ESR and CRP monitoring in prosthetic joint infections… *An inflammatory topic!*

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PROSTHETIC JOINT INFECTION (PJI)

INCIDENCE

- 1° hip/knee replacement: 1.5 to 2.5%
- Revision surgery: 3.2 to 5.6%

COST

- > $50,000 / episode

PROSTHETIC JOINT INFECTION (PJI)

REVISION SURGERY ↑ morbidity

- ↑ OR time
- ↑ blood loss
- ↑ complications
- ↑ health care costs

PROSTHETIC JOINT INFECTION (PJI)

TWO-STAGE RE-IMPLANTATION

- Removal of prosthesis + debridement
- Antibiotics x 4 to 6 weeks
* Confirm of eradication of infection
- Re-implantation

PROSTHETIC JOINT INFECTION (PJI)

TWO-STAGE RE-IMPLANTATION

- Success rate ~87%
- Improved outcomes if persistent infections identified & re-implantation delayed

PROSTHETIC JOINT INFECTION (PJI)

DIAGNOSIS OF PERSISTENT INFECTION

- Symptoms often low-grade or absent!
- Gold Standard
  - Identification of causative organism from aspirated synovial fluid or peri-prosthetic tissue
  - Biopsy confirming presence of inflammatory cells

→ **PROBLEM =** high rate of false negatives & invasiveness

So, how can we easily identify a patient with a persistent prosthetic joint infection???

ESR?

CRP?

ESR & CRP

- Markers of inflammation
- ESR – rate at which RBCs sediment in 1 hour
  - "normal" 0-20 mm/h
- CRP – produced in liver, activates complement system
  - "normal" < 10 mg/L

CLINICAL QUESTION

- In a patient undergoing a two-stage revision procedure for a prosthetic joint infection (PJI), are ESR and CRP measurements useful in monitoring response to antibiotic therapy?
  - Identification of persistent infection?
  - Prediction of PJI recurrence?

Search Strategy

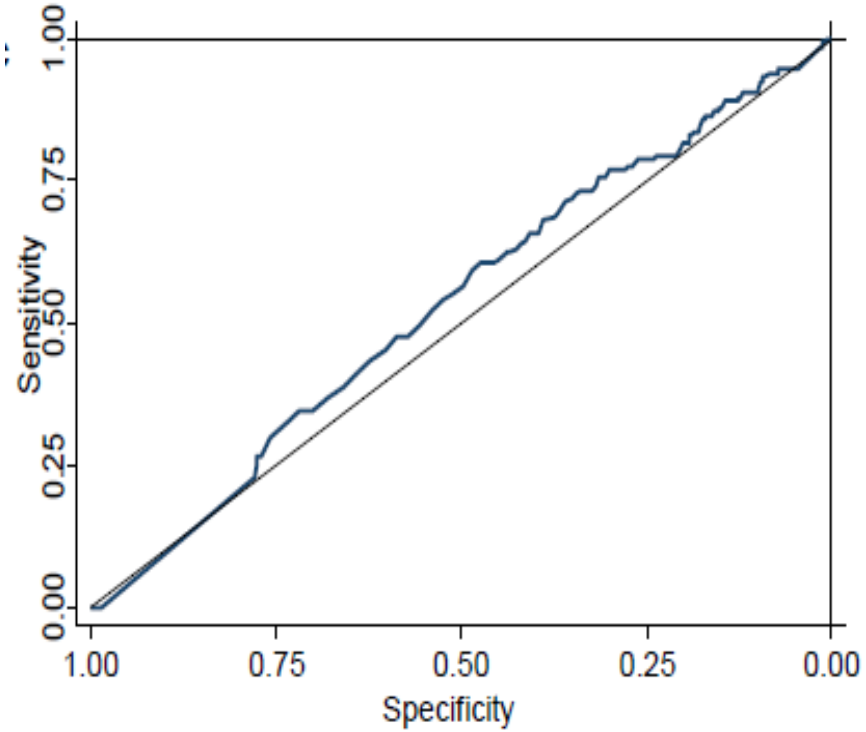
Databases	Embase, Medline, IPA, Cochrane
Search Terms	erythrocyte sedimentation rate, blood sedimentation, C-reactive protein, prosthetic joint infection, prosthesis infection, drug monitoring, treatment outcome, sensitivity and specificity, antibacterial agents
Limits	English, Human, ESR/CRP linked to clinical outcome
Results	-4 retrospective cohort studies -1 prospective cohort study

Bejon et al.

