retro/prospective
  - QI
  - Reviews/meta-analysis
  - Medical education
  - Letters to the editor
  - Survey based
  - Book chapters

"Put a pencil to his temple,
connected it to his brain
And he wrote his first refrain..."



BASIC

Leukemia Research 53 (2017) 39–49

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

CPX-351 exhibits potent and direct *ex vivo* cytotoxicity against AML blasts with enhanced efficacy for cells harboring the FLT3-ITD mutation

Max J. Gordon[a], Paul Tardi[b], Marc M. Loriaux[c,g], Stephen E. Spurgeon[d,g], Elie Traer[d,g], Tibor Kovacsovics[e], Lawrence D. Mayer[b], Jeffrey W. Tyner[f,g,*]

[a] Department of Internal Medicine, Oregon Health & Sciences University, Portland, OR, USA
[b] Jazz Pharmaceuticals, Suite 250 – 887 Great Northern Way, Vancouver, BC V5T 4T5, Canada
[c] Department of Pathology, Oregon Health & Science University, Portland, OR, USA
[d] Division of Hematology & Medical Oncology, Oregon Health & Science University, Portland, OR, USA
[e] Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, Huntsman Cancer Hospital, The University of Utah, Salt Lake City, USA
[f] Department of Cell, Developmental & Cancer Biology, Oregon Health & Science University, Portland, OR, USA
[g] Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

ARTICLE INFO

Article history:
Received 18 September 2016
Received in revised form 8 December 2016
Accepted 10 December 2016
Available online 12 December 2016

Keywords:
CPX-351
Cytarabine
Daunorubicin
Leukemia
Cytotoxicity

ABSTRACT

Purpose: Identify AML patients most likely to respond to CPX-351, a nano-scale liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio.
Methods: We examined the *ex vivo* cytotoxic activity of CPX-351 against leukemic cells isolated from 53 AML patients and an additional 127 samples including acute lymphoblastic leukemia, myelodysplastic syndrome/myeloproliferative neoplasms, or chronic lymphocytic leukemia/lymphoma. We assessed activity with respect to common molecular lesions and used flow cytometry to assess CPX-351 cellular uptake.
Results: AML specimen sensitivity to CPX-351 was similar across conventional risk groups. FLT3-ITD cases were five-fold more sensitive to CPX-351. CPX-351 was active across other indications with nearly all cases exhibiting IC_{50} values markedly lower than reported 72-h plasma drug concentration in patients receiving CPX-351. The range and distribution of CPX-351 IC_{50} values were comparable for AML, CLL, and ALL, whereas MDS/MPN cases were less sensitive. CPX-351 uptake analysis revealed a correlation between uptake of CPX-351 and cytotoxic potency.
Conclusions: Our findings are consistent with clinical data, in which CPX-351 activity is retained in high-risk AML patients. *Ex vivo* analysis of cytotoxic potency may provide a means to identify specific AML subsets, such as FLT3-ITD, that benefit most from CPX-351 and warrant additional clinical evaluation.

1. Introduction

CPX-351 is a nano-scale (100 nm diameter) low-cholesterol liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio shown to be optimally synergistic both *ex vivo* and *in vivo*. Improvements in efficacy over the conventional free drug combination were observed in several preclinical studies [1–4]. In a randomized controlled Phase 2 clinical trial of newly diagnosed acute myeloid leukemia (AML) in the elderly, CPX-351 produced superior response rates, and in secondary AML, superior event free survival (EFS) and overall survival (OS) [5]. A randomized phase 2 trial of CPX-351 *vs* investigator's choice after first relapse demonstrated superior response rates, EFS and overall survival in patients with poor risk disease treated with CPX-351 [6]. Consequently, the aim of CPX-351 clinical development is to replace conventional cytarabine plus anthracycline therapy in several AML patient populations where it is considered standard of care.

The basis of the efficacy improvements observed with CPX-351 are attributable to 1) elevated cytarabine:daunorubicin concentra-

* Corresponding author at: Department of Cell and Developmental Biology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA.
E-mail address: tynerj@ohsu.edu (J.W. Tyner).

RESEARCH BRIEF

Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of *BRCA2* Reversion Mutations Associated with Resistance to PARP Inhibitors

David Quigley[1,2], Joshi J. Alumkal[3,4], Alexander W. Wyatt[5], Vishal Kothari[1,6], Adam Foye[1,7], Paul Lloyd[1,7], Rahul Aggarwal[1,7], Won Kim[1,7], Eric Lu[3], Jacob Schwartzman[3], Kevin Beja[5], Matti Annala[5,8], Rajdeep Das[1,6], Morgan Diolaiti[1], Colin Pritchard[9], George Thomas[3,10], Scott Tomlins[11], Karen Knudsen[12], Christopher J. Lord[13], Charles Ryan[1,7], Jack Youngren[1,7], Tomasz M. Beer[3], Alan Ashworth[1,14], Eric J. Small[1,7], and Felix Y. Feng[1,8]

ABSTRACT Approximately 20% of metastatic prostate cancers harbor mutations in genes required for DNA repair by homologous recombination repair (HRR) such as *BRCA2*. HRR defects confer synthetic lethality to PARP inhibitors (PARPi) such as olaparib and talazoparib. In ovarian or breast cancers, olaparib resistance has been associated with HRR restoration, including by *BRCA2* mutation reversion. Whether similar mechanisms operate in prostate cancer, and could be detected in liquid biopsies, is unclear. Here, we identify *BRCA2* reversion mutations associated with olaparib and talazoparib resistance in patients with prostate cancer. Analysis of circulating cell-free DNA (cfDNA) reveals reversion mutation heterogeneity not discernable from a single solid-tumor biopsy and potentially allows monitoring for the emergence of PARPi resistance.

SIGNIFICANCE: The mechanisms of clinical resistance to PARPi in DNA repair–deficient prostate cancer have not been described. Here, we show *BRCA2* reversion mutations in patients with prostate cancer with metastatic disease who developed resistance to talazoparib and olaparib. Furthermore, we show that PARPi resistance is highly multiclonal and that cfDNA allows monitoring for PARPi resistance. *Cancer Discov; 7(9); 999–1005. ©2017 AACR.*

See related commentary by Domchek, p. 937.
See related article by Kondrashova et al., p. 984.
See related article by Goodall et al., p. 1006.

[1]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco (UCSF), San Francisco, California. [2]Department of Epidemiology and Biostatistics, UCSF, San Francisco, California. [3]Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon. [4]Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, Oregon. [5]Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, British Columbia, Canada. [6]Department of Radiation Oncology, UCSF, San Francisco, California. [7]Division of Hematology and Oncology, UCSF, San Francisco, California. [8]Institute of Biosciences and Medical Technology, University of Tampere, Tampere, Finland. [9]Department of Laboratory Medicine, University of Washington, Seattle, Washington. [10]Department of Pathology, Oregon Health & Science University, Portland, Oregon. [11]Department of Pathology, University of Michigan School of Medicine, Ann Arbor, Michigan. [12]Department of Cancer Biology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania. [13]The CRUK Gene Function Laboratory and Breast Cancer Now Research Centre, The Institute of Cancer Research, London, United Kingdom. [14]Department of Medicine, UCSF, San Francisco, California.

Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

D. Quigley and J.J. Alumkal contributed equally to this article.

Corresponding Authors: Felix Y. Feng, UCSF Helen Diller Family Comprehensive Cancer Center, Box 0128, San Francisco, CA 94158. Phone 415-502-7222; E-mail: Felix.Feng@ucsf.edu; Eric J. Small, Eric.Small@ucsf.edu; and Alan Ashworth, Alan.Ashworth@ucsf.edu

doi: 10.1158/2159-8290.CD-17-0146

CLINICAL—PROSPECTIVE OR RETROSPECTIVE

Atherosclerosis 267 (2017) 19–26

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry

Stephen M. Amrock [a], P. Barton Duell [b], Thomas Knickelbine [c], Seth S. Martin [d], Emily C. O'Brien [e], Karol E. Watson [f], Joanna Mitri [g], Iris Kindt [h], Peter Shrader [e], Seth J. Baum [i], Linda C. Hemphill [j], Catherine D. Ahmed [k], Rolf L. Andersen [l], Iftikhar J. Kullo [m], Dervilla McCann [n], John A. Larry [o], Michael F. Murray [p], Robert Fishberg [q], John R. Guyton [r], Katherine Wilemon [k], Matthew T. Roe [e], Daniel J. Rader [s], Christie M. Ballantyne [t], James A. Underberg [u], Paul Thompson [v], Dannielle Duffy [w], MacRae F. Linton [x], Michael D. Shapiro [b], Patrick M. Moriarty [y], Joshua W. Knowles [k, z], Zahid S. Ahmad [aa, *]

[a] Department of Medicine, Oregon Health & Science University, Portland, OR, USA
[b] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA
[c] Minneapolis Heart Institute Foundation, Minneapolis, MN, USA
[d] Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
[e] Duke Clinical Research Institute, Durham, NC, USA
[f] UCLA Center for Cholesterol and Lipid Management, Los Angeles, CA, USA
[g] Joslin Diabetes Center, Harvard Medical School Boston, MA, USA
[h] The FH Foundation, Pasadena, CA, USA
[i] Seth J. Baum, MD, Preventive Cardiology Inc., Boca Raton, FL, USA
[j] Massachusetts General Hospital, Boston, MA, USA
[k] The FH Foundation, South Pasadena, CA, USA
[l] Lancaster General Health/Penn Medicine, Lancaster, PA, USA
[m] Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
[n] Central Maine Heart and Vascular Institute/Central Maine Medical Center (CMMC), Lewiston ME, USA
[o] The Ohio State University Medical Center, Columbus, OH, USA
[p] Geisinger Health System, Forty Fort, PA, USA
[q] Atlantic Health System, Springfield, NJ, USA
[r] Duke University Medical Center, Durham, NC, USA
[s] University of Pennsylvania, Philadelphia, PA, USA
[t] Baylor College of Medicine, Houston, TX, USA
[u] New York University School of Medicine, New York, NY, USA
[v] Hartford Hospital, Hartford CT, USA
[w] Thomas Jefferson University, Philadelphia, PA, USA
[x] Vanderbilt University School of Medicine, Nashville, TN, USA
[y] University of Kansas Medical Center, Kansas City, KS, USA
[z] Division of Cardiovascular Medicine and Cardiovascular Institute, Department of Medicine, Stanford University, Stanford, CA, USA
[aa] Division of Nutrition and Metabolic Diseases, Department of Internal Medicine, University of Texas Southwestern, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 26 June 2017
Received in revised form
25 September 2017

ABSTRACT

Background and aims: Most familial hypercholesterolemia (FH) patients remain undertreated, and it is unclear what role health disparities may play for FH patients in the US. We sought to describe sex and racial/ethnic disparities in a national registry of US FH patients.

