

Markers of Infection: CRP, ESR and Procalcitonin

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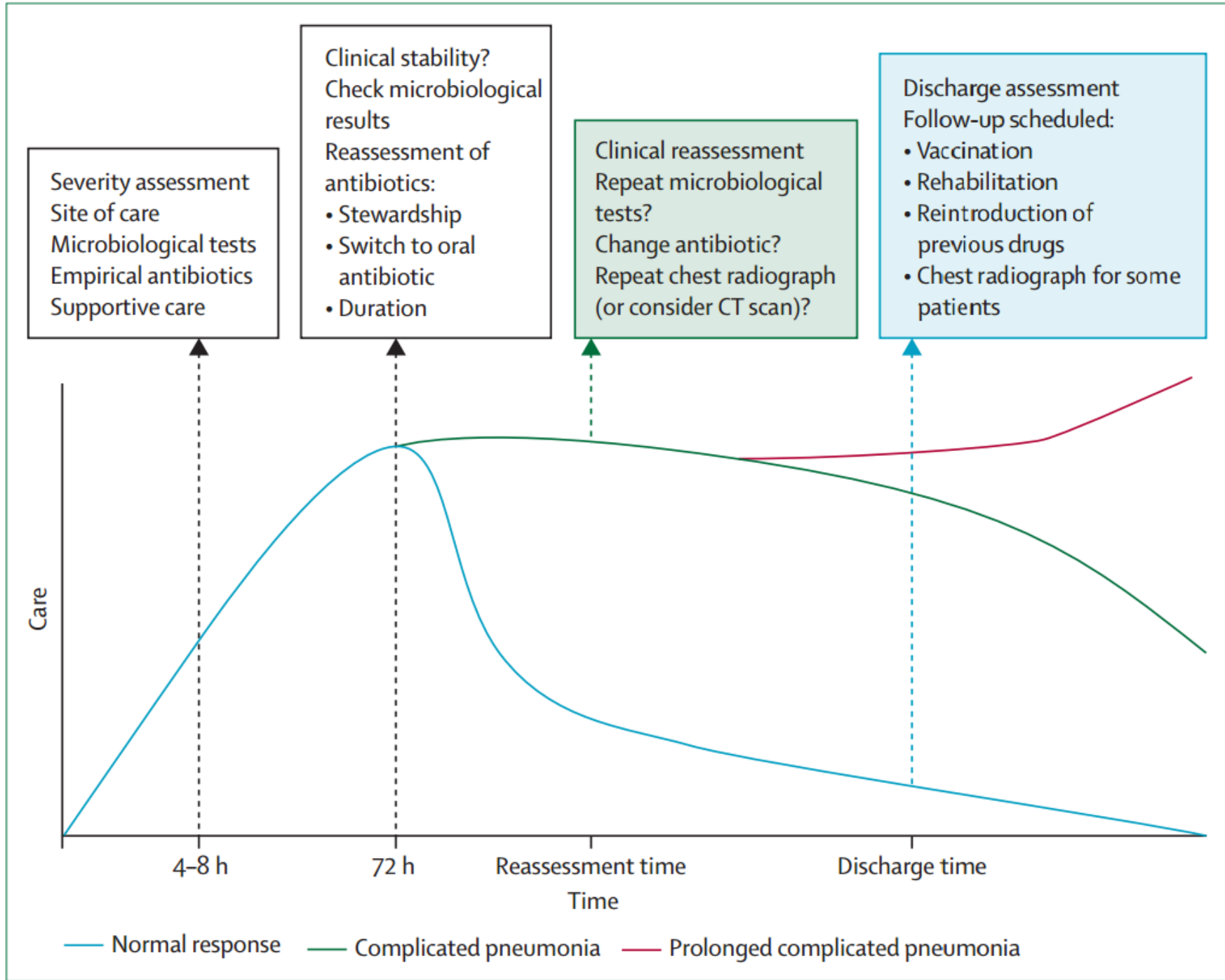
Harborview Medical Center &

