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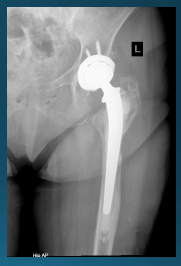
The diagnosis of infection: what tools are available?

What this is not…

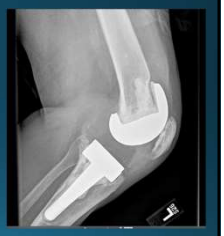
- What criteria do I follow??

- AAOS Guidelines
- Consensus Statements
- CDC
- MSIS
- Institutional Protocols
- 2018- New Definition/ JOA
- We can all agree
  - Exclude infection in every case



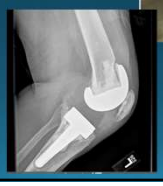
What this is…

- The bottom line with where we are now!
- Preview of some recent information and how this may be of use!!
- Ask a few clinically relevant questions
- Demonstrate how these can help with challenging cases



Where to start?

- Infection can present at any time
- Consider risk stratification
  - Prior infection
  - Obesity, inflammatory conditions, DM
  - Immunosuppression
  - Early loosening of implants
  - Early osteolysis



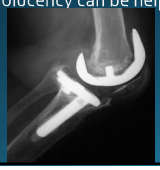
Where to start?- History/ PE

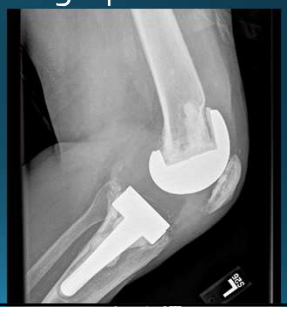
- Rest pain/ Night Pain
- Early I&D
- "Minor infection' after surgery that required abx
- Delayed healing or persistent drainage
- Usually puts you on the right track

- Examination
- Often unremarkable/ painful motion/ sudden change in functional status

Where to start? -Radiographs

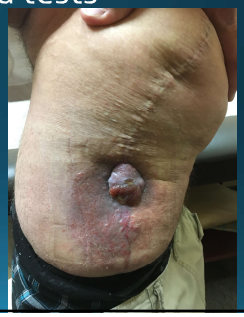
- Often times not helpful
- Obvious signs like periosteal reaction can be helpful
- Early osteolysis and radiolucency can be helpful



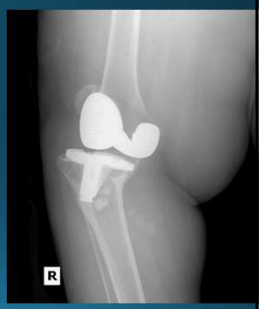


Where to start?- Blood tests

- Infalmmatory markers
  - ESR >30mm/hr (very sensitive, >94%
  - CRP >10mg/ L very sensitive >91%
  - Together sensitivity >97%



Does the presence of both an ESR and CRP below the PJI thresholds rule out the diagnosis of PJI?



BOTTOM LINE

- No!!
- Normal ESR/ CRP help you feel good but be careful
- Negative results
  - (ESR)
  - C-reactive protein (CRP)
  - →does NOT exclude the diagnosis PJI

BOTTOM LINE

- Combined ESR and CRP are also often falsely negative.
  - Johnson et al.
  - 11.1% false negative rate for combined ESR and CRP when the MSIS criteria were considered for diagnosis.
- Administration of therapeutic antibiotics
  - Prior to diagnostic work ups in PJI patients can be a cause for falsely negative ESR and CRP

Johnson AJ, Zywiel MG, Stroh A, Marker DR, Mont MA. Serological markers can lead to false negative diagnoses of periprosthetic infections following total knee arthroplasty. Int Orthop 2011;35:1621–6. doi:10.1007/s00264-010-1175-5.

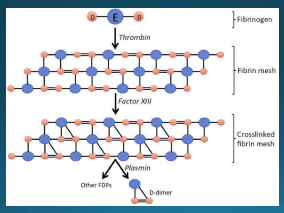
What to do in the Post operative period?

- Diagnosis of acute PJI in early postoperative period is also a challenge as these markers are usually elevated in this phase
- These values can be debated based on the timing of presentation
- Optimal magnitudes/ higher than conventional thresholds
  - Likely need for refinement of thresholds if ESR and CRP/ early PJI

Alijanipour P, Bakhshi H, Parvizi J. Diagnosis of periprosthetic joint infection: the threshold for serological markers. Clin Orthop 2013;471

Yi PH, Cross MB, Moric M, Sporer SM, Berger RA, Della Valle CJ. The 2013 Frank Stinchfield Award: Diagnosis of infection in the early postoperative period after total hip arthroplasty. Clin Orthop

What is the diagnostic accuracy and threshold of D-dimer in the diagnosis of PJI?