Open Access Cardiac surgery

openheart

Coronary artery bypass grafting in patients treated with thoracic radiation: a case–control study

Erin Amanda Fender,[1] Pranav Chandrashekar,[1] Jackson J Liang,[2] Priyank R Dhar,[3] Terence T Sio,[4] John M Stulak,[5] Ryan J Lennon,[6] Joshua P Slusser,[6] Jonathan B Ashman,[4] Robert C Miller,[4] Joerg Herrmann,[1] Abhiram Prasad,[1] Gurpreet S Sandhu[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/openhrt-2017-000766).

To cite: Fender EA, Chandrashekar P, Liang JJ, *et al*. Coronary artery bypass grafting in patients treated with thoracic radiation: a case–control study. *Open Heart* 2018;5:e000766. doi:10.1136/openhrt-2017-000766

Received 18 December 2017
Revised 23 January 2018
Accepted 30 January 2018

[1]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA
[2]Division of Cardiovascular Disease, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[3]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
[4]Department of Radiation Oncology, Mayo Clinic, Scottsdale, Arizona, USA
[5]Division of Cardiovascular Surgery, Mayo Clinic, Rochester, Minnesota, USA
[6]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Dr Erin Amanda Fender; fender.erin@mayo.edu

ABSTRACT

Background and aim Thoracic radiation therapy (XRT) for cancer is associated with the development of significant coronary artery disease that may require coronary artery bypass grafting surgery (CABG). Contemporary acute surgical outcomes and long-term postoperative survival of patients with prior XRT have not been well characterised.
Methods This was a retrospective, single-centre study of patients with a history of thoracic XRT who required CABG and who were propensity matched against 141 controls who underwent CABG over the same time period. The objectives were to assess early CABG outcomes and long-term survival in patients with prior XRT.
Results Thirty-eight patients with a history of previous thoracic XRT underwent CABG from 1994 to 2013. The median time from XRT exposure to surgery was 7.9 years (IQR: 2.5–18.4 years). Perioperative adverse events were similar in the XRT group and controls; however, there was a trends lower utilisation of internal mammary artery (IMA) grafts in the XRT group (89%vs98%, P=0.13). After a median postoperative follow-up of 5.4 years (IQR 0.9–9.4 years), no difference in long-term all-cause mortality was observed.
Conclusion Patients with prior thoracic XRT who undergo CABG have similar long-term all-cause mortality compared with controls. Isolated CABG after thoracic XRT is not associated with higher perioperative complications, but IMA graft use may be limited by prior XRT.

Key messages

What is already known about this subject?
Thoracic radiation is known to accelerate the development of coronary, pericardial and valvular heart disease. Conflicting data have been published on the impact of previous radiation on the outcomes of cardiac surgery, but these data may be confounded by the need for combined coronary artery bypass grafting (CABG) and valvular surgery and patient comorbidities.

What does this study add?
This was a propensity-matched study of patients undergoing isolated CABG without the confounding impact of combined valve surgery. When compared with controls, patients with previous radiation exposure did not experience an increase in surgical complications and had similar long-term survival. However, there was a non-significant trend towards fewer internal mammary artery (IMA) grafts.

How might this impact on clinical practice?
Previous radiation did not increase postoperative complications or long-term mortality in isolated CABG patients, but fewer IMA grafts were used. The survival benefit of CABG is driven by IMA to left anterior descending artery grafts. Preoperative IMA angiography should be performed, and if a suitable IMA is not identified, percutaneous revascularisation should be considered as it has been proven safe and effective in this population. Furthermore, this population is at increased risk for later development of valvular disease, and by avoiding an early sternotomy for coronary revascularisation, the risk of subsequent valve surgeries may be lessened.

INTRODUCTION

External beam radiation therapy (XRT) is used for a wide range of malignancies and has substantially improved cancer survival.[1 2] As cancer survival has improved, the long-term sequelae related to radiation heart disease are becoming more prevalent. Radiation heart disease is associated with a high incidence of ischaemic heart disease that requires revascularisation.[3 4] Coronary artery bypass graft surgery (CABG) improves long-term survival in patients with obstructive left main coronary artery or triple vessel disease.[5–8] However, in patients with previous thoracic XRT, cardiac surgery has been associated with increased perioperative complications and higher long-term mortality.[9–13] The contemporary performance of isolated CABG in the XRT population has not been adequately assessed, and given recent trial data supporting the role of percutaneous interventions in treating three vessel and left main coronary disease, it is critical to establish the relative risks and benefits of surgical revascularisation in this potentially

Accepted: 29 May 2018
DOI: 10.1111/ejh.13105

ORIGINAL ARTICLE

WILEY Haematology

Off-label use of 4-factor prothrombin complex concentrate is common despite little known benefit: A retrospective study

Carlton D. Scharman[1] | Joseph J. Shatzel[2] | Edward Kim[3] | Thomas G. DeLoughery[2]

[1]Department of Internal Medicine, Oregon Health & Science University, Portland, OR, USA
[2]Division of Hematology & Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA
[3]School of Medicine, Oregon Health & Science University, Portland, OR, USA

Correspondence
Joseph J. Shatzel, Department of Hematology & Oncology, Oregon Health & Science University, Portland, OR, USA.
Email: shatzel@ohsu.edu

Abstract

Background/Objective: While four-factor prothrombin complex concentrate (4F-PCC) is FDA-approved for reversal of warfarin-induced major bleeding, its use in real-world settings is unclear. This study's objective was to identify indications leading to 4F-PCC use and associated outcomes at a single university hospital.
Methods: This was a retrospective cohort study of patients receiving 4F-PCC over a 22-month period. A dose was "on-label" if given for reversal of warfarin-induced coagulopathy in patients with major bleeding or requiring urgent surgeries/procedures; other doses were "off-label".
Results: A total of 165 doses of 4F-PCC in 154 patients were given. Sixty-one percent of doses were on-label, while 39% were off-label. Intracranial hemorrhage was the most common indication (55% of doses). On-label patients had significantly higher rate of INR normalization and survival to hospital discharge than off-label patients. There was no difference in time to INR normalization, time to hemostasis, or incidence of thromboembolic complications.
Conclusions: Off-label use of 4F-PCC is likely common, occurring in nearly 40% of drug administrations at our center. Larger-scale prospective trials studying specific indications are needed for validation in off-label settings. Until such evidence is available, given potential harms historically displayed by off-label use of other hemostatic agents, limiting off-label 4F-PCC use is recommended.

KEYWORDS
anticoagulants, antidotes, drug evaluation, factor VIIa, hemorrhage, prothrombin complex concentrate

1 | INTRODUCTION

Four-factor prothrombin complex concentrate (4F-PCC) has been approved in the United States since 2013 for reversal of warfarin-induced coagulopathy in patients with major bleeding and for reversal of warfarin to allow for urgent surgical or invasive procedures. This approval was based on a randomized controlled trial comparing 4F-PCC to plasma in warfarin-associated major bleeding, which showed improvement in hemostasis and more rapid INR correction with 4F-PCC.[1] A similar study assessing the efficacy of 4F-PCC vs plasma for reversal of warfarin-associated intracranial hemorrhage again found benefit and was stopped early as the degree of intracranial hematoma expansion was significantly reduced with 4F-PCC.[2] This has led to major guidelines suggesting 4F-PCC over plasma for reversal of warfarin-associated major bleeding.[3] Major guidelines also suggest 4F-PCC be considered for reversal of direct oral anticoagulants (DOACs), although emphasize that data are limited and largely based on preclinical data and studies in healthy volunteers, with no prospective randomized data in patients with DOAC-associated bleeding yet reported.[4–6]

Major bleeding is not uncommon and can occur due to a variety of etiologies. There is a natural tendency on the part of providers to

QUALITY IMPROVEMENT

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY DECEMBER 2017, VOL. 38, NO. 12

ORIGINAL ARTICLE

Effect of Clinical Variables on the Volume of Blood Collected for Blood Cultures in an Adult Patient Population

R. Logan Jones, BS;[1] Harlan R. Sayles, MS;[2] Paul D. Fey, PhD;[3] Mark E. Rupp, MD[1]

OBJECTIVE. To identify clinical variables that influence blood culture volume recovery.

DESIGN. Retrospective chart review and linear model analysis.

SETTING. A 621-bed Academic Medical Center with a Clinical Laboratory that processes 20,000+ blood cultures annually and dedicated phlebotomy staff for venipuncture.

PATIENTS. Consecutive patients requiring blood culture.

METHODS. Over a 6-day period, blood volume was determined in 568 culture bottles from 128 unique adult patients, and clinical data from the time of phlebotomy were extracted from hospital electronic medical records. Conditional hierarchical linear models with random effects for patient and phlebotomy occasion were utilized to analyze correlations between values collected from the same patient and during the same phlebotomy occasion.

RESULTS. Blood samples obtained from a central venous catheter yielded, on average, 2.53 mL more blood (95% CI, 1.63–3.44 mL; $P < .001$) than those from peripheral venipuncture, and aerobic bottles contained 0.38 mL more blood (95% CI, 0.1–0.67 mL; $P = .009$) than the anaerobic bottles. The remaining clinical variables (eg, hospital department, patient age, body mass index, gender, mean arterial pressure, concomitant systemic antibiotic use, and Charlson comorbidity index score) failed to reach statistical significance ($P < .05$) in relation to volume.

CONCLUSIONS. Blood cultures obtained from central venous catheters contain significantly greater volume than those obtained via peripheral venipuncture. These data highlight the clinically significant issue of low culture volume recovery, indicate that diagnostic and prognostic tools that rely on volume-dependent phenomena (ie, time to positivity) may require further validation under usual clinical practice circumstances, and suggest goals for future institutional performance improvement.

Infect Control Hosp Epidemiol 2017;38:1493–1497

Blood cultures are an invaluable diagnostic tool for the detection of potentially life-threatening infections. Results of blood cultures can provide a definitive diagnosis, direct the therapeutic course, and offer key prognostic information.[1] The performance of automated blood culture systems is volume dependent; decreased sensitivity or specificity is associated with under- or overfilling blood culture bottles.[2–7] Furthermore, optimization of the volume of blood collected can decrease the time to positivity, thus potentially expediting appropriate diagnosis and treatment.[8–11]

Factors that influence culture contamination include proper skin preparation, the use of dedicated phlebotomy teams, single versus double needles for bottle inoculation, and blood draw site (ie, peripheral venipuncture versus central venous catheter access).[12] Additionally, higher volumes of blood collection are associated with reduced levels of blood contamination.[13,14]

Diagnostic errors associated with blood cultures due to decreased test performance and improper interpretation carry serious consequences. Poor test sensitivity can lead to false-negative results that may delay diagnosis and therapy, leading to increased patient morbidity and mortality. False-positive results or contamination can lead to longer hospital stays, unnecessary antibiotic use, and additional laboratory testing.[15] The financial impact is estimated at $3,000 in excess healthcare costs per contaminated culture.[16]

A recent internal quality control study performed at the University of Nebraska Medical Center (unpublished) indicated that blood culture volumes were not meeting recommended levels and that draw site was implicated as a possible reason for the insufficient volumes. The goal of this survey of blood cultures was to model the impact of draw site and other clinical variables on the volume of blood cultures in usual dinical practice circumstances.

