**Academic Half Day – Rheumatologic Emergencies**

**Facilitator Guide**

**Agenda**

**1:05-1:20pm Theory Burst**

**1:20-1:50pm Small group case 1**

**1:50-2:00pm Expert questions**

**2:00-2:10pm Break**

**2:10-3:20 Small group cases 2-4**

**3:20-3:30: Expert questions**

**Case 1**

Mr. Room is a 72-year-old male with a history of type 2 DM, rheumatoid arthritis, HTN, and CKD2 who presents with 3 days of right ankle pain. The ankle has been progressively painful to the touch with limited range of motion. He states the pain started suddenly when he woke up in the morning. He has not had any fall or recent injury. He denies fever, chills, night sweats.

Meds: metformin, methotrexate, adalimumab, atorvastatin, hydrochlorothiazide

VS: T 99.5, HR 90, RR 18, BP 144/82

Exam: erythema and swelling over the lateral R ankle and dorsal foot with extreme tenderness to palpation. Active and passive ROM is limited by pain. No evidence of inflammation in any other joints.

WBC 11, Hgb 13, Plt 200

Renal: Na 135, K 3.7, Cl 100, HCO3 28, BUN 18, Cr 1.3

Uric acid 7.8

ESR 60 CRP 10

Xray of the ankle shows soft tissue swelling, no gas, no fractures.

1. **How would you categorize the patient’s current complaint? Maybe try a problem representation?**
	1. Problem representation: Elderly, immunocompromised adult with RA presents with acute monoarticular arthritis
	2. *Facilitators: encourage discussion of the difference between monoarticular, oligoarticular and polyarticular arthritis and how that informs the differential*
		1. Monoarticular (involving one joint): infectious (including gonococcal, non-gonococcal bacterial, TB, fungal, lyme, COVID), crystal arthropathy (gout, pseudogout), trauma, hemarthrosis, RA (less common), sarcoidosis (less common)
		2. Oligoarticular (2-4): RA, seronegative spondylarthropathies such as psoriatic arthritis, ankylosing spondylitis, reactive arthritis, IBD-associated arthritis. Even sarcoidosis as well.
		3. Polyarticular (5 or greater): RA, OA, psoriatic arthritis, SLE, reactive arthritis, parvovirus, lyme disease
2. **What is your differential diagnosis?**
	1. As above under monoarticular arthritis --- crystal or infectious arthropathy most likely since no hx of recent trauma.
	2. Seronegative spondyloarthropathies and RA *can also* present as monoarticular arthritis 10-20% of the time
3. **What is your next step in management?**
	1. Arthrocentesis for synovial fluid sampling
		1. What would you like to send?
			1. Cell count/diff, gram stain/culture, crystal analysis
			2. Chemistry studies (ie glucose, LDH, protein, complement) do not add value
	2. Any joint especially with prior damage and in setting of diabetes is more likely to be infected if presenting acutely
	3. Distinguishing between infection and gout is difficult (see below) --- the only way to unequivocally differentiate the two is to perform arthrocentesis with synovial fluid analysis.
	4. While septic arthritis is always high on the ddx of acute monoarthritis, an infected joint in an RA patient is frequently overlooked and is associated with delays in dx averaging 1-3 weeks, due to the presumption that the presentation might just be a flare up of the underlying disease.
4. **How would you interpret the following synovial fluid collections?**
	1. **WBC 90k 95% PMN:** most likely infectious
	2. **WBC 2k 25% PMN:** most likely noninflammatory
	3. **WBC 30k 60% PMN:** Inflammatory vs infectious? (Tough one)

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| **​** | **Noninflammatory​** | **Inflammatory ​****(RA, gout, etc)** | **Infectious​** | **Hemorrhagic​** |
| WBC Count​ | < 2000​ | 2000 – 20,000​ |  > 20,000​ | 1 WBC:1000 RBC​ |
| Percent PMNs​ | < 25%​ | 50-75%​ | >75%​ | <50%​ |

