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)

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%
- Persistent infection
  - Re-implantation into persistently infected joint →complications + further surgeries
  - Identification of persistent infections & delaying re-implantation → improved outcomes

PROSTHETIC JOINT INFECTION (PJI)

REVISION SURGERY ↑ morbidity

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

PROSTHETIC JOINT INFECTION (PJI)

DIAGNOSIS OF PERSISTENT INFECTION

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

→**PROBLEM:** high rate false negatives, subjective evaluation, invasive

Is there a test that can help 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
- Frequently used as indicator of infection resolution

But does the evidence support this???

CLINICAL QUESTION

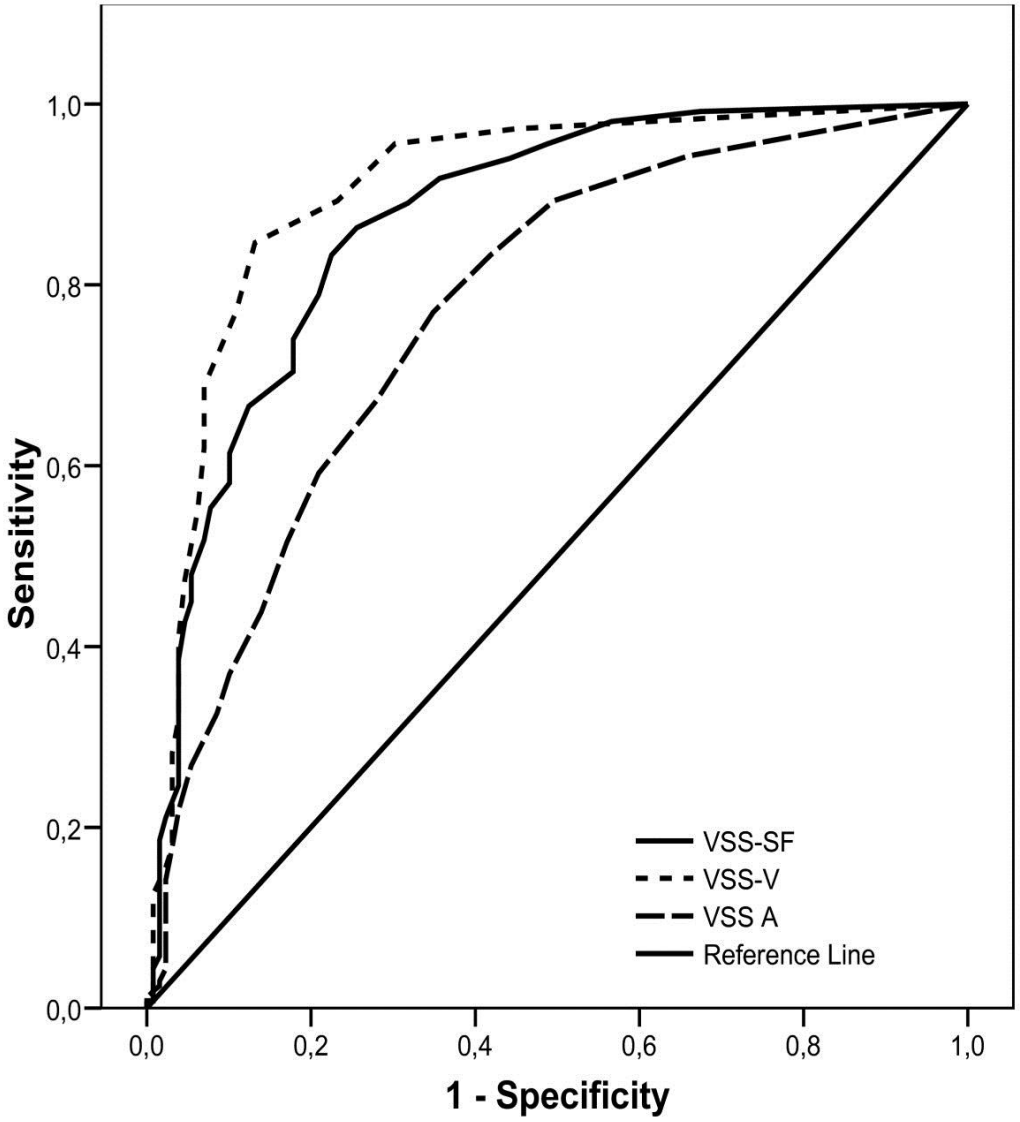
- In a patient undergoing a two-stage revision procedure for a prosthetic joint infection (PJI), are ESR and CRP measurements useful in monitoring response to antibiotic therapy?
  - Identification of persistent infection?
  - Prediction of PJI recurrence?