Affiliations: 1. Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska; 2. Department of Biostatistics, University of Nebraska Medical Center, Omaha, Nebraska; 3. Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska.

PREVIOUS PRESENTATION: This work was presented as an abstract at IDWeek on October 26, 2016, in New Orleans, Louisiana.

Received April 12, 2017; accepted October 16, 2017; electronically published November 21, 2017

 0899-823X/2017/3812-0014. DOI: 10.1017/ice.2017.230

» This article has been updated from its originally published version to correct Table 2. See the corresponding erratum notice, DOI: 10.3171/2017.3.SPINE15776a «

JNS SPINE

CLINICAL ARTICLE

J Neurosurg Spine 25:185–189, 2016

Hospital charges associated with "never events": comparison of anterior cervical discectomy and fusion, posterior lumbar interbody fusion, and lumbar laminectomy to total joint arthroplasty

Alan H. Daniels, MD,[1] Satoshi Kawaguchi, MD,[2] Alec G. Contag, BS,[2] Farbod Rastegar, MD,[2] Garrett Waagmeester, MD,[2] Paul A. Anderson, MD,[3] Melanie Arthur, PhD,[4] and Robert A. Hart, MD[2]

[1]Department of Orthopedics, Adult Spinal Deformity Service, Brown University, Warren Alpert Medical School, Providence, Rhode Island; [2]Department of Orthopedics and Rehabilitation, Oregon Health and Science University, Portland, Oregon; [3]Department of Orthopedics, University of Wisconsin, Madison, Wisconsin; and [4]Department of Humanities and Social Sciences, Oregon Institute of Technology, Klamath Falls, Oregon

OBJECTIVE Beginning in 2008, the Centers for Medicare and Medicaid Service (CMS) determined that certain hospital-acquired adverse events such as surgical site infection (SSI) following spine surgery should never occur. The following year, they expanded the ruling to include deep vein thrombosis (DVT) and pulmonary embolism (PE) following total joint arthroplasty. Due to their ruling that "never events" are not the payers' responsibility, CMS insists that the costs of managing these complications be borne by hospitals and health care providers, rather than billings to health care payers for additional care required in their management. Data comparing the expected costs of such adverse events in patients undergoing spine and orthopedic surgery have not previously been reported.

METHODS The California State Inpatient Database (CA SID) from 2008 to 2009 was used for the analysis. All patients with primary procedure codes indicating anterior cervical discectomy and fusion (ACDF), posterior lumbar interbody fusion (PLIF), lumbar laminectomy (LL), total knee replacement (TKR), and total hip replacement (THR) were analyzed. Patients with diagnostic and/or treatment codes for DVT, PE, and SSI were separated from patients without these complication codes. Patients with more than 1 primary procedure code or more than 1 complication code were excluded. Median charges for treatment from primary surgery through 3 months postoperatively were calculated.

RESULTS The incidence of the examined adverse events was lowest for ACDF (0.6% DVT, 0.1% PE, and 0.03% SSI) and highest for TKA (1.3% DVT, 0.3% PE, 0.6% SSI). Median inpatient charges for uncomplicated LL was $51,817, compared with $73,432 for ACDF, $143,601 for PLIF, $74,459 for THR, and $70,116 for TKR. Charges for patients with DVT ranged from $108,387 for TKR (1.5 times greater than index) to $313,536 for ACDF (4.3 times greater than index). Charges for patients with PE ranged from $127,958 for TKR (1.8 times greater than index) to $246,637 for PLIF (1.7 times greater than index). Charges for patients with SSI ranged from $168,964 for TKR (2.4 times greater than index) to $385,753 for PLIF (2.7 times greater than index).

CONCLUSIONS Although incidence rates are low, adverse events of spinal procedures substantially increase the cost of care. Charges for patients experiencing DVT, PE, and SSI increased in this study by factors ranging from 1.8 to 4.3 times those for patients without such complications across 5 common spinal and orthopedic procedures. Cost projections by health care providers will need to incorporate expected costs of added care for patients experiencing such complications, assuming that the cost burden of such events continues to shift from payers to providers.

http://thejns.org/doi/abs/10.3171/2015.11.SPINE15776

KEY WORDS never event; adverse event; complication; cost; hospital charge; infection; deep vein thrombosis; anterior cervical discectomy and fusion; lumbar

ABBREVIATIONS ACDF = anterior cervical discectomy and fusion; CA-SID = California State Inpatient Database; CMS = Centers for Medicare and Medicaid Service; DVT = deep vein thrombosis; HCUP = Healthcare Cost and Utilization Project; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; LL = lumbar laminectomy; PE = pulmonary embolism; PLIF = posterior lumbar interbody fusion; SSI = surgical site infection; THR = total hip replacement; TKR = total knee

ORIGINAL ARTICLE: Clinical Endoscopy

Gender disparities in gastroenterology fellowship director positions in the United States

Zibing Woodward, MD,[1,2] Zaida Rodriguez, MD,[1,3] Janice H. Jou, MD,[1,3] Kian Keyashian, MD,[1,3] Yiyi Chen, PhD,[1] Charles R. Thomas, Jr, MD,[4] Grace H. Elta, MD,[4] Sharlene L. D'Souza, MD[1,3]

Portland, Oregon, USA

Background and Aims: Despite a paucity of women occupying leadership positions in academic medicine, studies have shown a higher ratio of female representation in the program director position compared with division chief in multiple specialties. This study aims to determine whether this trend exists in 3-year gastroenterology fellowships in the United States and to evaluate for any factors that may affect these differences.

Methods: In 2015, data were collected for the 163 U.S. gastroenterology fellowship programs including program director, associate program director, division chief, gender distribution, program size, academic center affiliation, and geographic region.

Results: A higher percentage of men than women held the role of program director (82% vs 18%), associate program director (72% vs 28%), and division chief (93% vs 7%). Women in program leadership held lower academic rank than their male counterparts ($P < .0001$). The program director was more likely to be female if the division chief also was female ($P = .03$). Programs with a higher number of trainees tended to be led by a female program director ($P = .06$).

Conclusions: A gender disparity exists in all gastroenterology leadership roles, although the magnitude is smaller for program director and associate program director than the role of division chief. Further studies are needed to investigate the impact of this disparity on promotion and academic productivity. (Gastrointest Endosc 2017;86:595-9.)

Traditionally, women have been underrepresented in all fields of medicine, although the gender gap has been slowly decreasing over the past few decades. According to data from the Association of American Medical Colleges Physician Specialty Data Book, in 2013, women comprised 46% of trainees across all specialties, 35% of gastroenterology trainees, and 15% of practicing gastroenterologists.[1] This is in comparison to 10 years ago, when only a quarter of first-year gastroenterology fellows were women.[2,3] In recent years, although there is more gender parity for medical school applicants, matriculates, and residents across all specialties, the proportion of female academic faculty is only 38%.[4] This percentage decreases even further with higher academic rank; women account for only 21% of full professors, 16% of medical school deans, and 15% of department chairs.[4] Among full-time faculty, the only academic rank in which women outnumbered men was the clinical instructor level—the lowest rank.[4]

This gender disparity also is seen in the field of gastroenterology. A study by Burke et al[5] surveyed gastroenterology fellows 3 years, 5 years, and 10 years after graduation and showed that there was a larger proportion of women in academic practice at all time points surveyed[5,6]; however, even at 10 years after graduation, they had significantly lower academic ranks, with 30% holding the rank of associate professor as compared with

Abbreviations: ASGE, the American Society for Gastrointestinal Endoscopy.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2017.01.019

Received September 20, 2016. Accepted January 20, 2017.

Current affiliations: Oregon Health and Science University, Portland (1), The Oregon Clinic–GI South, Portland (2), Portland VA Health Care System, Portland, Oregon (3), University of Michigan Health System, Ann Arbor, Michigan (4).

Reprint requests: Zibing Woodward, MD, The Oregon Clinic–GI South, 19250 SW 90th Ave, Tualatin, OR 97062.

REVIEW/META-ANALYSES

American Journal of Nephrology

In-Depth Topic Review

Am J Nephrol 2018;48:96–107
DOI: 10.1159/000492033

Received: May 16, 2018
Accepted: July 4, 2018
Published online: August 15, 2018

When to Stop Eculizumab in Complement-Mediated Thrombotic Microangiopathies

Sven R. Olson[a] Eric Lu[b] Emilio Sulpizio[b] Joseph J. Shatzel[a] Jose F. Rueda[c] Thomas G. DeLoughery[a]

[a]Division of Hematology and Medical Oncology, Oregon Health and Science University, Knight Cancer Institute, Portland, OR, USA; [b]Department of Internal Medicine, Oregon Health and Science University, Portland, OR, USA; [c]Division of Nephrology and Hypertension, Oregon Health and Science University, Portland, OR, USA

Keywords
Thrombotic microangiopathy · Complement · Eculizumab · Thrombotic thrombocytopenic purpura · Hemolytic uremic syndrome · Atypical hemolytic uremic syndrome · Secondary hemolytic uremic syndrome · Transplant-associated-thrombotic microangiopathies · Drug-induced

Abstract
The terminal complement-inhibitor eculizumab has dramatically changed the management of patients with atypical hemolytic uremic syndrome (aHUS), and has also shown promise for treating certain forms of secondary HUS (sHUS), including that caused by drugs and solid-organ/hematopoietic stem cell transplant. While effective, eculizumab is costly and inconvenient. In this review, we evaluate the literature on eculizumab cessation in these diseases to better inform clinicians who consider stopping therapy. Reported relapse rates in aHUS after stopping eculizumab are as high as 30%, suggesting indefinite therapy is reasonable and that patients who choose to stop should be closely monitored. In sHUS, relapse is rare, justifying short courses of eculizumab.

Introduction

Thrombotic microangiopathies (TMA) are a group of disorders characterized by the combination of intravascular microangiopathic hemolytic anemia, thrombocytopenia, and micro- and macrovascular thrombosis. The latter pathologic findings can manifest as varying degrees of end-organ damage, most commonly renal failure or neurologic deficits. TMAs can be further subdivided into 3 categories: thrombotic thrombocytopenic purpura (TTP), typical hemolytic uremic syndrome (typical hemolytic uremic syndrome [HUS]), and the group of disorders known as complement-mediated TMAs (Table 1) [1–3].