1. **Evidence Based Medicine review, then review a few sensitivities, specificities, and likelihood ratios for septic arthritis.**
	1. What is sensitivity and specificity?
		1. Sensitivity = TP/TP+FN = if the patient is truly positive, what is the probability the test will be positive?
		2. Specificity = TN/TN+FP = if the patient is truly negative, what is the probability the test will be negative?
	2. What is a likelihood ratio?
		1. Used to assess how good a diagnostic test is and to help in selecting an appropriate diagnostic test/sequence of tests.
	3. Let’s review a few sensitivities/specificities of the most common clinical signs/symptoms with septic arthritis.

*Overall point, most clinical indicators and serum markers for septic arthritis have poor sensitivity. The most sensitive markers are SYNOVIAL WBC and PMN counts (each with sensitivities >90%).*

* Clinical indicators of infection are insufficiently sensitive.
	+ In multiple studies, joint pain (85% sensitive), a history of joint edema (78% sensitive), and fever (57% sensitive) are the only findings that occurred in more than 50% of patients --- and pain was the only finding that occurs in >80% of pts.
	+ Majority of patients with *bacterial* arthritis are febrile, but chills and spiking fevers are unusual (“sweats”: 27% sensitivity’ “rigors”: 19% sensitivity). Older or immunosuppressed adults are also less likely to present with fevers and leukocytosis.
* Lab markers:
	+ Acute-phase markers of infection are also unreliable. In a series of 243 episodes of septic arthritis, CRP was normal in 12%, ESR was normal in 30%, and serum WBC was elevated in only 50% of pts.
* Definitive diagnostic test: identification of bacteria in the synovial fluid (100% specific but only 55-80% sensitive depending on technique or gonococcal vs nongonococcal infection)

Other learning points:

* LR increased as the synovial fluid WBC count increased:
	+ <25 000/μL: LR, 0.32
	+ ≥25 000/μL: LR, 2.9
	+ >50 000/μL: LR, 7.7
	+ **>100 000/μL: LR, 28.0**
	+ On the same synovial fluid sample, a PMN count of at least **90% suggested septic arthritis with a LR of 4.4**, while a PMN count of less than **90% lowers the likelihood (LR, 0.34)**

**You arrange for an arthrocentesis for your patient and the fluid analysis is as follows:**

**Cloudy**

**WBC 70,000; PMNs 95%**

**Extracellular negatively birefringent needles**

**Gram stain and cultures are pending**

1. **What is your interpretation of the fluid analysis and next step in management?**
	1. Septic joint is an orthopedic emergency
		1. Damage can be irreversible after 72hrs
		2. Mortality rate for in-hospital septic arthritis ~10-15% despite use of antibiotics
	2. Further workup: Don’t forget about *blood cultures,* which are positive in ~50% of cases. Hematogenous spread is the most common source of septic arthritis (other causes include direct inoculation and local spread)
	3. BUT WHICH ANTIBIOTICS? WHICH BUGS?
		1. majority caused by staph aureus, then strep pneumonia. Can have gram negative including Pseudomonas, E coli, and Neisseria gonnorrhea.
		2. If gram positive: give vancomycin
		3. If gram negative diplococcus: treat for N gonnorrhea
		4. If gram negative rods, it depends:
			1. If IVDU or immunocompromised, treat for Pseudomonas (ie cefepime).
			2. If not, give ceftriaxone.
		5. If gram stain does not reveal any organisms:
			1. Does patient have history of crystal arthropathy? If yes, treat for it. If no, give vancomycin.
			2. If IVDU or immunocompromised, give vanc and anti-Pseudomonal coverage. If no, give vanc.
			3. If traumatic (ie joint penetration), give vanc and ceftriaxone.
2. **If the above patient had uncomplicated acute gout (no concern for septic arthritis after arthrocentesis), what treatment would be best?**
	1. 2020 ACR guidelines recommend Colchicine, NSAIDs and glucocorticoids as equivalent, cost-effective first line medications for flare of gout. Avoid NSAIDs/Colchicine in renal impairment. Use glucocorticoids cautiously in setting of infection. Note, intra-articular glucocorticoids can be used if systemic steroids are contraindicated. If all the above are contra-indicated, can consider IL-1 inhibitors although this is extremely costly.

