# When the cure becomes the cause

## Drug fever as an overlooked etiology of persistent fever

Grand Rounds November 19th 2025
Huntsville LEG - NOSM

# Conflict of interest disclosure

- No conflict or side gigs $
- Family physician for patient who’s case will be presented

# Case introduction: Ruth

- 22-year-old woman with systemic lupus erythematosus (SLE).
- Diagnosed in India at age 15; Hx of lupus nephritis and myocarditis
- Came to Canada as a student, no family physician
- Met in 2023 as hospitalist, in with joint pain, urinary symptoms, fever
    - Had been out of medication x 2 weeks at this time
- Took her on as a patient and referred to SLE clinic
    - Restarted on meds
        - Mycophenolate, hydroxychloroquine and prednisone

# Case Introduction: Ruth

- Serology remains active but stable through 2024
  - Minimal symptoms; occasional fever
    - 3 simple UTIs (K.pneumoniae x 2, lactobacillus)
    - Starting to question if fevers may be due to active SLE
    - Rheum considering biologic

| Component<br>Latest Ref Rng | 3/10/2023 | 21/11/2023 | 8/1/2024 |
|---|---|---|---|
| Anti-dsDNA<br><= 4 Negative, 5 - 9 Indeterminate, >= 10 Positive IU/mL | **>300 (H)** | **184 (H)** | **190 (H)** |

| Component<br>Latest Ref Rng | 3/10/2023 | 21/11/2023 | 8/1/2024 |
|---|---|---|---|
| C3 Complement<br>0.98 - 1.96 g/L | **0.60 (L)** | **0.60 (L)** | **0.77 (L)** |

| | 3/10/2023 | 21/11/2023 | 8/1/2024 |
|---|---|---|---|
| C4 Complement | **0.02 (L)** | **0.01 (L)** | **0.02 (L)** |

# Case Introduction: Ruth

- **Jan 2025: ER w 1 week of fevers**
  - Tx for presumed UTI at onset
  - BCs negative, AKI noted in ER (Cr 164) presumed to be 2o to dehydration
- Follow up arranged in SLE clinic
  - **Proteinuria in keeping w nephritis flare**
  - Prednisone up to 60 mg and mycophenolate dose optimized
  - Sent for urgent renal Bx
  - Referred to TB clinic to r/o latent TB considering possible need for cyclophosporin or biologic

# Case Introduction: Ruth

- **April 2025: Renal Bx**
  - Diffuse proliferative and membranous lupus nephritis, class IV/V
  - Admission for pyelonephritis following Bx
    - Urine + K. pneumonia
    - Mycophenolate held, stress dose steroids and course of cipro
- **May 2025: SLE clinic FU**
  - Plan for dual biologic approach: rituximab + belimumab
  - **Dx with latent TB**
    - + quantiferon TB test, neg CXR and acid-fast bacili
    - Need to hold off on biologic, cyclosporin initiated in meantime

# Case Introduction: Ruth

- **Juy 2025: TB clinic FU**
  - Needs treatment before biologic initiation
    - Rifampin 4 mo vs isoniazid 9 mo
      - Rifampin can decrease efficacy of cyclosporin/mycophenolate
    - **Rifampin 600 mg PO daily started on July 17 2025**

# Admission July 20-24

- Presents to ER with fever + vomiting x 48h
- T 39.5  HR 130  **BP 73/50**  RR 18  Sat 96%
- WBC 11 (neut 10.1), **Cr 449**
- **Dx: Sepsis nyd**
- Admitted to ICU on pressors, pip-tazo + vanco, stress dose steroids
- CXR neg
- Abdo CT - ?tubo-ovarian abscess (pelvic US normal, ovarian cyst)

# Admission July 20-24

- Blood cultures negative, urine culture negative, vaginal culture/STI screen negative
- Respiratory panel negative
- Anti-dsDNA: 29
- SLE clinic:
    - “ most consistent with **pre-renal azotemia secondary to volume depletion from GI losses,** likely related to **rifampin side effects**”
    - “We recommend **IV hydration** in hospital to correct the suspected volume depletion and **a temporary hold on rifampin pending reassessment of drug tolerance.**”
- Fever and AKI resolve quickly, d/c home on clavulin

# Admission Aug 6-13

- ER Aug 5 with 3 day history of fever
  - BW and urine done, Dx with viral illness and DC home
- ER Aug 6: back with fever (40oC) and vomiting, but “looks quite well”
- **Dx: Fever of unknown origin, infectious vs lupus flare**
- WBC: 3.2, Cr: 62
- Abdo US: Nil acute, CT: Pelvic lymphadenopathy
- **UC: Eneterobacter + E. Coli**
- Blood cultures and respiratory panel negative
- Anti-dsDNA: 31