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

RECEIVER OPERATOR CURVES (ROC)

- Sensitivity & specificity for every possible cut point
- Allows comparison of different tests for same condition without specifying cut-point

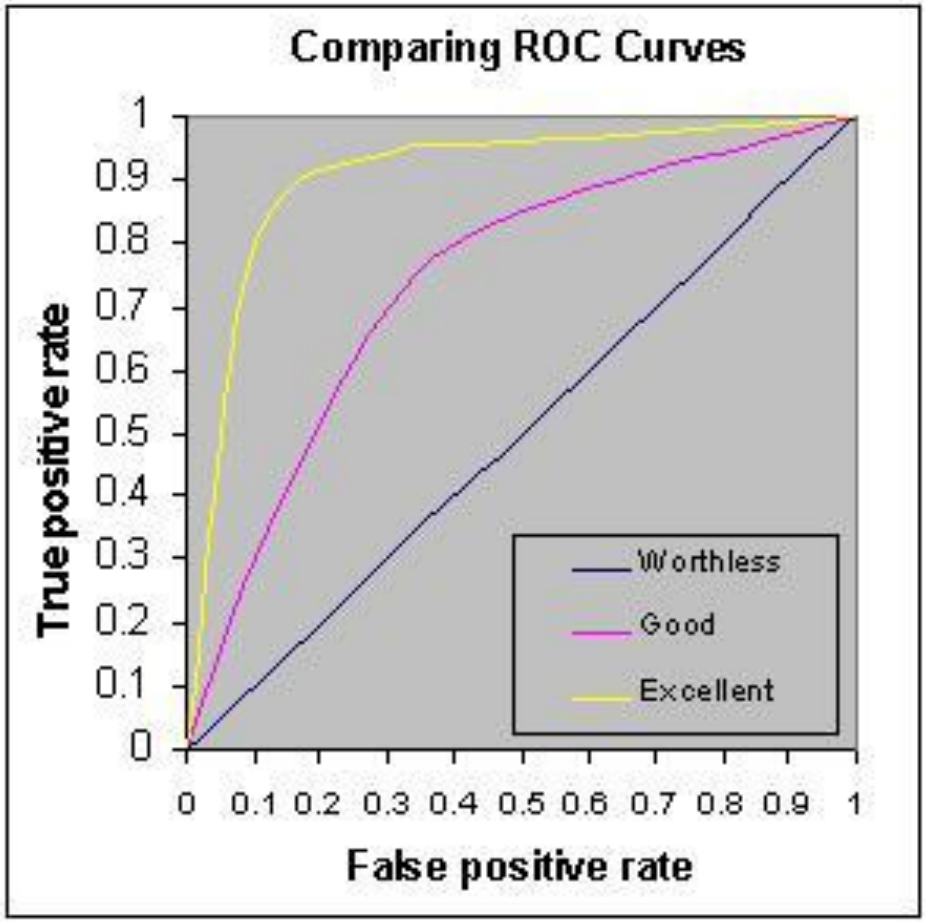


AREA UNDER ROC (AUROC)

- Measure of diagnostic accuracy
- Combines sensitivity and specificity
- Probability of correctly classifying patient

- E.g. AUC = 0.5

  →For given cutoff value, 50% chance of correctly classifying patient as sick or not sick



Serial measurement of the C-reactive protein is a poor predictor of treatment outcome in prosthetic joint infection

Philip Bejon[1,2*], Ivor Byren[1], Bridget L. Atkins[1,3], Matthew Scarborough[1], Andrew Woodhouse[1], Peter McLardy-Smith[1], Roger Gundle[1] and Anthony R. Berendt[1]