**Case 2**

28-year-old woman with a history of +ANA presents with several weeks fatigue, malaise, joint pains. No fevers or chills. Feels tired all the time, low energy. Has maybe lost 5 pounds unintentionally. Joint pains in wrists, fingers and ankles primarily. No rashes, but she does note some small ulcerations in her mouth. She thinks she is losing some hair. She has noticed her feet are slightly swollen and she has some puffiness around her eyes. She had joint pains and was referred to a rheumatologist years ago because her mother had rheumatoid arthritis. The rheumatologist told her she had a +ANA, but did not have rheumatoid arthritis like her mother.

Medications: None

VS: HR 80, RR 16, BP 160/96, 98% RA

Thin woman in no acute distress

Mild Periorbital edema bilaterally

RRR, no m/r/g

Lungs clear bilaterally

1+ LE pitting edema to mid-shins bilaterally

**The ER orders some basic labs on for your patient and they return as below…**

WBC 4.3k, Hgb 10, Plt 200

Na 136, K 4.5, Cl 110, HC03 18, BUN 35, Cr 3.0

AST 42, ALT 34, ALP 120, Tbili 1.1, Albumin 2.5

TSH: 2.1

1. **What is on the differential at this point? What additional testing would you like?**
2. *Note to Facilitators:* the differential of fatigue, arthralgias, and edema is broad. See if learners can tie together AKI with systemic symptoms.
3. A few ddx: SLE with lupus nephritis, scleroderma with renal crisis, ANCA associated vasculitis (MPA, EGPA, GPA), parvovirus infection, lyme disease, rheumatoid arthritis, disseminated gonococcal infection, cirrhosis, pulmonary HTN, HIV.
4. Other labs to order (learners do not have these):
	* 1. UA: 300 protein, moderate blood, 10-20 dysmorphic RBCs, 5-10 WBCs, RBC casts
		2. Complement levels: undetectable C3, normal C4
		3. Antibodies: ANA 1:320, diffuse pattern, + dsDNA, RF negative, antiCCP negative
		4. Bladder scan negative. POCUS renal US without hydro.
5. Do you want urine electrolytes?
	* 1. Not particularly helpful in this case, since we really are most concerned about glomerulonephritis with active urinary sediment.
6. **What are you most concerned about and what is the most likely diagnosis?**
	1. The presence of lupus nephritis should be suspected in patients with known SLE who develop an active urinary sediment (ie dysmorphic RBCs, casts, proteinuria), +Anti-dsDNA, and low complement.
	2. Lupus nephritis --- an immune complex GN that is a frequent complication of SLE (nearly 50% of pts with SLE will develop some renal dysfunction)
	3. Anti dsDNA is highly associated with lupus nephritis.
	4. LN is rapidly progressive and a major risk factor for morbidity and mortality in SLE; 10-30% of pts with LN will develop ESRD within months
	5. Overarching goal is early recognition and treatment in order to prevent CKD and ESRD
		1. 10-year survival improves from 46% to 95% if disease remission can be achieved
	6. All patients with SLE should be evaluated for renal dysfunction at initial diagnosis and q3-4 months thereafter even if they do not have symptoms of kidney disease, and with any SLE flare
7. **What is the next step in management?**
	1. Renal biopsy to diagnose and stage lupus nephritis
		1. Clinical threshold not well defined, but if SLE related renal involvement is suspected and there is significant proteinuria (~≥300 mg/d) or active urine sediment then generally recommended
	2. Renal bx is graded on a scale of I-VI depending on where the immune complex deposits and the treatment is largely determined based on this histological class. This is beyond the scope of today, but if you’re interested, consider a Rheum fellowship 😊
8. **How do you treat it?**
	1. As above, it depends on the histological class.
	2. High dose steroids, MMF vs cyclophosphamide.
		1. By the time LN is clinically apparent the kidney is already inflamed due to the accumulation of autoantibody-containing immune complexes. Therefore, pts are treated with anti-inflammatory agents to immediately slow down intrarenal inflammation and to allow for healing to begin.
	3. Treatment aim is clinical remission, prevention of relapse, and minimizing adverse side-effects with the eventual goal of preserving renal function
9. **On HD3, the patient suddenly develops a cough productive of streaks of bloody sputum and oxygen drops to 76%, put on non-rebreather with saturations up to 88%. The CXR appears below (QR code). What is your differential for this finding and what would you order next?**
	1. Flash pulmonary edema, DAH related to SLE, pulmonary capillaritis related to ANCA-associated vasculitis (GPA, MPA, EGPA, or Anti-GBM disease), atypical infection, PE (given all the inflammation).
	2. Highly concerning for DAH given her diagnosis of active lupus with diffuse infiltrates and hemoptysis. Need to consider this as it has high mortality if undiagnosed.
		1. In this case, her DAH is 2/2 SLE, but if she presented with DAH without a known diagnosis of SLE, always consider what is causing DAH (vasculitis, multiple autoimmune disorders, drugs, infections, even malignancies).
	3. Next steps would likely include intubation and bronchoscopy (plus probably CT, ABG, and infectious workup as well)