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March 14, 2017

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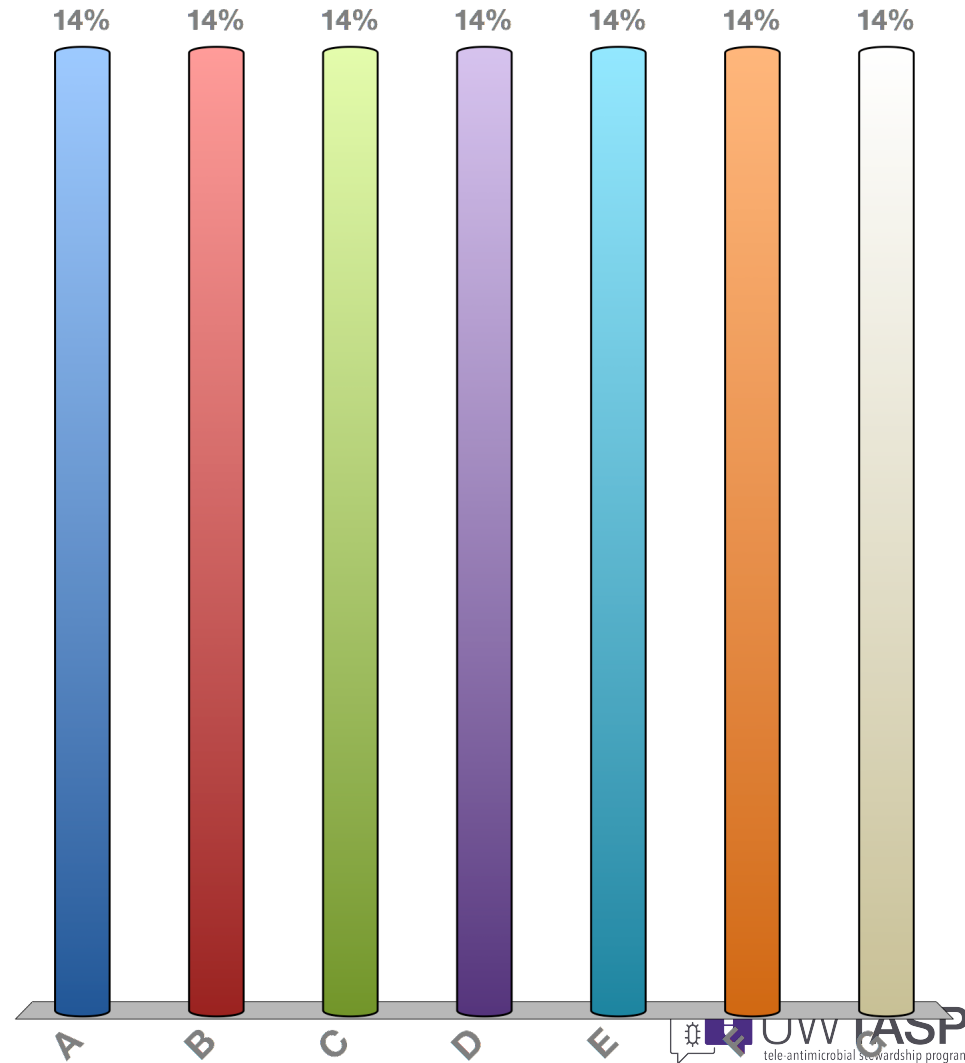


Erythrocyte Sedimentation Rate (ESR)

- A non-specific marker of *inflammation*, including Autoimmune disorders (PMR, SLE) and some cancers (multiple myeloma)
- Measures the rate at which RBCs fall in a test tube
- Reported as the millimeters of plasma at the top portion of the tube after 1 hour (mm/hr) (available tests: Westergren, modified Westergren, micro-ESR)
- Represents elevation in globulins and/or fibrinogen = *surrogate marker*

What conditions can affect the ESR?

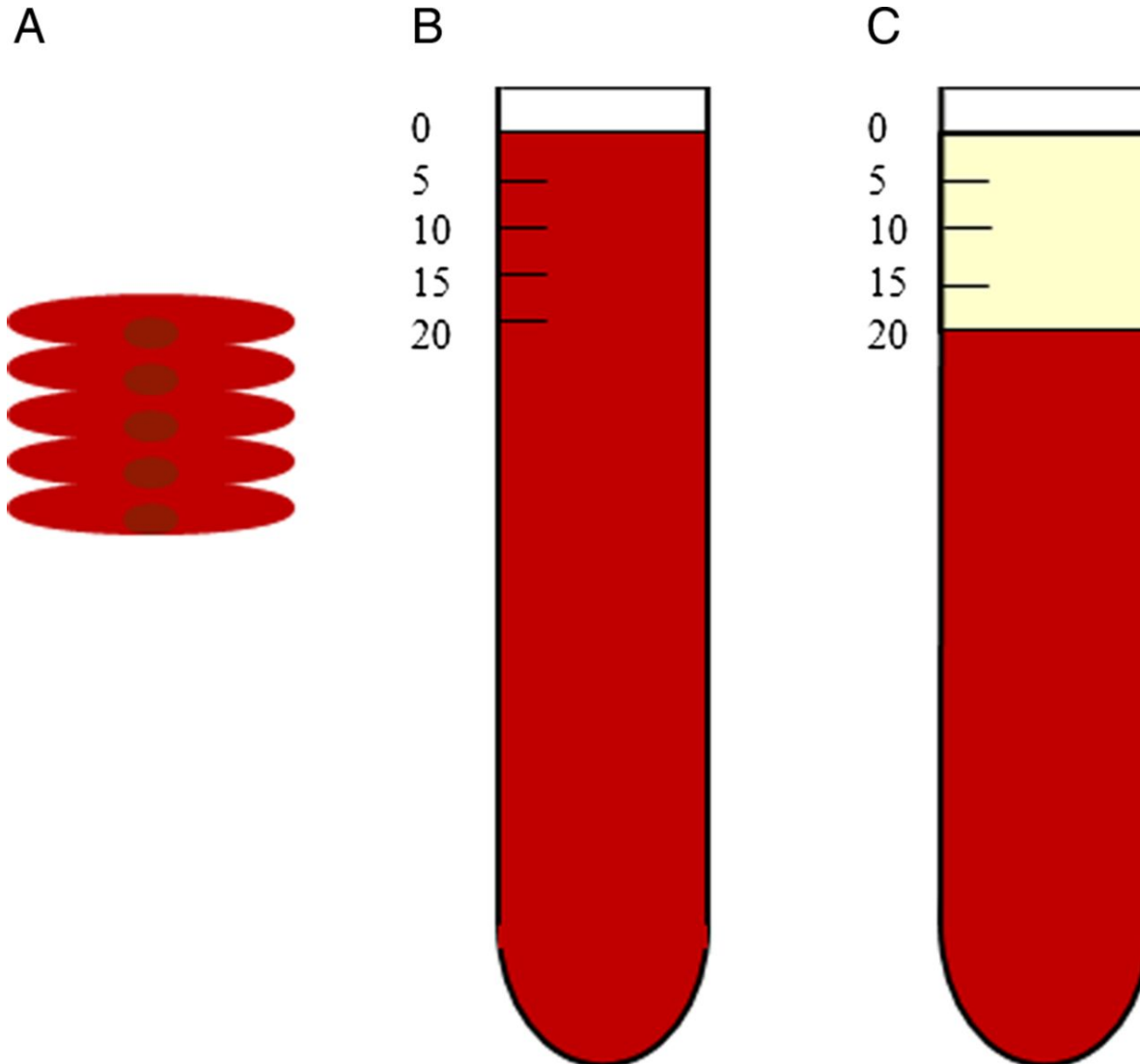
- A. Pregnancy
- B. Rheumatic fever
- C. Age
- D. Obesity
- E. Tube is cooled
- F. All of the above
- G. Only A and C