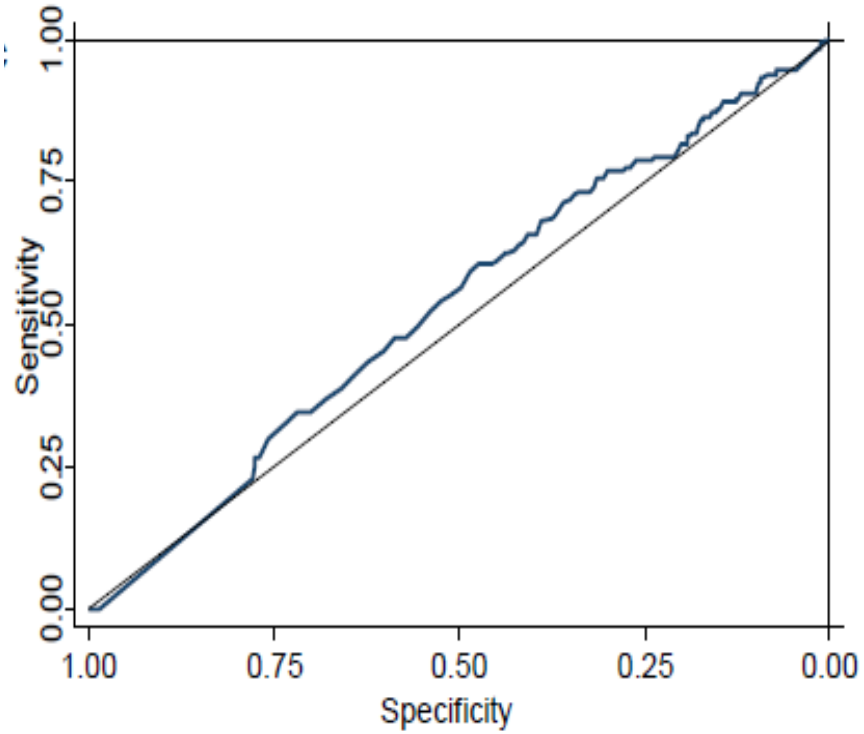
J Antimicrob Chemother 2011; **66**: 1590–1593

Bejon et al.

Design	Retrospective single center cohort
N	151
Indication for antibiotics	PJI – hip, knee, elbow
Duration of abx	6 weeks IV
ESR/CRP measurements	CRP qwk x 6 wks, then 2-3x/yr
Time to re-implantation	Median 120 d
Follow-up	Median 2y
Outcome	Treatment failure: draining sinus, further revision surgery, amputation of affected limb

RESULTS

Predicting 1 year treatment failure	
	AUROC
CRP	0.55



AUTHOR'S CONCLUSIONS

- CRP has low sensitivity and specificity as a diagnostic test → poor test of cure
- Recommend against routine monitoring

LIMITATIONS

- Limited reporting of raw data
- Wide scatter of individual CRP values
- No adjustment for confounders

Staged Revision for Knee Arthroplasty Infection

What Is the Role of Serologic Tests Before Reimplantation?

Elie Ghanem MD, Khalid Azzam MD,
Mark Seeley MD, Ashish Joshi MD, MPH,
Javad Parvizi MD, FRCS

Clin Orthop Relat Res (2009) 467:1699–1705

Ghanem et al.

Design	Retrospective single center cohort
N	109, mean age 68y
Indication for antibiotics	TKA infection
Duration of abx	6 weeks IV
ESR/CRP measurements	ESR & CRP prior to resection & prior to re-implantation
Time to re-implantation	Mean 107 d
Follow-up	Mean 2.8y
Outcome	Persistent infection: subsequent revision surgery for PJI or positive intra-op culture