TTP is caused by a congenital or acquired deficiency in the metalloprotease ADAMTS13, resulting in impaired

Received: 23 July 2018 | Revised: 13 August 2018 | Accepted: 14 August 2018
DOI: 10.1111/ejh.13165

REVIEW ARTICLE

WILEY Haematology

Arterial thrombosis in unusual sites: A practical review

Matthew O'Donnell[1] | Joseph J. Shatzel[1,2] | Sven R. Olson[1] | Molly M. Daughety[1] | Khanh P. Nguyen[3] | Justine Hum[4] | Thomas G. DeLoughery[1]

[1]Division of Hematology-Oncology, Oregon Health & Science University, Portland, Oregon
[2]Biomedical Engineering, Oregon Health & Science University, Portland, Oregon
[3]Division of Vascular Surgery, Oregon Health & Science University, Portland, Oregon
[4]Division of Gastroenterology, Oregon Health & Science University, Portland, Oregon

Correspondence
Joseph J. Shatzel, Department of Hematology and Oncology, Oregon Health & Science University, Portland, OR.
Email: shatzel@ohsu.edu

Abstract
While cardiovascular disease is common, occasionally hematologists and other practitioners will encounter patients with arterial thrombosis/infarction in unusual sites, without clear cause or obvious diagnostic and treatment paradigms. Contrary to the more commonly encountered cerebrovascular accident and cardiovascular disorders, the various infarctions outlined in this review have unique presentations, pathophysiology, workup, and treatments that all hematologists should be aware of. This review outlines the current literature on arterial thrombosis, with consideration given to anatomic sources and hypercoagulable associations, while focusing on the epidemiology, pathophysiology, provoking factors, and current recommended treatments for intracardiac thrombus, primary aortic mural thrombus, visceral infarctions, and cryptogenic limb ischemia to provide a useful and practical review for the practitioner.

KEYWORDS
arterial thrombosis, coagulation disorder, hypercoagulable, infarction

1 | INTRODUCTION TO ARTERIAL THROMBOSIS

While common forms of arterial disease such as stroke and myocardial infarction are well studied and appropriate treatment algorithms are well described, occasionally, practitioners will encounter patients with thrombosis in other arteries; the cause and treatment of which is not entirely obvious or well studied. In this section, we will review the current data on arterial thrombosis, describing anatomic sources and hypercoagulable associations, and outline the epidemiology, pathophysiology, clinical presentation, etiology, and treatment of intracardiac thrombus, primary aortic mural thrombus, visceral infarctions, and cryptogenic limb ischemia. (Table 1).

2 | ARTERIAL THROMBOSIS—ANATOMIC CONSIDERATIONS

Arterial thrombosis most often occurs in association with atherosclerosis. In cryptogenic cases, arterial thrombosis may result from an anatomic source, the most common of which is cardioembolic, such as intracardiac thrombus, atrial appendage thrombus, patent foramen ovale with paradoxical embolus, and valvular vegetation. The minimal workup we consider in truly cryptogenic cases is assessment for a cardioembolic source (Figure 1) including a transthoracic echocardiogram in conjunction with injection of agitated saline contrast and color Doppler imaging in order to detect a patent foramen ovale. Due to the unique nature of intracardiac thrombi and primary aortic mural thrombi, the following sections will outline the epidemiology, etiology, and management of these entities.

3 | INTRACARDIAC THROMBI

Left ventricular (LV) thrombus most commonly occur after myocardial infarction, particularly in cases of large anterior STEMI in the distribution of the left anterior descending coronary artery[1]; however, hypereosinophilia remains an important cause documented in various case reports.[2] Anteroapical infarcts result in poor contraction of the LV muscle and stasis of intracavitary blood flow. This relative stasis of blood is thought to increase the risk of thrombus formation. One recent systematic review revealed the rate of LV thrombi in the postpercutaneous coronary intervention (PCI) era after all STEMI was 2.7% and 9.1% after anterior STEMI.[3] The major risk of

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Journal of Thrombosis and Thrombolysis (2018) 46:22–23
https://doi.org/10.1007/s11239-018-1648-8

CrossMark

More efficacious, equally safe: a meta-analysis comparing the safety of direct oral anticoagulants versus aspirin

Jeffrey Y. Bien[1] · Derrick L. Tao[2] · Molly M. Daughety[3] · Thomas G. DeLoughery[3] · Joseph J. Shatzel[3]

Published online: 22 March 2018

Whether aspirin carries a favorable safety profile compared to direct oral anticoagulants (DOACs) remains a topic of controversy. A recent study by Hsu et al. illustrates how providers often preferentially choose aspirin for patients they perceive to be at high risk of bleeding, noting that over 38% of patients who qualify for additional anticoagulation per guidelines are actually managed on aspirin alone in real life practice [1].

Past investigations comparing the safety profile of aspirin against warfarin reveal no observable difference in bleeding events [2]. In turn, DOACs have been shown to be consistently safer than warfarin, with pooled analysis demonstrating decreased rates of total bleeding, major bleeding, and fatal bleeding [3]. However, data directly comparing the safety and efficacy of aspirin against DOACs has been sparse until recently.

The 2017 publication of the EINSTEIN CHOICE trial marked only the second large randomized controlled trial comparing aspirin to full-dose DOACs [4]. The trial found rivaroxaban to be significantly more effective at preventing recurrent venous thromboembolism (VTE) in high-risk patients than aspirin. Before it, the AVERROES trial showed apixaban was significantly more effective at preventing embolic strokes in patients with atrial fibrillation than aspirin [5]. Importantly, neither trial detected a significant increase in bleeding rates with DOACs when compared to aspirin. The results of the aforementioned studies independently suggest that DOACs are significantly more effective at preventing thromboembolic events than aspirin, while carrying an equivalent safety profile.

In order to better clarify the bleeding risks of DOACs versus aspirin, we used data from the two recently-published, phase III trials—EINSTEIN CHOICE and AVERROES-to perform a pooled meta-analysis using a Mantel–Haenszel random-effects model. In total, 3915 patients were treated with a therapeutic dose DOAC (apixaban 5 mg BID or rivaroxaban 20 mg daily) and 3922 were treated with varied doses of aspirin (81 mg [46.9%], 100 mg [27.6%], 162 mg [18.5%], 243 mg [1.9%], 324 mg [5.0%], and unknown dose [0.2%]). Our analysis detected no statistically significant difference in major bleeding events (1.27 vs. 1.07%; $p = 0.42$) or clinically-relevant, non-major bleeding events (3.22 vs. 2.65%; $p = 0.14$) between the two groups (Table 1).

Based on the results of our pooled analysis, we conclude that aspirin is not appreciably safer than DOACs in terms of bleeding risk. If, by chance, a true difference in bleeding risk does exist, it is likely small and not clinically relevant. Therefore, given the superior efficacy of secondary VTE prevention in high-risk patients (HR 0.34; $p < 0.01$) [4] and stroke prevention in atrial fibrillation (HR 0.45; $p < 0.01$) [5], these results suggest that DOACs should always be preferentially used over aspirin in these populations.

While current guidelines endorse the use of DOACs for the primary prevention of stroke in atrial fibrillation, these same guidelines continue to include aspirin as a possible therapeutic option for patients with atrial fibrillation with a low CHADS2-VASC score [6]. Furthermore, major society guidelines continue to endorse the consideration of aspirin for secondary prevention of venous thromboembolism in patients perceived to carry too high of a bleeding risk for anticoagulation [7]. We speculate that the persistence of these guidelines is both due to, and helps encourage, a popular but ill-conceived and non-empirical notion that aspirin is "safer". The resultant real-world prescribing practices are described by Hsu et al. in which nearly 40% of patients

✉ Jeffrey Y. Bien
bien@ohsu.edu

[1] Department of Medicine, Oregon Health & Science University, Box OP30, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
[2] School of Medicine, Oregon Health & Science University, Portland, OR, USA
[3] Division of Hematology and Medical Oncology, Oregon Health & Science University, Knight Cancer Institute, Portland, OR, USA

COMMENT/LETTER TO EDITOR/CORRESPONDENCE

Comment

Choice of control group in randomised trials of cancer medicine: are we testing trivialities?

Several trials in cancer medicine over the past 5 years share two common features: first, they were used—or were intended to be used—to seek marketing authorisation from the US Food and Drug Administration (FDA) or European Medicines Agency, and second, they test an experimental group against a weak comparator that is infrequently used in practice. The choices of comparators in four trials—those of ibrutinib and rituximab versus rituximab in Waldenström's macroglobulinaemia,[1] ibrutinib versus chlorambucil in rituximab against rituximab alone for patients with Waldenström's macroglobulinaemia. At 30 months of follow-up, ibrutinib plus rituximab improved progression-free survival compared with rituximab alone.[1] However, rituximab is rarely recommended as the sole first-line therapy, typically being reserved for slowly progressive disease. In an observational dataset, which had the limitation of being self-reported, only 24 (13%) of 180 patients with Waldenström's macroglobulinaemia received single-agent rituximab.[1] Moreover, ibrutinib has already been shown to have single-agent activity and is approved for second-line therapy. Is it then surprising that addition of an active agent improves time to progression?

On March 4, 2016, ibrutinib received front-line approval for lymphocytic leukaemia on the basis of an RCT testing it against single-agent chlorambucil in elderly patients.[2] However, as noted by Jeff Sharman and colleagues in a survey of a large US registry at the time of the study, "only 40 of 889 patients with chronic lymphocytic leukaemia (4·5%) received chlorambucil monotherapy as first-line therapy".[6] Moreover, Sharman and colleagues point out that "Chlorambucil has served as a comparator in trials of bendamustine, alemtuzumab, ofatumumab, and obinutuzumab, and improved progression-free survival have been reported with each agent."[6] Thus, the use of single-agent chlorambucil appears to be a poorly justified and, in clinical practice, infrequently used choice of control.

In 2015, nivolumab was compared with dacarbazine for melanoma.[4] The trial investigators enrolled patients between January, 2013, and February, 2014. However, ipilimumab was approved for melanoma on March 25, 2011, and was shown to confer survival benefit if added to dacarbazine in the same year.[7] Thus, dacarbazine seems have been chosen, despite it being known to be an inferior comparator at the time of the study.

All these trials were done with the goal of expeditious regulatory approval in the USA and Europe in broad, front-line patient populations, but used control groups that often did not reflect the current standard of care in those nations. The results of these trials answer the technical question of whether the experimental group is superior to the control group, but they do not address the health-care provider's principal question: is this experimental therapy superior to the treatment I offer my patients?