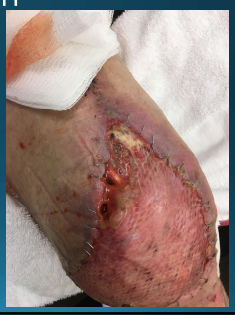
BOTTOM LINE

- D-dimer appears to be a sensitive and specific test
- May outperform both CRP/ ESR even when they are combined
  - sensitivity of 89% and a specificity of 93%.
- Recommended threshold for serum D-dimer is 850 ng/mL.
- Serum D-dimer/ great utility /early postoperative PJIs.
- Drops below the recommended threshold by postoperative day two

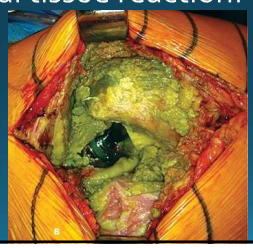
Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation. J Bone Joint Surg Am 2017;99:1419–27. doi

What's next- Aspiration

- Maybe the best test?
- WBC, Differential
- Leucocyte esterase
- Alpha Defensin
- Maximize the yield by maximizing the antibiotic free period prior to aspiration



How is PJI diagnosed in the presence of adverse local tissue reaction?



BOTTOM LINE

- Challenging/ common tests/ falsely positive
  - ESR, CRP, WBC count and differential & synovial fluid alpha defensin have all been reported to have higher than expected false positives in ATLR
- Leukocyte esterase in synovial fluid appears feasible, inexpensive and a reliable test for diagnosis of PJI in ALTR.
- There is no supporting evidence for other synovial fluid biomarkers in diagnostic of PJI in presence of ATLRs
  - CRP, IL-1, IL-6, IL-8, IL-17A, interferon-γ, tumor necrosis factor, cathelicidin LL-37,

ALTR- What to do?

- Manual synovial fluid WBC count and differential
- Leukocyte esterase reagent strips can also be used as an adjunct to diagnosis (excellent rule out test)
  - Assuming the sample does not have large amounts of metallic debris or blood that will make interpretation of the colorimetric strip unreliable
- Intraoperative frozen sections appear to be a reasonable test.

Tischler EH, Plummer DR, Chen AF, Della Valle CJ, Parvizi J. Leukocyte Esterase: Metal-on-Metal Failure and Periprosthetic Joint Infection. J Arthroplasty. 2016;31(10):2260-2263. doi:10.1016/j.arth.2016.03.012

Is there a role for sonication of implants retrieved during explantation?

BOTTOM LINE

- Yes. Several studies have demonstrated that sonication of explanted orthopedic prostheses is a viable method for detecting pathogens
  - Particularly in the setting of culture negative infections.
- But… This must be available to you?
  - Not at my hospital
- Split the samples into multiple sonicate fluid samples/ Sen/Spec
  - Nearly 100%
  - Janz V, Wassilew GI, Hasart O, Tohtz S, Perka C. Improvement in the detection rate of PJI in total hip arthroplasty through multiple sonicate fluid cultures. *J Orthop Res*. 2013;31(12):2021-2024.

Janz V, Wassilew GI, Kribus M, Trampuz A, Perka C. Improved identification of polymicrobial infection in total knee arthroplasty through sonicate fluid cultures. *Arch Orthop Trauma Surg*. 2015;135(10):1453-1457.

What is the role of alpha-defensin in the diagnosis of PJI?