1. **The patient is intubated and bronchoscopy performed with increasingly bloody return on serial aliquots. How is this treated?**
	1. This is diffuse alveolar hemorrhage. Typically, supportive respiratory care with pulse dose steroids + further immunosuppression (cyclophosphamide, MMF, rituximab, and possibly PLEX) depending on the underlying etiology.

**Case 3**

Cardi O. Lipin is a 28-year-old female presents with acute onset respiratory distress and severe left leg pain. Left lower extremity leg pain began 48 hours prior and has increased in severity. She awoke this morning feeling short of breath which prompted her to come to the ER.

PMHx: LLE DVT diagnosed 7 months ago, attributed to presumptive prolonged travel, anticoagulated since diagnosis x 6 months

Obstetric History: G3P0 (*for facilitators, this means 3 pregnancies, 0 live births*)

VS: HR 112, RR 26, BP 110/60, 90% on 6L

Female in moderate respiratory distress

Tachycardic, regular

Lungs clear bilaterally, tachypnea

Abdomen soft, nontender

Left leg is pale and cool below the knee, pulses are not palpable at PT or DP, toes are purple

Lacy pattern to skin on right leg, abdomen, arms (livedo reticularis)

1. **What is your differential diagnosis for this patient?**
	1. PE (possibly massive based on hemodynamics), LE arterial occlusion, sepsis 2/2 PNA c/b DIC, occult malignancy, systemic vasculitis
	2. Concern for both venous and arterial thrombosis in a young female with a history of miscarriage should raise concern for antiphospholipid antibody syndrome (can occur either as a primary condition or in the setting of an underlying disease, SLE)
2. **What would you like to order?** *(facilitators: learners do NOT have these labs; please give them the results of the labs as they ask for them)*
	1. CBC: WBC 11k, Hgb 12, Platelets 55,000 (to eval for anemia, thrombocytopenia)
	2. Renal: Na 135, K 3.7, Cl 100, HCO3 27, BUN 14, Cr 0.8
	3. INR 1.6, aPTT: 54s (for DIC/coagulopathy)
	4. hsTroponin 126 -> 130 and BNP 250 (to eval for strain related to presumed PE)
	5. ECG – sinus tachycardia, no ischemic changes
	6. CTPA – pending
	7. CTA left leg – pending
	8. TTE ordered
3. **What are the next steps in laboratory investigation?**
	1. Order antiphospholipid antibodies:
		1. Lupus anticoagulant
		2. Anticardiolipin antibody
		3. Anti-Beta-2-glycoprotein-I antibody
	2. Positive tests for all 3 is associated with the highest risk of thrombosis
	3. Would be reasonable to also test for
	4. How do you diagnose antiphospholipid syndrome?
		1. Refer to the appendix in the back.