In several cases, the experimental agent had already shown activity in the disease, and was already approved for a later line of therapy; thus it should not be surprising that, when moved forward in therapy, the drug delays time to progression. However, whether the drug is best used as initial therapy or in a later line remains unanswered.

As a profession, we oncologists must recognise that the most precious resources in the clinical trials system are the patients. Patients are finite and scarce, particularly those with less common malignancies, such as metastatic melanoma or Waldenström's macroglobulinaemia. Vincent Rajkumar, a professor at the Mayo Clinic (Rochester, MN, USA), recently wrote regarding these trials, "For drugs on the market, the RCT has to be fair and not biased. The control has to be [standard of care]."[8] Adding, "when these kind of trials are published, we need to be honest that they cannot be used to change practice".[10]

The solution to the problem is for regulatory agencies to demand that registration studies compare novel drugs to the most frequently used therapies in that setting. Real world data can help to clarify which control groups are representative. While agencies like the FDA lack a comparative effectiveness authority, the agency does have the ability to halt trials that use control groups beneath the standard of care. Exercise of this

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TO THE EDITOR: Mark et al. evaluated quality of life in patients treated with ICDs as compared with optimal medical management. However, the outcomes measured in this study may not capture important psychosocial factors such as anxiety or the effect of a preexisting psychiatric diagnosis.

A limited number of studies suggest that ICD implantation and subsequent shocks may exacerbate symptoms of anxiety, fear, and agoraphobia.[1,2] Although Mark et al. report that data provide some support for the use of ICDs in patients with severely reduced systolic dysfunction, none of the outcome measures specifically addressed fear, anxiety, or both. We wonder whether anxiety-specific instruments such as the State–Trait Anxiety Index were included in the structured interviews.

JOURNAL of MEDICINE

There may be an increased risk of psychosocial dysfunction among patients with preexisting psychiatric diagnoses who undergo ICD implantation.[3] In order to assess the generalizability of these data to populations with a higher prevalence of coexisting psychiatric conditions, it would be helpful to know about the baseline prevalence of psychiatric illness in the study by Mark et al.

Robin M. Telerant, M.D.
Nathan Boyer, M.D.
Devan Kansagara, M.D.

Oregon Health and Sciences University
Portland, OR 97239
telerant@ohsu.edu

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Dreicer et al. Blood Cancer Journal 2017;7:4
DOI 10.1038/s41408-017-0009-8

Blood Cancer Journal

CORRESPONDENCE Open Access

Clinically meaningful benefit: real world use compared against the American and European guidelines

Jessica J. Dreicer[1], Sham Mailankody[2], Farhad Fahkrejahani[3] and Vinay Prasad[4,5,6]

Although some cancer drugs offer large, indisputable benefits[1], many drugs improve outcomes only marginally[2]. Recognizing the need to develop therapies of meaningful benefit to our patients, both the American Society of Clinical Oncology (ASCO)[3] and the European Society of Medical Oncology (ESMO)[4] have issued expert guidelines stating the magnitude of benefit that is clinically meaningful. These groups define clinically meaningful as whether drugs meet benchmarks of improvements in overall and progression free survival. For example, the ASCO guidelines propose that a new chemotherapeutic result in a relative increase in the median OS of at least 20% or 2.5–6 months[3].

Prior groups have compared approved drugs[5] and randomized trials[6] against the ASCO and ESMO thresholds; however, to our knowledge, no analysis has compared the ASCO and ESMO thresholds against oncologist's use of the phrase "meaningful benefit" in the published literature.

We sought biomedical articles where authors explicitly endorsed or stated that some numerical improvement in a clinical outcome seen in a randomized controlled trial constituted a meaningful benefit for a particular cancer indication.

We searched Google Scholar with the terms "meaningful benefit" and "oncology" or "meaningful benefit" and "cancer," and limited our results to 2014 and 2015, as we were concerned with recent usage. Each article was reviewed by J.J.D. who identified the claim of meaningful benefit. Our study was conducted between November 2015 and March 2016.

Articles were excluded if: the article did not pertain to the field of oncology, the authors did not refer to a specific drug or combination, the authors were not claiming a meaningful benefit (i.e., they were saying a meaningful benefit does not exist), or the article did not reference a randomized trial and no such trial could be found.

We extracted changes in overall survival (OS), progression free survival, or other clinical endpoints between intervention and control arms that were deemed meaningful benefit. Descriptive statistics is provided. We

Table 1 Cancer types where meaningful benefit was used

Cancer types reported in the advanced or metastatic setting	
Cancer type	**Instances**
Pancreatic	8
Breast	7
Non-small cell lung	7
Prostate	6
Colorectal	6
Myeloproliferative neoplasm	3
Melanoma	2
Thyroid	2
Glioblastoma	2
Ovarian	2
Gastric	1
Neuroendocrine	1
Acute myeloid leukemia	1
Germ-cell	1

Correspondence: Vinay Prasad (prasad@ohsu.edu)
[1]Department of Medicine/OHSU, Portland, OR 97239, USA
[2]Myeloma Service/Memorial Sloan Kettering Cancer Center, New York City, NY, USA
Full list of author information is available at the end of the article

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MEDICAL EDUCATION

Clay et al. Crit Ultrasound J (2016) 8:11
DOI 10.1186/s13089-016-0047-7

Critical Ultrasound Journal

ORIGINAL ARTICLE Open Access

Teaching the internist to see: effectiveness of a 1-day workshop in bedside ultrasound for internal medicine residents

Ryan D. Clay[1,3], Elizabeth C. Lee[1], Marc F. Kurtzman[1] and Renee K. Dversdal[2*]

Abstract

Background: A growing body of evidence supports the use of bedside ultrasound for core Internal Medicine procedures and increasingly as augmentation of the physical exam. The literature also supports that trainees, both medical students and residents, can acquire these skills. However, there is no consensus on training approach.

Aim: To implement and study the effectiveness of a high-yield and expedited curriculum to train internal medicine interns to use bedside ultrasound for physical examination and procedures.

Setting: The study was conducted at a metropolitan, academic medical center and included 33 Internal Medicine interns.

Program description: This was a prospective cohort study of a new educational intervention consisting of a single-day intensive bedside ultrasound workshop followed by two optional hour-long workshops later in the year. The investigation was conducted at Oregon Health & Science University in Portland, Oregon. The intensive day consisted of alternating didactic sessions with small group hands-on ultrasound practice sessions and ultrasound simulations. A 30-question assessment was used to assess ultrasound interpretation knowledge prior to, immediately post, and 6 months post intervention.

Results: Thirty-three interns served as their own historical controls. Assessment performance significantly increased after the intervention from a mean pre-test score of 18.3 (60.9 % correct) to a mean post-test score 25.5 (85.0 % correct), *P* value of <0.0001. This performance remained significantly better at 6 months with a mean score of 23.8 (79.3 % correct), *P* value <0.0001. There was significant knowledge attrition compared to the immediate post-assessment, *P* value 0.0099.

Conclusions: A single-day ultrasound training session followed by two optional noon conference sessions yielded significantly improved ultrasound interpretation skills in internal medicine interns.

Keywords: Bedside ultrasound, Physical examination, Point-of-care ultrasound, Graduate medical education, Ultrasound education, Internal Medicine education

Background

The twenty-first century has witnessed a dramatic and rapid expansion of the availability and use of technology in patient care. Improvement of pre-existing technologies, such as the miniaturization of ultrasound devices, has significantly expanded the range of use for these devices. Trauma Surgery pioneered the use of point-of-care ultrasound. Emergency Medicine followed by Critical Care then embraced and popularized bedside, provider-performed ultrasound, beginning in the 1970s. Many bedside ultrasound applications have been validated, and several specialties have ACGME training requirements for training in ultrasound. The Internal Medicine community has been slower to incorporate

*Correspondence: dversdar@ohsu.edu
[2] Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, OP-30, Portland, OR 97239, USA
Full list of author information is available at the end of the article

BRIEF REPORT

Use of Electronic Health Record Simulation to Understand the Accuracy of Intern Progress Notes

Christopher A. March, MD
Gretchen Scholl, BS
Renee K. Dversdal, MD
Matthew Richards, MD
Leah M. Wilson, MD
Vishnu Mohan, MD
Jeffrey A. Gold, MD

ABSTRACT

Background With the widespread adoption of electronic health records (EHRs), there is a growing awareness of problems in EHR training for new users and subsequent problems with the quality of information present in EHR-generated progress notes. By standardizing the case, simulation allows for the discovery of EHR patterns of use as well as a modality to aid in EHR training.

Objective To develop a high-fidelity EHR training exercise for internal medicine interns to understand patterns of EHR utilization in the generation of daily progress notes.

Methods Three months after beginning their internship, 32 interns participated in an EHR simulation designed to assess patterns in note writing and generation. Each intern was given a simulated chart and instructed to create a daily progress note. Notes were graded for use of copy-paste, macros, and accuracy of presented data.

Results A total of 31 out of 32 interns (97%) completed the exercise. There was wide variance in use of macros to populate data, with multiple macro types used for the same data category. Three-quarters of notes contained either copy-paste elements or the elimination of active medical problems from the prior days' notes. This was associated with a significant number of quality issues, including failure to recognize a lack of deep vein thrombosis prophylaxis, medications stopped on admission, and issues in prior discharge summary.

Conclusions Interns displayed wide variation in the process of creating progress notes. Additional studies are being conducted to determine the impact EHR-based simulation has on standardization of note content.

Introduction

The electronic health record (EHR) has become the major source of clinical information and documentation in health care. Consequently, graduate medical education trainees spend an increasing amount of time with the EHR.[1,2] With increased EHR use, a growing number of problems related to the integrity and quality of information has been communicated, including the use of word processing "copy-paste" functionality and predefined macros to populate notes; wide variations in individual use of these functionalities have also been reported.[3,4] This affects users' ability to cognitively process the large volume of information within the record in an effective manner, especially when related to the recognition of issues that can cause patient harm.[5]

Consequently, a number of core competencies for EHR-based education of new learners has been proposed.[6,7] However, the ideal method to optimize EHR training remains to be established. At Oregon Health & Science University (OHSU), we have employed high-fidelity simulation to create training exercises that mimic real world clinical cases to train and assess EHR competencies for medical students and residents; participation in these exercises significantly improves effective EHR use.[8,9]

In this article, we describe the creation of an EHR simulation exercise based on progress notes as part of an intern learning week, as well as the lessons learned with respect to intern EHR use patterns.

Methods

Three months after beginning residency, all OHSU internal medicine interns participated in a weeklong "Intensive/Boot Camp" designed to prepare them to handle common problems and procedures. During this week, interns were split into groups of 5 or 6 members, and then rotated through 6 predefined stations throughout the week.