Alpha-defensins are antimicrobial peptides released by neutrophils

- Two commercially available methods for measuring alpha-defensin in synovial fluid
  - (1) the enzyme-linked immunosorbent assay-based alpha-defensin immunoassay (Zimmer Biomet, Warsaw, IN, USA), which gives a numeric readout within 24 hours
  - (2) the alpha-defensin lateral flow test (Zimmer Biomet, Warsaw, IN, USA), which gives a binary readout within minutes

- Both the sensitivity and specificity of the alpha-defensin laboratory test exceed 95% when using the MSIS consensus criteria for PJI as a gold standard

Institution	N	Gold Standard	Sensitivity	Specificity
Rothman Institute	149	MSIS Criteria	97% (3637)	96% (107/112)
Mayo Arizona	61	MSIS Criteria	100% (33/33)	95% (83/87)
Cleveland Clinic	111	MSIS Criteria	100% (24/24)	98% (53/54)
ENDO Klinik	156	MSIS Criteria	97% (28/29)	97% (123/127)
Cleveland Florida	70	MSIS Criteria	97% (34/35)	97% (34/35)
Combined	**547**		**98.1% (95%CI: 95-100%)**	**96.4% (95%CI:94-98%)**

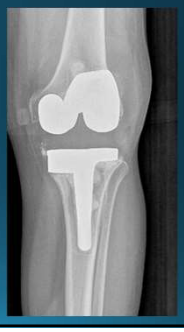
Lateral flow test -when compared to the same standard (MSIS)
Not quite as strong- but almost as sensitive and specific

Alpha Defensin- *Special Considerations*

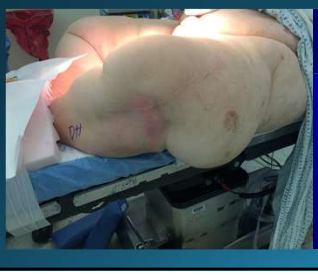
- No Use when aspirated sample is from a saline lavage
- No Use in Pure blood aspirates, simple contamination does not appear to affect the test.
- Metallosis - 30% false positive alpha-defensin rate.
- Immediate post-operative aspirates/ likely hematoma/ Hold on Biomarker assays 4-6 weeks
- The alpha-defensin /not validated /setting of a spacer block

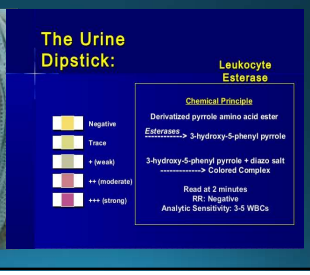
BOTTOM LINE

- Measurement of alpha-defensin in synovial fluid is a valuable complement to existing diagnostic criteria for PJI.
- Alpha-defensin laboratory test appears to be the most sensitive and specific single test available



Are point of care/rapid tests for diagnosing PJI validated and useful?





POC Testing- LE/ Lateral Flow

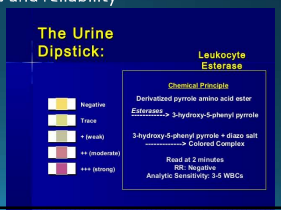
- Meta-analysis of *Suen et al.*
  - Pooled sensitivity and specificity of the Synovasure lateral flow test was quite similar, being 77.4% (95% CI, 63.7 to 87.0%) and 91.3% (95% CI, 82.8 to 95.8%), respectively
- Systematic review of *Wyatt et al.*
  - Nearly 2,000 patients from 5 studies, the pooled diagnostic sensitivity and specificity of LE for PJI was 81% (95% CI, 49% to 95%) and 97% (95% CI, 82% to 99%), respectively

Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The Alpha-Defensin Immunoassay and Leukocyte Esterase Colorimetric Strip Test for the Diagnosis of Periprosthetic Infection: A Systematic Review and Meta-Analysis. *J Bone Joint Surg Am.* 2016;98:992-1000.

Suen K, Keeka M, Ailabouni R, Tran P. Synovasure 'quick test' is not as accurate as the laboratory-based alpha-defensin immunoassay: a systematic review and meta-analysis. *Bone Joint J.* 2018;100-B:66-72.

BOTTOM LINE

- Yes!
  - Several point of care tests/ diagnostic workup of PJI
- Literature supports the usefulness and reliability
  - Leukocyte Esterase (LE) test strip
  - Alpha Defensin lateral flow test kit



What does the future hold?

- Next generation sequencing/ WOW!
- NGS parallelization of the sequencing reactions generates hundreds of megabases to gigabases of nucleotide sequence reads in a single instrument run. This has enabled a drastic increase in available sequence data
- Identify anything!
- Rothman Data and identifying failures

Conclusion

- Multiple pieces to the puzzle

Should PJI caused by P. acnes be treated the same as other bacterial causes of PJI?

BOTTOM LINE

- Yes. Periprosthetic joint infections (PJI) caused by Propionibacterium acnes should be treated in
- the same fashion as other causes of PJI.

BOTTOM LINE

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