Design	Retrospective single center cohort
N	151
Indication for antibiotics	PJI
Case definition	Clinical syndrome AND bacterial growth or neutrophilic infiltrate on histology from peri-prosthetic tissue samples or persistent sinus tract
ESR/CRP measurements (median no.)	CRP qwk x 6 wks, then 2-3x/yr (7; IQR 3-13)
Time to re-implantation	Median 120 d
Follow-up	2y

RESULTS

Predicting 1 year treatment failure	
	AUROC
CRP	0.55



AUTHOR'S CONCLUSIONS

- CRP has low sensitivity and specificity as a diagnostic test
- CRP monitoring is a poor test of cure

$\Rightarrow$ Recommend against routine monitoring during treatment of PJI

Ghanem et al.

Design	Retrospective single center cohort
N	109
Indication for antibiotics	TKA infection
Case definition	Subsequent revision surgery or positive intra-operative culture
ESR/CRP measurements (median no.)	ESR & CRP prior to resection & prior to re-implantation
Time to re-implantation	Mean 107 d
Follow-up	2.8y

RESULTS - Ghanem

Predicting need for revision surgery		
	Sensitivity (%)	**Specificity (%)**
Mean ESR/CRP before re-implantation		
ESR = 30 mm/h	65	32
CRP = 2 mg/L	29	73
Δ ESR/CRP resection to re-implantation		
ESR > 10 mm/h	67	25
CRP > 2 mg/L	63	23

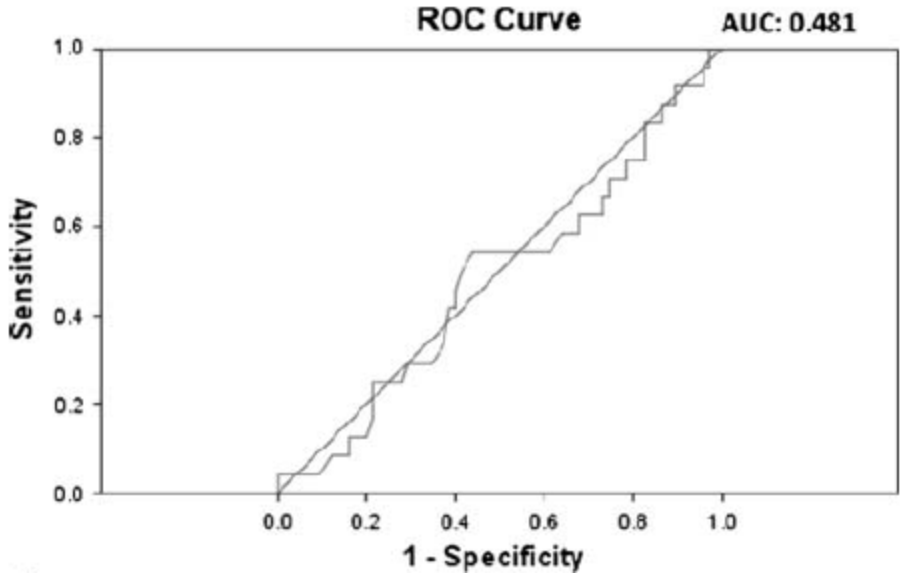
RESULTS - Ghanem

Predicting need for revision surgery	
	AUROC
Mean ESR/CRP before re-implantation	
ESR	0.503
CRP	0.545
Δ ESR/CRP resection to re-implantation	
ESR	0.481
CRP	0.468