OHSU health care employs EpicCare (Epic Systems, Madison, WI) as its enterprise EHR. All interns received 1.5 days of Epic training delivered by the OHSU Epic Training Team at the beginning of residency. Training includes instruction on real world task completion relevant to interns' clinical practice.

DOI: http://dx.doi.org/10.4300/JGME-D-15-00201.1

Editor's Note: The online version of this article contains a table of 28 core competencies for intern electronic health record use.

BRIEF REPORT

Transitioning Toward Competency: A Resident-Faculty Collaborative Approach to Developing a Transitions of Care EPA in an Internal Medicine Residency Program

Brian Chan, MD, MPH
Honora Englander, MD
Kyle Kent, MD
Sima Desai, MD, FACP
Adam Obley, MD
David Harmon, MD, MPH
Devan Kansagara, MD, MCR

Abstract

Background Residency training and evaluation are moving toward competency-based models. Managing transitions of care is 1 of 16 entrustable professional activities (EPAs) that signal readiness for independent internal medicine practice. Methods for developing EPAs are evolving within the medical education community.

Objective We describe a process for developing a transitions-of-care EPA for internal medicine inpatient and ambulatory settings using an iterative, consensus-building, resident-faculty collaborative approach.

Methods We used an independent rank-ordering process and successive consensus group meetings to cull an initial list of 142 developmental Milestones to the 15 most relevant to transitions of care for internal medicine patients in an academic medical center and affiliated Veterans Administration hospital. Four senior internal medicine residents and 4 internal medicine faculty members representing inpatient and ambulatory practice settings identified examples of specific tasks and evaluative techniques for each Milestone.

Results We demonstrate a feasible resident-faculty collaboration to develop transitions of care as an EPA for an internal medicine training program. Inclusion of residents along with faculty provided broader insights as well as an important learning opportunity for trainees.

Conclusions Our process demonstrated the feasibility of designing an EPA, but questions remain about how entrustment-based evaluation can be implemented in clinical settings. Our framework may serve as a foundation for EPA development in other areas of clinical practice.

Brian Chan, MD, MPH, is Primary Care Research Fellow, Department of General Internal Medicine, University of California, San Francisco; **Honora Englander, MD,** is Associate Professor of Medicine, Department of Medicine, Oregon Health & Science University, and Staff Physician, Central City Concern; **Kyle Kent, MD,** is Assistant Professor of Medicine, Department of Medicine, Portland VA Medical Center/Oregon Health & Science University; **Sima Desai, MD, FACP,** is Associate Professor and Residency Program Director, Department of Medicine, Oregon Health & Science University; **Adam Obley, MD,** is Assistant Professor, Department of Medicine, Portland VA Medical Center/Oregon Health & Science University; **David Harmon, MD, MPH,** is Assistant Professor, Department of Medicine, Oregon Health & Science University; and **Devan Kansagara, MD, MCR,** is Associate Professor, Department of Medicine, Portland VA Medical Center/Oregon Health & Science University.

Funding: The authors report no external funding source for this study.

Conflict of interest: The authors declare they have no competing interests.

The authors would like to thank Dr Thomas Cooney for providing invaluable insights during the conceptualization phase of this project.

Corresponding author: Brian Chan, MD, MPH, Division of General Internal Medicine, San Francisco General Hospital, University of California, San Francisco, CA UCSF Box 1364, San Francisco, CA 94143-1364, 858.922.9801, chanb@medsfgh.ucsf.edu

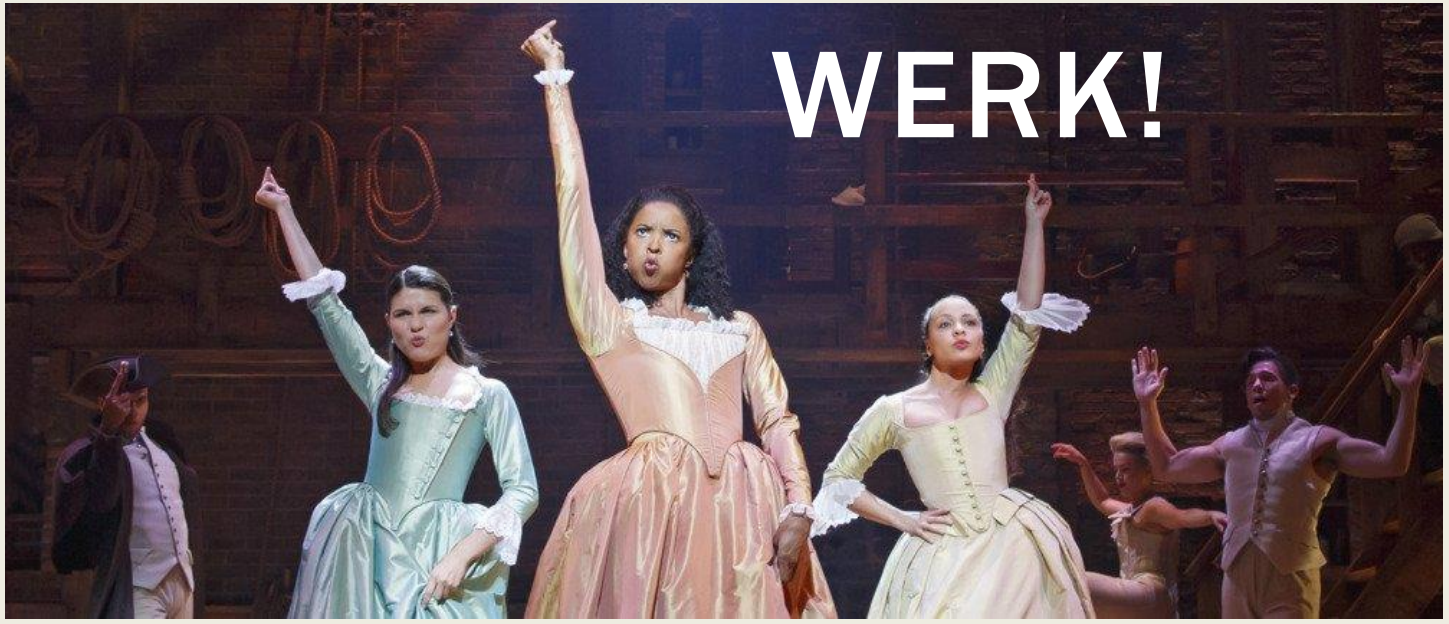
Introduction

Entrustable professional activities (EPAs) are the core activities that, together, define tasks to be executed by an unsupervised trainee once he or she has attained sufficient mastery.[1–5] The EPA framework is now used to organize the key developmental Milestones that serve as performance benchmarks of trainee assessment.[6] A Milestones task force made up of educators and experts convened by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Internal Medicine defined 142 developmental Milestones across 16 proposed EPAs.[7,8] Methods to operationalize EPAs and incorporate Milestones into their framework are evolving.[3,9–11]

Managing transitions of care, including patient hand-offs from one care setting to another, is a proposed EPA of interest in the era of duty hour limits and specialized care teams.[12] Prior work on how to incorporate Milestones into

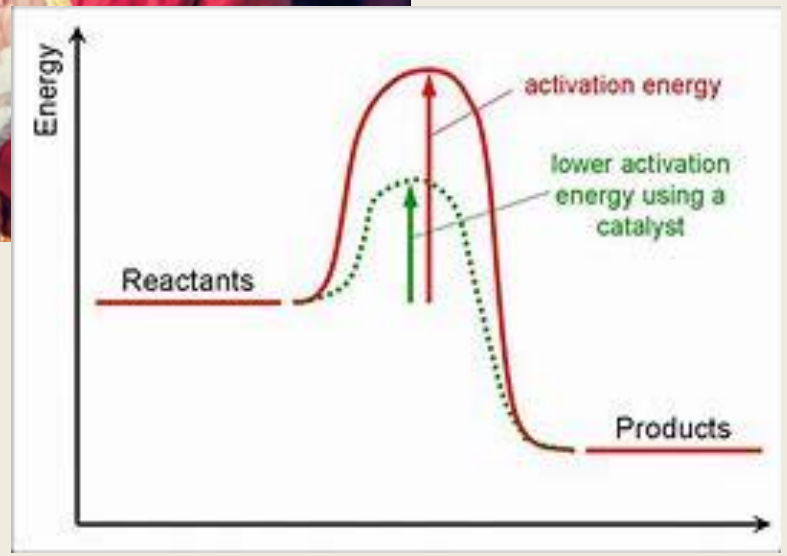
RESEARCH

- How do you find a project?
- How do you get started on a project?
  - An idea in need of a project?
  - A project in need of help?
  - Find a mentor
  - Find a work-group
  - IRB
  - Authorship
  - Statistics help
  - Write!



RESEARCH

" What comes next? …You're on your own. Awesome. Wow. Do you have a clue what happens now?



A WORD ABOUT IMPACT FACTOR

- Does impact factor truly matter???
  - Right niche
  - Right audience
  - Best chance of getting published v shooting for the stars?
  - Role of the mentor
  - Role of the Cover Letter

Appendix Table. Top 100 Medical Journals, by 5-Year Impact

IF Rank, Journal Title	Medical Journal Citations in 2014	Articles Published in 2009-2013	IF
1. *CA Cancer J Clin*	13 181	100	131.81
2. *N Engl J Med*	95 400	1754	54.39
3. *Annu Rev Immunol*	5650	121	46.69
4. *Nat Rev Cancer*	15 340	346	44.34
5. *Lancet*	60 497	1416	42.72
6. *Nat Rev Immunol*	12 762	342	37.32
7. *JAMA*	35 370	1140	31.03
8. *Cancer Cell*	13 844	508	27.25
9. *Lancet Oncol*	16 793	640	26.24
10. *Lancet Neurol*	11 109	452	24.58

Annals of Internal Medicine / Impact factor

19.384

2017

European Journal of Haematology

Edited By: Karl-Anton Kreuzer

Impact factor: 2.595

Journal of General Internal Medicine /

3.701

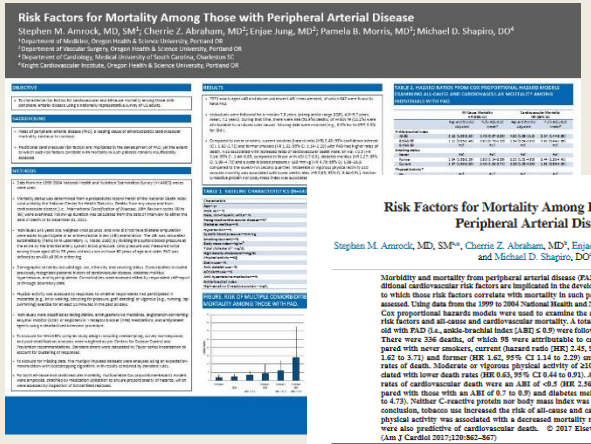
2016

JGIM is ranked #1 in the Google Scholar H-5 Index of Primary Health Care, with a 2016 H-5 Index of 61.