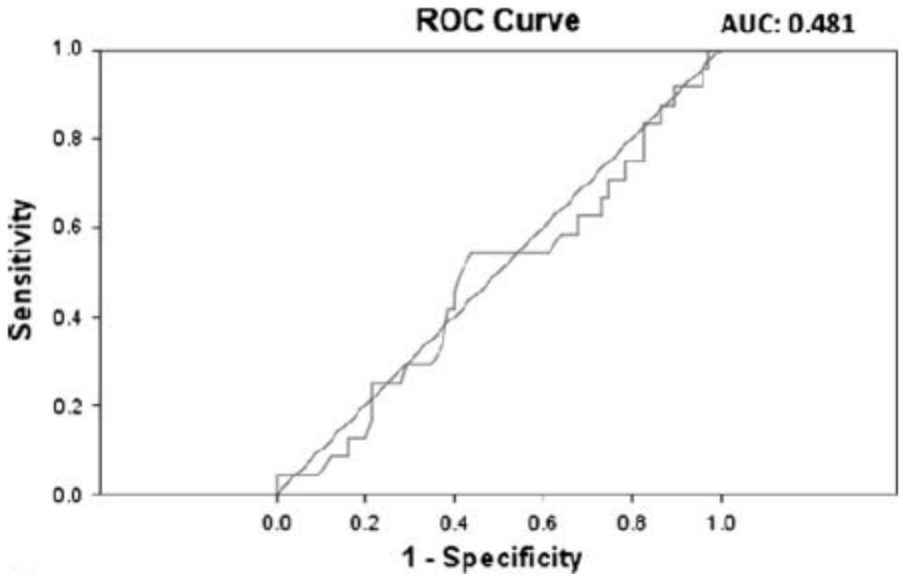
RESULTS

Predicting need for revision surgery		
	Sensitivity (%)	**Specificity (%)**
Mean ESR/CRP before re-implantation		
ESR > 30 mm/h	65	32
CRP > 20 mg/L	29	73
Δ ESR/CRP resection to re-implantation		
ESR > 10 mm/h	67	25
CRP > 20 mg/L	63	23

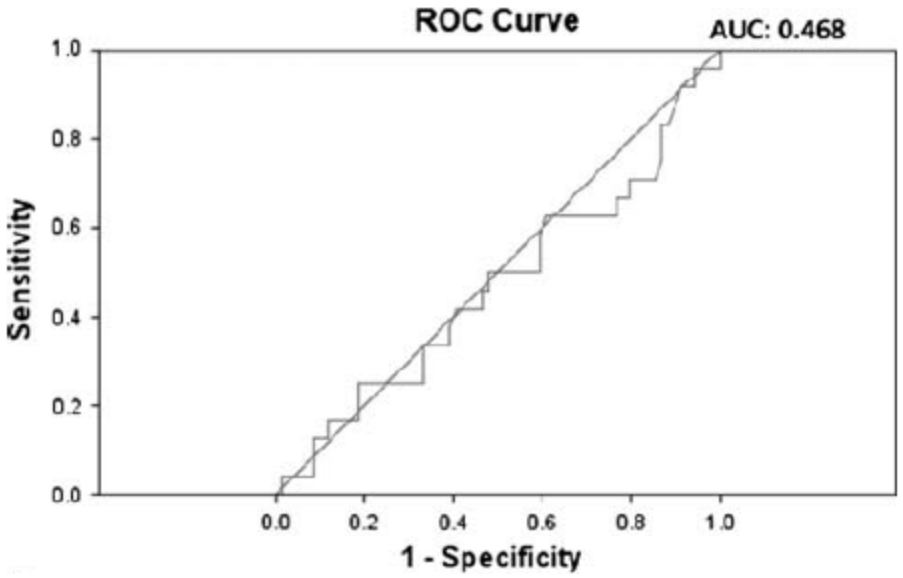
RESULTS

Δ ESR/CRP resection to re-implantation

ESR



CRP



AUTHOR'S CONCLUSIONS

- ESR or CRP unable to differentiate infection eradication and persistence
- Deferring re-implantation until normalization of all serological markers not scientifically supported
- Combination of clinical and laboratory factors should determine timing of re-implantation

LIMITATIONS

- Timeframe from resection to re-implantation varied widely
- Low rate of PJI recurrence
- Different organism cultured in 6 of 23 persistent infections

What is the Role of Serological Testing Between Stages of Two-stage Reconstruction of the Infected Prosthetic Knee?

Sharat K. Kusuma MD, MBA, Joseph Ward BA, Marc Jacofsky PhD, Scott M. Sporer MD, Craig J. Della Valle MD

Clin Orthop Relat Res (2011) 469:1002–1008

Kusuma et al.