# Admission Aug 6-13

- Started on **ceftriaxone**
- **Continued to have ++ fevers x 3 days**
- Switched to **pip-tazo**, continued to have **fevers for 2 more days**
- Defervesced Aug 11, eating and drinking
- Stepped down to clavulin and d/c home

# Fever of Unknown Origin (FUO)

- Fever in the absence of identified cause despite reasonable investigations and the persistence of fever for a sufficient time to rule out self-limiting fevers. (NEJM 2022)
    - Time-dependant criteria debatable (?-3 weeks)

**Minimal FUO Evaluation**

Basic laboratory testing (e.g., CBC, complete metabolic panel), blood cultures (2 sets), serologic tests for HIV, echocardiography, and CT of the chest, abdomen, pelvis, and other regions on the basis of symptoms and examination; ESR and CRP are commonly obtained

Consider temporary discontinuation of new and potentially offending medications

**Advanced FUO Evaluation**

Additional testing should be performed on the basis of the patient history, physical examination, epidemiology, exposures, imaging, and the results of the laboratory assays ordered as part of the minimal FUO evaluation (e.g., serologic or PCR testing for zoonotic or tickborne illness or endemic mycoses, evaluation for hepatitis viruses); include workup for tuberculosis or testing for rheumatologic and thyroid disorders (e.g., RF, ANA, TSH)

Consider biopsy (rash, temporal artery, lymph nodes, masses, other lesions) as appropriate

# Fever of Unknown Origin (FUO)

**TABLE 1**

**Common Causes of Fever of Unknown Origin**

| Subgroup | Causes |
|---|---|
| Infection (20% to 40%) | Bacterial |
| | Abdominal or pelvic abscesses |
| | Dental abscesses |
| | Endocarditis |
| | Sinusitis |
| | Tuberculosis (especially extrapulmonary/disseminated) |
| | Urinary tract infection |
| | Viral |
| | Cytomegalovirus |
| | Epstein-Barr virus |
| Malignancy (20% to 30%) | Colorectal cancer |
| | Leukemia |
| | Lymphoma (Hodgkin and non-Hodgkin) |
| Noninfectious inflammatory disease (10% to 30%) | Connective tissue diseases |
| | Adult Still disease |
| | Rheumatoid arthritis |
| | Systemic lupus erythematosus |
| | Granulomatous disease |
| | Crohn disease |
| | Sarcoidosis |
| | Vasculitis syndromes |
| | Giant cell arteritis |
| | Polymyalgia rheumatica |
| | Temporal arteritis |
| Miscellaneous (10% to 20%) | Drug induced |
| | Factitious fever |
| | Thromboembolic disease |
| | Thyroiditis |

*Adapted with permission from Hersch EC, Oh RC. Prolonged febrile illness and fever of unknown origin in adults.* Am Fam Physician. *2014;90(2):93.*

# Drug fever

- Fever coinciding with drug exposure and resolving after discontinuation, with no alternative cause.
- Not a single clinical entity
- Occurs in ~3–5% of adverse drug reactions
- ~3-7% of nosocomial fevers attributed to drugs.

# When to consider drug fever

- Persistent fever with no cause despite broad infectious and autoimmune testing
- New medications started in last days to weeks or patient is on high risk meds

# When to consider drug fever

- **Timing:** Onset 1–2 weeks after drug initiation (range hours–months).
- **Pattern:** Hectic fever pattern is the most common (continuous but fluctuating)
  - continuous, remittent, or intermittent also possible
  - relative bradycardia is common
- **General appearance:** Well or unaware of fever; though can be unwell.
- **Rash:** 30% of patients
- **Neurologic, neuromuscular or autonomic abnormalities**
- **Comorbidities:** HIV, CF, immunocompromised/suppressed, hospitalized

# Drug fever: Mechanisms

- Hypersensitivity reactions — most common mechanism.
- Hyperthermia syndromes (e.g., NMS, serotonin syndrome).
- Extension of pharmacologic effect (e.g., chemotherapy).
- Altered thermoregulation (e.g. Anticholinergics)
- Direct pyrogenic or infusion-related reactions (amphotericin B).