Impact Factor	BMJ Case Reports does not have an Impact Factor. Case reports are rarely cited and so the Impact Factor would always be low. We measure the success of BMJ Case Reports not on citation but on its educational value to healthcare professionals wherever they practice.

MILEAGE & MOMENTUM

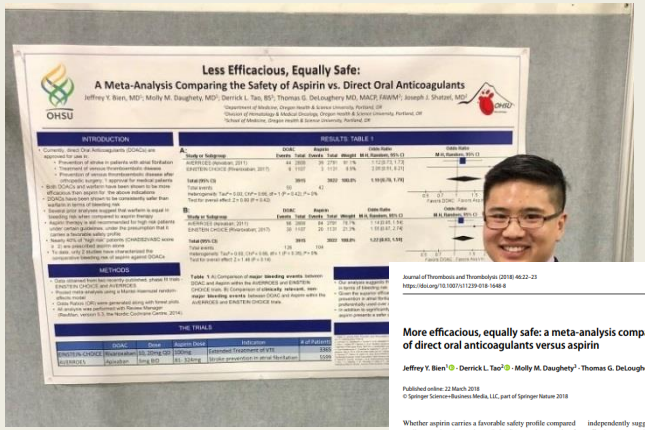
- Abstract to poster/presentation to publication
  - *…And poster to poster to poster!*


Risk Factors for Mortality Among Those with Peripheral Arterial Disease

Stephen M. Amrock, MD, SM[1]; Cherrie Z. Abraham, MD[2]; Enjae Jung, MD[2]; Pamela B. Morris, MD[2]; Michael D. Shapiro, DO[4]


Risk Factors for Mortality Among Individuals With Peripheral Arterial Disease

Stephen M. Amrock, MD, SM[a,*], Cherrie Z. Abraham, MD[b], Enjae Jung, MD[b], Pamela B. Morris, MD[c], and Michael D. Shapiro, DO[d]


Less Efficacious, Equally Safe:
A Meta-Analysis Comparing the Safety of Aspirin vs. Direct Oral Anticoagulants

Jeffrey Y. Bien, MD[1]; Molly M. Daugherty, MD[2]; Derrick L. Tao, BS[3]; Thomas G. DeLoughery MD, MACP, FAWM[2]; Joseph J. Shatzel, MD[2]


Journal of Thrombosis and Thrombolysis (2018) 46:22–23
https://doi.org/10.1007/s11239-018-1648-8

More efficacious, equally safe: a meta-analysis comparing the safety of direct oral anticoagulants versus aspirin

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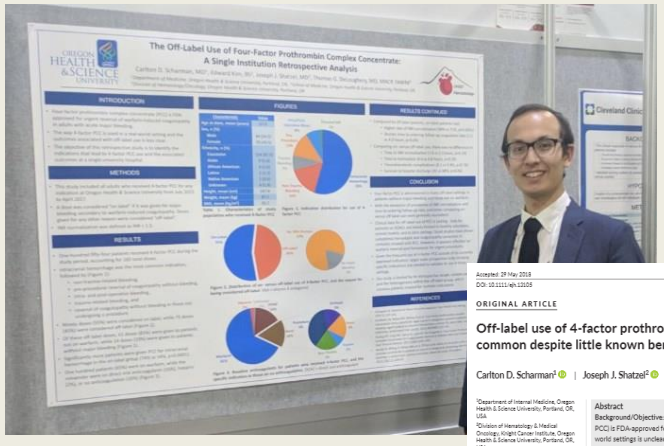
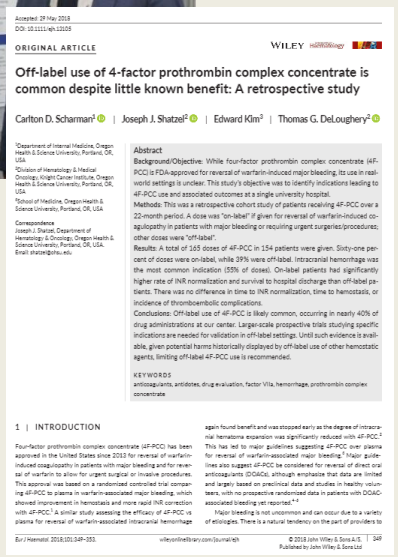

The Off-Label Use of Four-Factor Prothrombin Complex Concentrate: A Single Institution Retrospective Analysis


Accepted: 29 May 2018
DOI: 10.1111/ajh.25026

ORIGINAL ARTICLE

WILEY

Off-label use of 4-factor prothrombin complex concentrate is common despite little known benefit: A retrospective study

Carlton D. Scharman[1] | Joseph J. Shatzel[2] | Edward Kim[2] | Thomas G. DeLoughery[2]

GET THEE TO A...CONFERENCE!

Christopher Jackson
@seis_matters
Follow

As conference season starts for some, it's time for a reminder that posters are *not* a poor 2nd-choice to a talk. You research is not worse because of the format you present it in. Propagation of this idea is hurtful. Some choose this format deliberately. Don't devalue them 😡

4:18 AM - 30 Nov 2018

Alison Koleszar
@akoleszar
Follow

Poster sessions are my favorite part of conferences. Don't we attend conferences to interact with each other and exchange ideas? Poster sessions (face-to-face conversation!) facilitate discussion. Seeing a talk feels passive-- seeing a poster feels active. #AGU18

AGU100 ADVANCING EARTH AND SPACE SCIENCE

Christopher Jackson
@seis_matters

Geologist @basinsIC| ❤️ @EarthArXiv & @lobefringe|Professional Midlander|Tries really hard|#BlackInSTEM|#Blackademic| 🚶🚲⚒️|DE24

“GET THE JOB DONE”

- LOCAL VENUES
  - Oregon ACP
  - NW SGIM
  - Oregon Geriatric Society
  - Oregon Critical Care
  - IDSO (Image Challenge)
  - Oregon Gut Club
  - OHSU GME Performance Excellence Week
  - OHSU Research week
  - OHSU Alumni Association paper of the year

A WORD ABOUT IMPACT FACTOR

Rison *et al. Journal of Medical Case Reports* (2017) 11:198
DOI 10.1186/s13256-017-1351-y

Journal of Medical Case Reports

EDITORIAL Open Access

How to choose the best journal for your case report

Richard A. Rison[1,2*], Jennifer Kelly Shepphird[3] and Michael R. Kidd[4,5]

Choose the right journal: Think. Check. Submit.
The "Think. Check. Submit." campaign arose in response to concerns about publishing practices, and the effort is supported by a coalition of scholarly publishing organizations. "Think. Check. Submit." takes a positive approach to help researchers identify credible journals, providing up-to-date guidance for choosing where to publish [18, 19]. To ascertain whether a journal is trusted, authors are advised to follow this checklist:

- Do you or your colleagues know the journal?
  - Have you read any articles in the journal before?
  - Is it easy to discover the latest papers in the journal?
- Can you easily identify and contact the publisher?
  - Is the publisher name clearly displayed on the journal website?
  - Can you contact the publisher by telephone, email, and post?
- Is the journal clear about the type of peer review it uses?
  - Does the journal site explain what these fees are for and when they will be charged?
- Do you recognize the editorial board?
  - Have you heard of the editorial board members?
  - Do members of the editorial board mention the journal on their own websites?

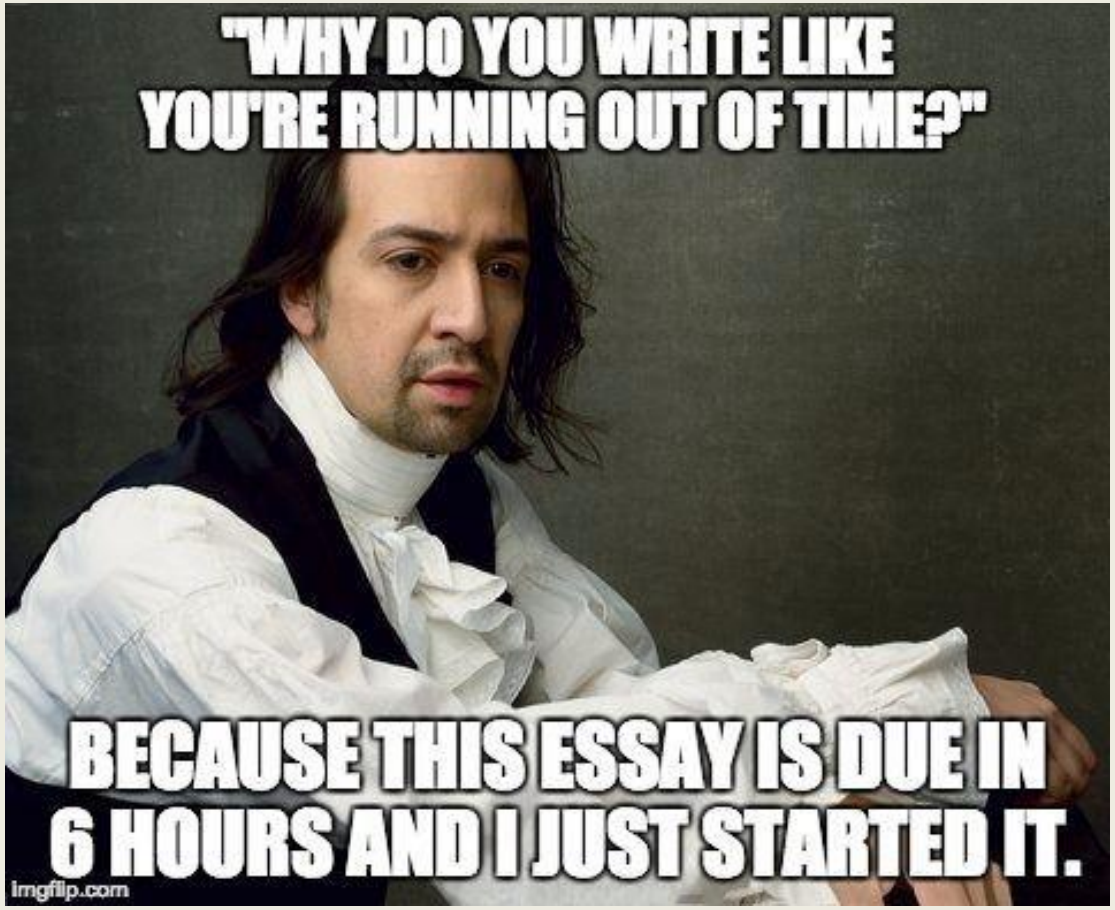
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5522590/pdf/13256_2017_Article_1351.pdf

SUBMISSION PROCESS

- The dreaded “Submission Checklist” and “Author Instructions”
  - Spell check, grammar, etc…
  - Title page
  - Word counts
  - Image formatting (300 DPI)
  - Cover letter
  - Conflict of Interest forms, etc.
- Muscle memory!
- *Frontload, frontload, frontload*

“WAIT FOR IT”

- If not accepted:
  - Read any reviewer comments
  - Try another journal
    - Try to modify (if needed for new journal) and resubmit as quickly as possible while everything is still fresh
    - Apply feedback from prior reviewers
- If accepted with revisions
  - Respond and resubmit ASAP
- When published:
  - DISSEMINATE!
  - DISSEMINATE!
  - DISSEMINATE!