Design	Retrospective dual center cohort
N	76, mean age 66y
Indication for abx	TKA infection
Duration of abx	6 weeks IV
ESR/CRP measurements	ESR & CRP prior to resection & prior to re-implantation
Time to re-implantation	Mean 74 days
Follow-up	2.8y
Outcome	Persistent infection: 2 (+) intra-op cultures OR $\geq$ 2 of i) at least 1 (+) culture, ii) histopathology c/w infection, iii) grossly infected tissues

RESULTS

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	

AUTHOR'S CONCLUSIONS

- No ESR or CRP cutoff with useful AUC values
- ESR and CRP not reliable for diagnosing persistent infection between stages
- Waiting until ESR and CRP have "normalized" not reliable strategy
- Synovial WBC at re-implantation had highest AUC of 0.71

LIMITATIONS

- No definitive criteria for persistent infection
- Small number of persistent infections
- Inflammatory response in persistent infection did not generate large increases in inflammatory markers
- No adjustment for confounders

Poor performance of microbiological sampling in the prediction of recurrent arthroplasty infection

Maximilian Schindler · Panayiotis Christofilopoulos · Blaise Wyssa · Wilson Belaieff · Christian Garzoni · Louis Bernard · Daniel Lew · Pierre Hoffmeyer · Ilker Uçkay

International Orthopaedics (SICOT) (2011) 35:647–654

Schindler et al.

Design	Retrospective single center cohort
N	58, mean age 68y
Indication for abx	PJI
Duration of abx	44 days
ESR/CRP measurements	CRP qweek x 3 wks & within 15d of re-implantation
Time to re-implantation	153 days
Follow-up	Mean 3.3y
Outcome	Recurrent PJI

RESULTS - Schindler

CRP > 10 mg/L at re-implantation for identifying recurrent infection	
Sensitivity (%)	17
Specificity (%)	81
PPV (%)	13
NPV (%)	86

AUTHOR'S CONCLUSIONS

- More rapid CRP decrease in patients without recurrent infections, though not statistically significant
- CRP is a poor predictor of PJI recurrence

LIMITATIONS

- Small number of persistent infection cases
- Infection with new pathogen counted as recurrence
- Did not explicitly define recurrent PJI

Perioperative Testing for Persistent Sepsis Following Resection Arthroplasty of the Hip for Periprosthetic Infection

Sanjai K. Shukla, MD,* Joseph P. Ward, BA,* Marc C. Jacofsky, PhD,†
Scott M. Sporer, MD,* Wayne G. Paprosky, MD,* and Craig J. Della Valle, MD*

The Journal of Arthroplasty Vol. 25 No. 6 Suppl. 1 2010

Shukla et al.

Design	Prospective single center cohort
N	86, mean age 64
Indication for abx	THA infection
Duration of abx	6 weeks IV
ESR/CRP measurements	ESR and CRP prior to resection & prior to re-implantation
Time to re-implantation	Mean 75 days
Follow-up	NR
Outcome	Persistent infection: $\geq$ 2 positive intra-op cultures OR at $\geq$ 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

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 to reliably identify persistent infection
- Synovial WBC most useful test w/ AUC of 0.81
- Combining serological markers + WBC did not improve test performance

LIMITATIONS

- Low rate of persistent infection
- Wide range of time to re-implantation

COSTS

- ESR = $10.61
- CRP = $10.31
- Fluid cell count = $28.77
- Prosthetic joint infection = $50,000

LIKELIHOOD RATIOS

- Odds of given test result in patient with disease
  Odds of given test result in patient without disease
- LR(+) - ability to rule-in disease
  - 2 to 5 = poor to fair test
  - > 10 = good test
- LR(-) - ability to rule-out disease
  - 0.5 to 0.2 = poor to fair test
  - < 0.1 = good
- Independent of pre-test probability

SUMMARY

	ESR mm/h CRP mg/L At re-implant	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 OF LIMITATIONS

- Design: observational, retrospective
- Low number of persistent infections
- No definitive criteria for persistent infection
- Variable baseline ESR/CRP, timing of ESR/CRP measurements, length of follow-up
- Use of antibiotic-impregnated spacer
- Lack of hard clinical outcomes

MY RECOMMENDATIONS

- Likelihood ratios indicate that neither test increases post-test probabilities
- No discrete cut points for accurate identification of infection
- Downward trend observed in both eradicated and persistent infections
- May result in inappropriate patient management decisions

$\Rightarrow$ **Recommend against routinely monitoring ESR and CRP for patients undergoing two-stage revision for PJI**

Questions