**Case continued…**

**12 hours after presentation she develops right sided facial droop and is unable to move her right arm. MRI confirms an ischemic stroke involving the right MCA territory.**

1. **What diagnosis does this patient now presumptively have?**
	1. Catastrophic antiphospholipid antibody syndrome (CAPS) --> widespread thrombosis with multiorgan failure
		1. Rare, life-threatening for of APS with micro and macro vascular complications.
	2. Preliminary dx of CAPS:
		1. 3+ organ systems/tissues
		2. Development all within 1 week
		3. Histopathology consistent with small vessel occlusion
		4. Lab confirmation of APL antibodies
	3. All 4 criteria met = DEFINITE CAPS (can see appendix for further details)
2. **How do you treat this patient?**
	1. Thrombosis -> anticoagulation with heparin and then Warfarin (NOT DOAC)
		1. Acute ischemic stroke should initially be treated with antiplatelet in the first 48 hours given the increased risk of hemorrhagic conversion with AC, especially when the infarcted area is >30%
	2. Wide-spread inflammatory process -> high dose glucocorticoids
	3. Presence of antiphospholipid antibodies -> remove via plasmapheresis and exchange
		1. plasma exchange or IVIG (IgG and IgM are the mediators of this widespread thrombosis)
	4. Mortality is VERY high: >50% despite anticoagulant and immunosuppressive treatment

**Case 4**

30-year-old woman with a history of systemic scleroderma associated with Raynaud’s syndrome, GERD and mild intermittent asthma presents to your office for routine follow up. She complains of a bifrontal headache for the past 3 days. No visual changes. No vomiting, photophobia, or phonophobia.

Meds: omeprazole

VS: T 98, HR 74, RR 16, 186/98

Thin woman in no acute distress

Pupils are equal and reactive, no papilledema

Regular rate and rhythm, no m/r/g

Lungs clear bilaterally

Abdomen soft, nontender, no bruits over renal arteries

Tightening of the skin around the mouth, over the hands, feet, chest and abdomen

You review her chart, and her blood pressure was 128/74 one month ago and similar again at another visit 2 weeks ago when she received a steroid burst for asthma exacerbation.

Labs in the ER are below:

Na 135, K 3.8, Cl 105, HCO2 28, BUN 65, Cr 2.7

WBC 6.0, Hgb 9.0, Plt 67

UA: 1+ protein; no cells or casts

1. **What additional labs do you want to get and why?**
	1. LDH 700; haptoglobin <30, concerning for hemolytic anemia
	2. Peripheral blood smear - positive for schistocytes and helmet cells
	3. ANA w/ reflex – pending (question for the expert, worth repeating? Depends on prior testing?)
	4. Complement levels – low-normal
2. **What does this patient have? What are you most concerned about on your differential?**
	1. Scleroderma Renal Crisis (SRC) --> caused by an acute deterioration in renal function
		1. Typical presentation is an acute, rapid rise in serum Cr consistent with AKI, a bland urinalysis with non–nephrotic-range proteinuria, elevated BP +/- malignant HTN, and signs of hemolysis
	2. High risk features for SRC: diffuse SSC (rather than limited), diffuse or recent rapid increase in skin thickening, anti-RNA polymerase III antibodies, and mod-high glucocorticoid use (15 mg pred daily).
		1. This matters because below…
	3. No gold standard definition, but proposed clinical criteria:
		1. SSC with high risk features + EITHER
			* Acute increase in BP (>140/90), SBP >30 from baseline, DBP >20 from baseline
			* AKI
		2. SSC without high risk + elevated BP + AKI + ONE of below
			* MAHA
			* Target organ dysfunction (retinopathy, encephalopathy, heart failure)
			* Kidney biopsy results
	4. Must have high suspicion for diagnosis because 25% of cases can occur before an official diagnosis of scleroderma has been made, 10% present without high blood pressure, and 90% mortality if untreated.
		1. Your clinical clues are going to be some of your high risk features (above).
3. **Why does this occur?**
	1. Pathophysiology not very well understood but leading theory (also in appendix):
		1. Insult/injury to endothelial cells -> intimal thickening, proliferation, and an absence of inflammatory cells within the renal vasculature -> narrowed afferent renal arterioles -> decrease in renal blood flow -> glomerular ischemia and hyperplasia of the juxtaglomerular apparatus and subsequent renin release (hyperreninemia) -> malignant HTN
	2. SRC is a VASCULAR, not an inflammatory, disease
4. **What is the treatment for this condition?**
	1. ACE inhibitor --> i.e. captopril
	2. Why captopril?
		1. It is simply the most studied drug in SRC and also has a significantly shorter half-life compared to other ACEi allowing for rapid titration to achieve BP goals
		2. Start low (6.25-12.5mg) and titrate every 8 hours
	3. Goal to get BP to normal within 72 hours
	4. Signs of hemolysis can improve prior to change in creatinine
	5. ARBs not as beneficial as ACEi (less studied). In a 2018 study of experts, consensus was to recommend ACEi, followed by CCB, then ARBs, and to avoid BB.
	6. If BP still uncontrolled after increasing captopril, add an IV antihypertensive agent.
5. **Could we prevent scleroderma renal crisis if we add an ACEi to our patients with scleroderma?**
	1. No evidence for prophylactic ACEI
	2. Observational studies suggest ACEi may increase the risk of developing SRC (HR 2.6) and death (HR 2.4)
	3. However, ARBs and CCBs were not associated with the development of SRC.
	4. Among patients who are already on an ACEi for treatment of HTN, some experts recommend replacing ACEi with another antihypertensive agent in patients with high risk scleroderma (diffuse SSc, RNA polymerase III abs, mod-high glucocorticoids).
	5. When to stop captopril? Often continued for life after SRC, but no evidence to guide discontinuation…maybe a question for the expert?

**-------------- Break / Expert questions ---------------**

**Appendix:**

1. SRC Pathophysiology



1. CAPS and APS classification criteria

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| **APS classification criteria** |
| **Clinical criteria**  |
| 1. Vascular thrombosis:
2. ≥ 1 clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ
 |
| 1. Pregnancy morbidity:
2. ≥ 1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
3. ≥ 1 premature births of a morphologically normal neonate before the 34th week of gestation because of: preeclampsia, severe preeclampsia, or recognized features of placental insufficiency, or
4. ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
 |
| **Laboratory criteria**  |
| 1. Lupus anticoagulant present in plasma, on ≥2 occasions at least 12 weeks apart
2. Anticardiolipin antibody of IgG and/or IgM isotype, in medium or high tighter on ≥ 2 occasions, at least 12 weeks apart
3. Anti-β2-glycoprotein-I antibody of IgG and/or IgM isotype, in medium or high tighter on ≥ 2 occasions, at least 12 weeks apart
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| **CAPS classification criteria** |
| **Preliminary classification criteria for CAPS** : |
| 1. Evidence of involvement of three or more organs, systems, and/or tissues
 |
| 1. Development of manifestations simultaneously or in less than 1 week
 |
| 1. Confirmation by histopathology of small-vessel occlusion
 |
| 1. Laboratory confirmation of the presence of antiphospholipid antibodies
 |
|    |
| **Definite CAPS:** All 4 criteria are met  |
|  |
| **Probable CAPS:** |
| * 1. All 4, except only 2 organs, systems, and/or tissues
 |
| * 1. Criteria 1, 2, and 3
 |
| * 1. Criteria 1, 2, and 4
 |
| * 1. Criteria 1, 3, and 4 with the development of a 3rd event more than 1 week but within 1 month of presentation despite anticoagulation
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1. Lupus Nephritis