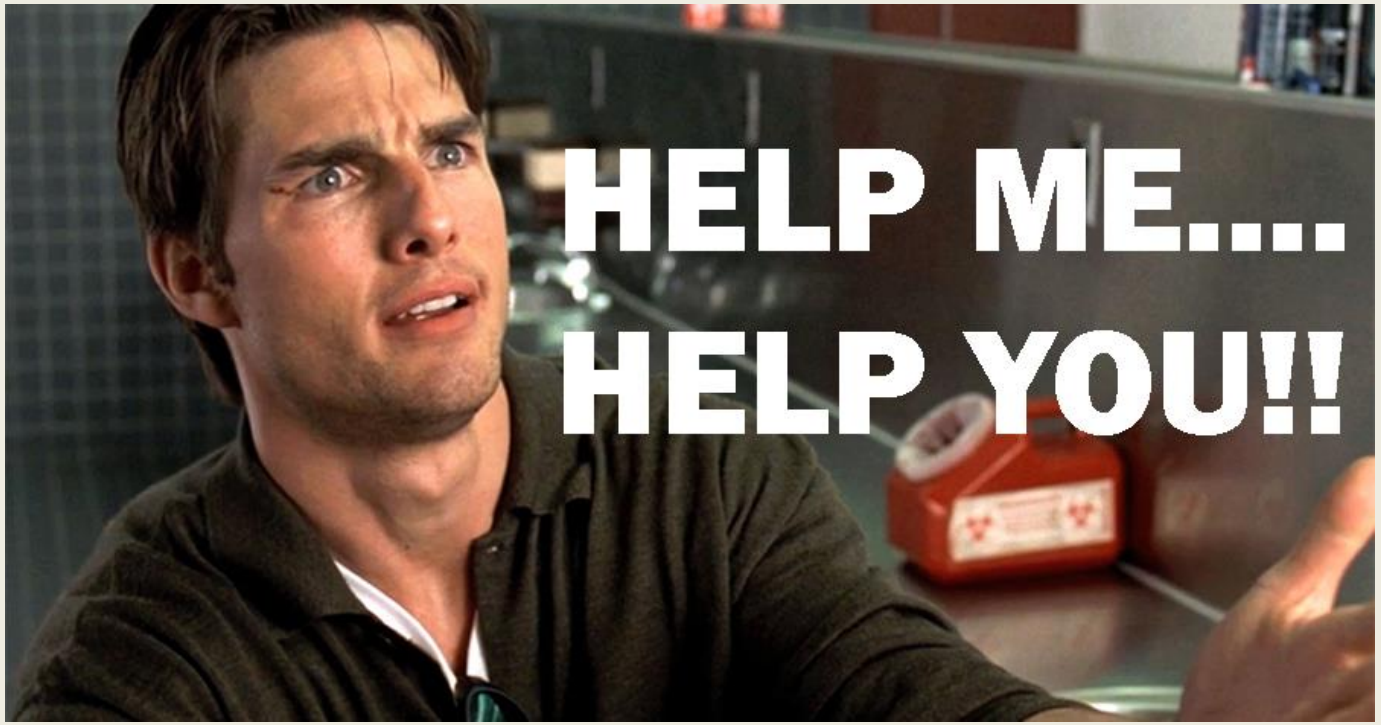


#OHSUSCHOLARSHIP

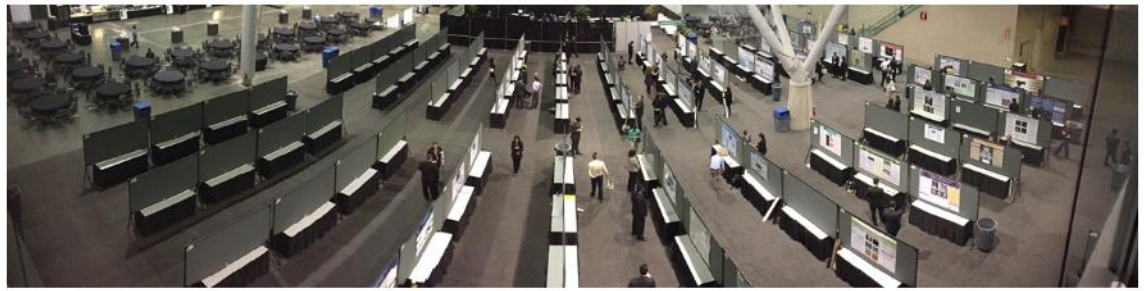
- Barriers:
  - Time
    - Rotations
    - Life
    - Time lag—what was that MRN number?
    - Taylor submission type to the time you have
  - Experience
    - Incomplete knowledge of the submission options
  - Partner
    - Lack of mentor
    - Nervous to approach mentor
    - Other residents/students?
  - Lack of organization
  - Activation energy
  - Carpal tunnel from spending too much time on EPIC/CPRS

RESOURCES AT OHSU

- Digital Based Resources:
  - Website
  - Newsletters
  - Emails
- People:
  - Assistant PD for Scholarship
  - Linked APDs
  - SPeAR
  - Liaisons
  - Word on the street (other residents)
- Curriculum:
  - Noon conferences
  - ????



Scholarship

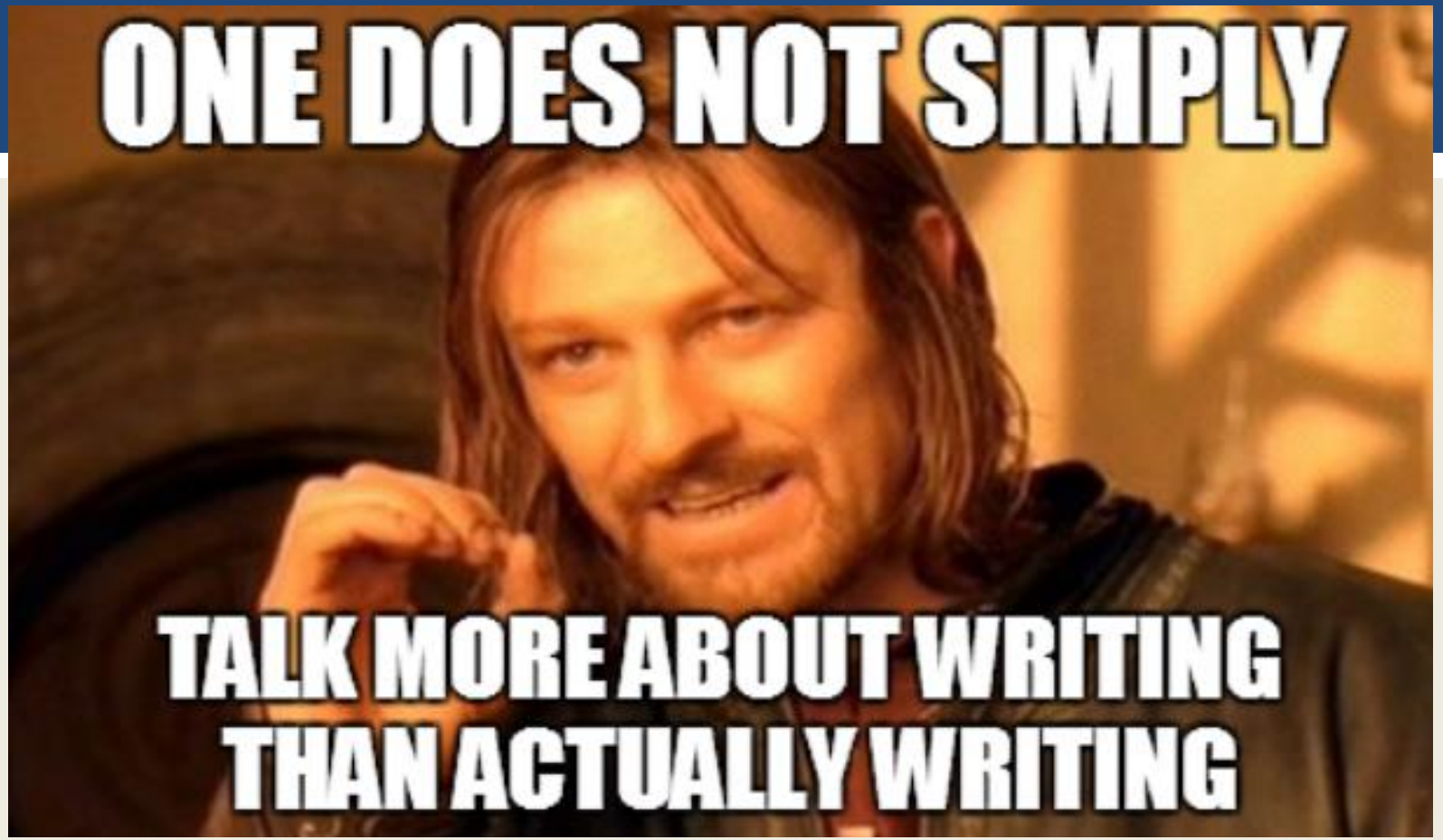


Scholarly activity is an integral part of clinical training for OHSU residents. It is an essential component of creating a love of life-long learning and clinical curiosity in all areas of medicine. Scholarship can also easily be a fun and fulfilling niche within a clinical practice. Scholarship may take many forms, including clinical/translational research, journal review articles or book chapter publications, case reports and clinical images, quality improvement projects, and presentation of abstract or oral presentations at local, regional, or national conferences and society meetings.

Since 2013, residents have been required to participate in a minimum of two scholarly activities per year for inclusion in their educational portfolio as follows:

At least one of the following:

- First author and presenter of a regional or national poster presentation (eg. SGIM, ACP, IDSA, ASN, DDW, ACC, ACG, or any other conference)


ONE DOES NOT SIMPLY
TALK MORE ABOUT WRITING
THAN ACTUALLY WRITING

QUESTIONS?

#OHSUSCHOLARSHIP

- Summary:
  - Do something
  - Find passion and excitement in this “extra” work
  - Make it count
  - Make it count more than once
  - Don’t go at it alone
  - Keep your eyes open
  - Ask!