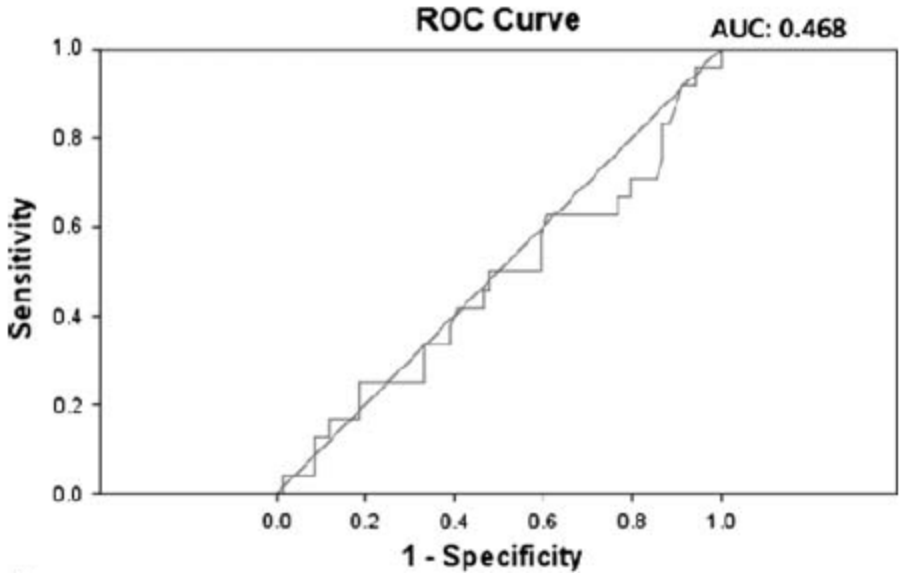
RESULTS - Ghanem

∆ ESR/CRP resection to re-implantation

ESR



CRP



AUTHOR'S CONCLUSIONS

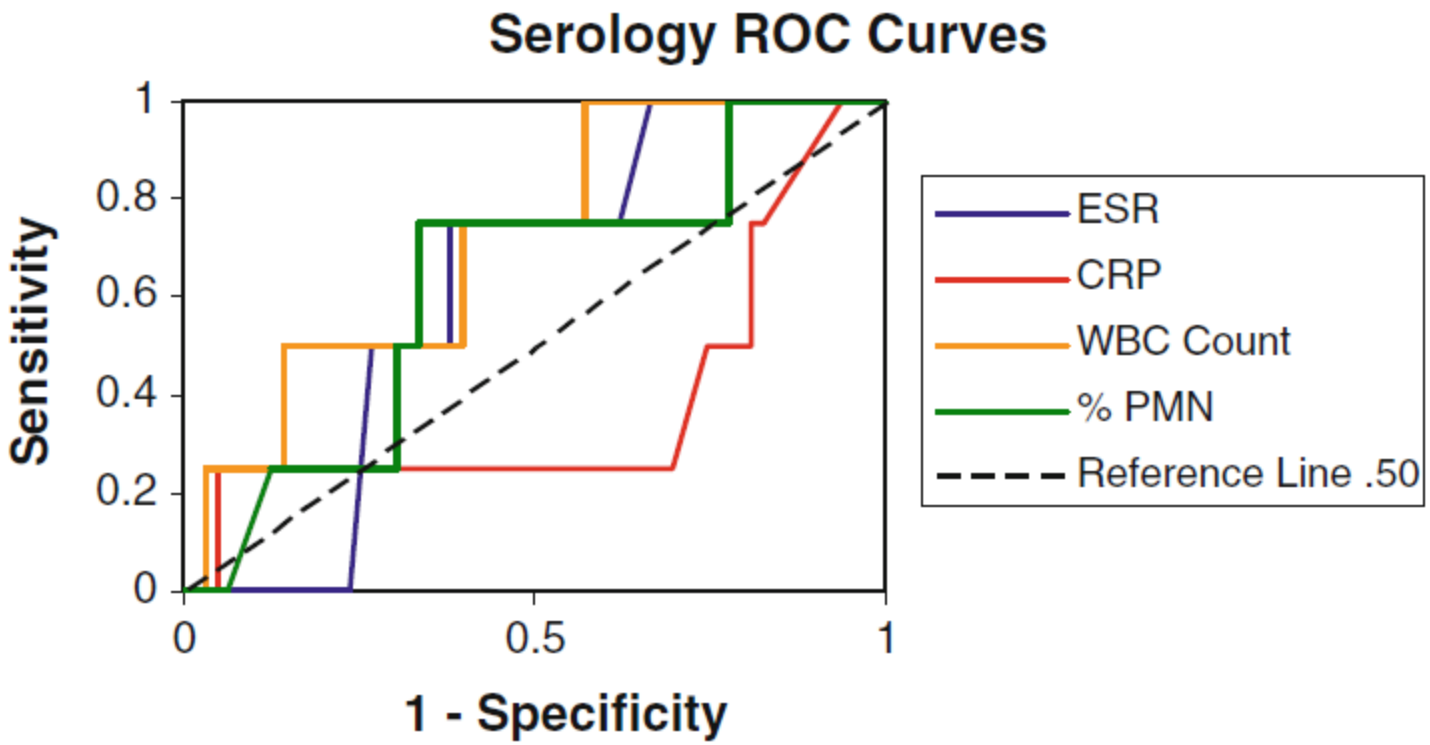
- No absolute level or change in ESR or CRP differentiated infection eradication and persistence
- Deferring re-implantation until normalization of all serological markers not scientifically supported
- A combination of clinical and laboratory factors should determine timing of re-implantation

Kusuma et al.