# Drug fever: Hypersensitivity

- Hypersensitivity reactions
  - Most common mechanism
  - Onset: 7-10 days
  - Drug of metabolite trigger hypersensitivity reaction
  - Risk factors:
    - Some genetic predispositions
      - Ex: Abacavir, anticonvulsants, prostaglandins
    - Some viral infections increase risk (HIV*, CMV, EBV)

# Drug fever: Hypersensitivity

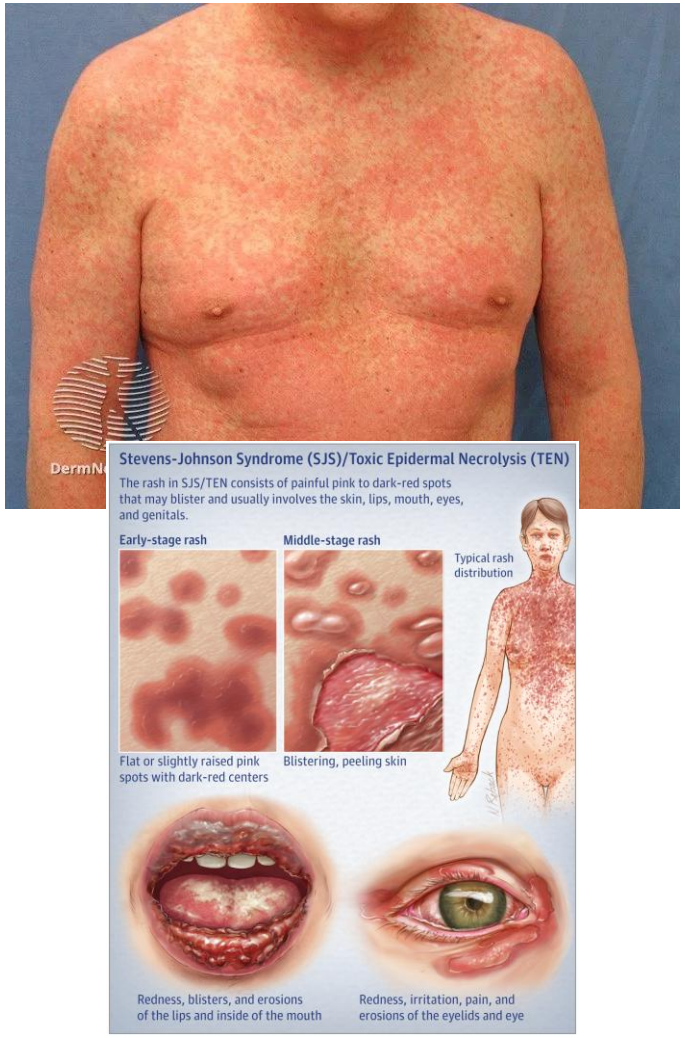
- Anticonvulsants (1:5000)
  - Fever in 5-6 days, illness resembling mono or lymphoma-like
  - Also associated with DRESS
- Minocycline
  - Often accompanied by eosinophilia, can have  joint, liver, lung or skin involvement
  - Pt often taking for months to years before reaction; often missed for this reason
- Other antimicrobials
  - Most common medication class associated with drug fever **(⅓)**
  - **Beta-lactams**, sulfanomides, nitrofurantoin, TB meds
  - CF patients are particularly at risk (piperacillin, carbapenems)

# Drug fever: Hypersensitivity

- Allopurinol
  - Rare but severe complication of long-term use
  - Often associated with cutaneous manifestations (DRESS, SJS/TENS)
  - Median time to reaction is 8-9 weeks
  - East asian ethnic group, concurrent use of diuretics, renal impairment
- Heparin
- Immune checkpoint inhibitors

# Drug fever: DRESS/SJS

| | DRESS | SJS/TEN |
|---|---|---|
| Latency | 2-8 weeks | 4-28 days |
| Rash | Morbilliform | Painful erythematous macules with purpuric centers → vesicles/bullae → sloughing |
| Mucosal involvement | 50% have mild mucosal involvement, rarely with erosions | >90% have severe mucosal involvement with bleeding at 2 or more sites |
| CBC | Eosinophilia and atypical leukocytosis | Lympopenia |
| Hepatitis | 50% or more | <10% |
| Kidney | Tubulointerstitial nephritis | Prerenal azotemia |
| Skin biopsy | Dermal edema with infiltration by lymphocytes and eos | Full-thickness epidermal necrosis |



# Drug fever: Hyperthermia syndromes

- **Malignant hyperthermia**
  - Onset 0.5-2h
  - General anesthesia (muscle depolarizing agents or inhaled anesthetic)
  - Sudden onset fever 40oC+, muscle rigidity, hemodynamic instability
  - Usually on third exposure
  - Autosomal dominant trait in 50%, men>women, children <15 yo
  - Primary defect is a mutation in the gene for the skeletal muscle ryanodine receptor (RyR1)

# Drug fever: Hyperthermia syndromes

- **Neuroleptic malignant syndrome**
  - Onset 1-2 weeks
  - High fever, muscle rigidity, altered mental state, dysautonomias
  - Dopamine-depleting agents
    - Antipsychotics, antiemetics (metoclopramide)
  - Significant mortality if not promptly diagnosed and treated (withdrawal of medication)
- **Parkinsonism-hyperpyrexia syndrome**
  - Abrupt withdrawal of dopaminergic agents / dopamine agonists

# Drug fever: Hyperthermia syndromes

- **Serotonin syndrome**
  - Onset within hours
  - Excess agonist activity of serotonin on 5HT1A/12 receptors
  - MAOi (**linezolid**), triptans, ergots, cyclobenzaprine, lamotragine, dextromethorphan, ondansetron, amphetamines
  - Agitation, confusion, diaphoresis, tachycardia, rigidity, clonus, tremors
- **Anticholinergic fever**
  - Onset within hours
  - Anticonvulsants, antiemetics, antidepressants, muscle relaxants
  - Mad as a hatter, **hot as a hare**, dry as a bone, blind as a bat, red as a beet
- **Exogenous thyroid hormone**

# Drug fever: Chemotherapy and infusion reactions

- **Chemotherapy**
  - Onset 3-4 days
  - Cell necrosis and lysis release various pyogenic substances
  - Resulting inflammatory response and cytokine activation
  - Common chemo regimen for melanoma causes fever in 40-60%
- **Infusion reactions**
  - Ampho-B, bleomycin have intrinsic pyogenic properties that are poorly understood
  - Older formulations of vanco/gentamycin, thought to be due to impurities

# Admission Sept 3-13

- Called my office for work note for fever
- Fever x 3 days, up to 40oC
- Feeling well, no focal Sx
- Called rheum on call for advice before sending pt to ER
- Suggested same course; ER, stress dose pred, hold mycophenolate and empiric Abx
- Pt feels well and wanted to wait despite recommendation to go to ER
- Called next am, still having fever of 40oC, on her way to ER

# Admission Sept 3

- **Admitting Dx: Urosepsis**
- CXR nil acute
- Started on IV ceftriaxone
- Respiratory panel, urine culture and blood cultures negative; anti-dsDNA at baseline
- Echo - neg
- 3 days into admission questionable early PNA on CXR, **switched to pip-tazo**
- 5 days into admission - still unwell and febrile; **stepped up to meropenem and azithromycin** in efforts to cover for ?resistant enterobacter from old urine culture

# Admission Sept 3-13

- Sept 10
- Conversation with rheum
  - Not infectious, ongoing fevers despite very broad Abx coverage and no convincing focus/cultures
  - Not favoured to be lupus flare given no response to pred and no anti-dsDNA increase
  - **Discontinue all Abx INCLUDING rifampin** and repeat cultures, anti-dsDNA and C3/4
- Sept 12: Fevers resolved, feeling much better
- Sept 13: Discharged home, diagnosed with drug fever

# Clinical Pearls and Pitfalls

- Not all fevers are infectious in nature, keep a broad Ddx including drug fever
    - Patient looks well
    - Persistent fevers, not improving with Abx
    - Persistent negative septic work-up
- Almost any medication can cause drug fever; review med list early on
- Remember the big bad syndromes, but consider that fever can be only symptom of a drug reaction
- Drug fever remains Dx of exclusion


Or is it...?

# Since September...

- STEMI w LAD thrombus
  - Suspected to be due to antiphospholipid antibody syndrome
  - On LMWH, awaiting 3 mo Tx to do lupus anticoagulant test
- Started on isoniazid -> admission for drug fever within 1 week
- Just started on levofloxacin x 6 months
- Still awaiting initiation of biologics for SLE

# References


- Someko H, Yamada A, Kobayashi K, et al. Prevalence of Drug Fever among Cases of Nosocomial Fever: Intern Med. 2024;63:1193–1202.
- NEJM 2022;386:463–471 — Fever of Unknown Origin.
- UpToDate 2025 — Drug Fever; Evaluation of FUO.
- AAFP 2022 — Evaluation of Fever of Unknown Origin in Adults.