Design	Retrospective dual center cohort
N	76
Indication for abx	TKA infection
Duration of abx	6 weeks IV
Case definition	2 positive intraoperative cultures OR at least 2 of i)at least 1 positive culture, ii) histopathology consistent with infection, iii) grossly infected tissues seen in OR
ESR/CRP measurements (median no.)	ESR & CRP prior to resection & prior to re-implantation
Time to re-implantation	NR
Follow-up	2.8y

RESULTS - Kusuma

Predicting persistent infection –		
Mean ESR/CRP pre-re-implantation		
	Sensitivity (%)	**Specificity (%)**
ESR 44 mm/h	67	62
CRP 18 mg/L	17	94
	AUROC	
ESR	0.62	
CRP	0.39	


Serology ROC Curves
Sensitivity
1
0.8
0.6
0.4
0.2
0
0
0.5
1
1 - Specificity
ESR
CRP
WBC Count
% PMN
Reference Line .50

AUTHOR'S CONCLUSIONS

- Unable to define ESR or CRP cutoff with useful AUC values
- Synovial WBC count at re-implantation had highest AUC of 0.71
- ESR and CRP are not reliable for diagnosing persistent infection between stages
- Waiting until ESR and CRP have "normalized" is not reliable

Schindler et al.

Design	Retrospective single center cohort
N	58
Indication for abx	PJI
Duration of abx	44 days
Case definition	Pre-implantation aspiration, open biopsy, intra-operative cultures, intra-operative status
ESR/CRP measurements (median no.)	CRP qweek x 3 wks & within 15d of re-implantation
Time to re-implantation	153 days
Follow-up	3.3y

RESULTS - Schindler

CRP > 10 mg/L at re-implantation for identifying recurrent infection	
Sensitivity (%)	17
Specificity (%)	81
PPV	0.13
NPV	0.86

AUTHOR'S CONCLUSIONS

- More rapid CRP decrease in patients without recurrent infections, though non-statistically significant
- Prospective trial of CRP during 2-stage exchange is warranted

Shukla et al.

Design	Prospective single center cohort
N	86
Indication for abx	THA infection
Duration of abx	6 weeks IV
Case definition	≥ 2 positive intra-operative cultures OR at least 2 of i) at least 1 positive intra-op culture, ii) intra-op histopathology c/w infection, iii) sinus tract or grossly infected tissues intra-op
ESR/CRP measurements	ESR and CRP prior to resection & prior to re-implantation
Time to re-implantation	Mean 75 days
Follow-up	NR

RESULTS - Shukla

Identifying persistent infection – mean ESR/CRP pre-re-implantation		
	Sensitivity (%)	**Specificity (%)**
ESR 48 mm/h	78	55
CRP 6 mg/L	**67**	55
	AUROC	
ESR	0.76	
CRP	0.55	

AUTHOR'S CONCLUSIONS

- ESR and CRP often do not normalize even if infection is eradicated
- Unable to identify discrete threshold that reliably identified persistent infection
- Most useful test was synovial WBC
- Combining serological markers + WBC did not improve test performance

SUMMARY OF LIMITATIONS

- Observational design
- Low number of persistent infections
- Difficult to identify true infection control or persistence
- Optimal timing of ESR or CRP measurements?

COST

- ESR = $10.61
- CRP = $10.31
- Fluid cell count = $28.77

SUMMARY

	Pre-re-implantation ESR mm/h CRP mg/L	Sensitivity	Specificity	LR(+)	LR(-)
Shukla	**ESR > 48** CRP > 6	78 67	55 55	1.7 1.5	**0.4** 0.6
Ghanem	ESR > 30 CRP > 2	65 29	32 73	0.96 1.1	1.1 0.97
Kusuma	**ESR > 44** **CRP > 18**	67 17	62 94	1.8 **2.8**	**0.5** 0.9
Bejon	CRP	NR	NR	?	?
Schindler	CRP > 10	17	81	0.9	1

SUMMARY

	Marker	AUROC
Shukla	ESR CRP	0.76 0.55
Ghanem	ESR CRP	0.503 0.545
Kusuma	ESR CRP	0.62 0.39
Bejon	CRP	0.55
Schindler	CRP	NR

MY RECOMMENDATIONS

- Likelihood ratios of various cut-points indicate that neither test increases post-test probabilities of persistent infection
- Downward trend is seen in both cured and persistently infected patients

$\Rightarrow$ **Recommend against routinely monitoring ESR and CRP for patients on antibiotic therapy for PJI**

Questions