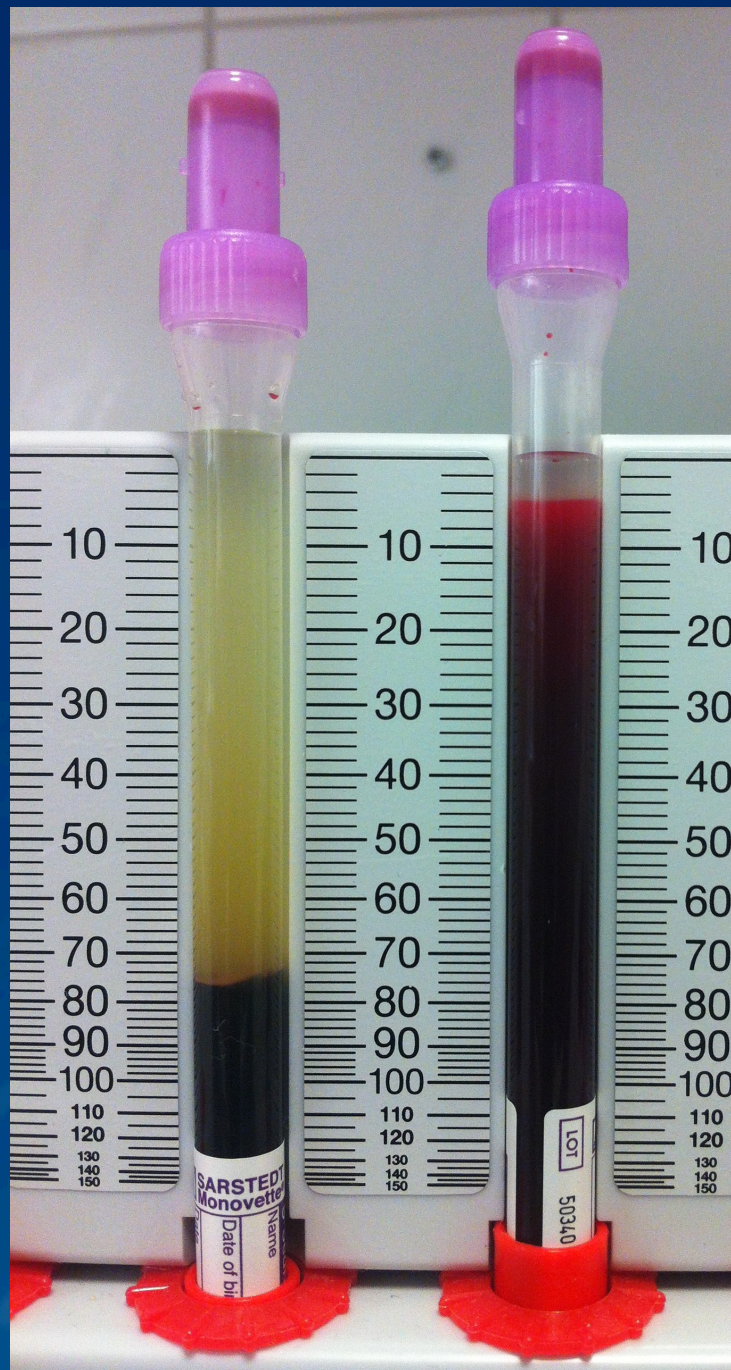


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Rouleaux of red blood cells.





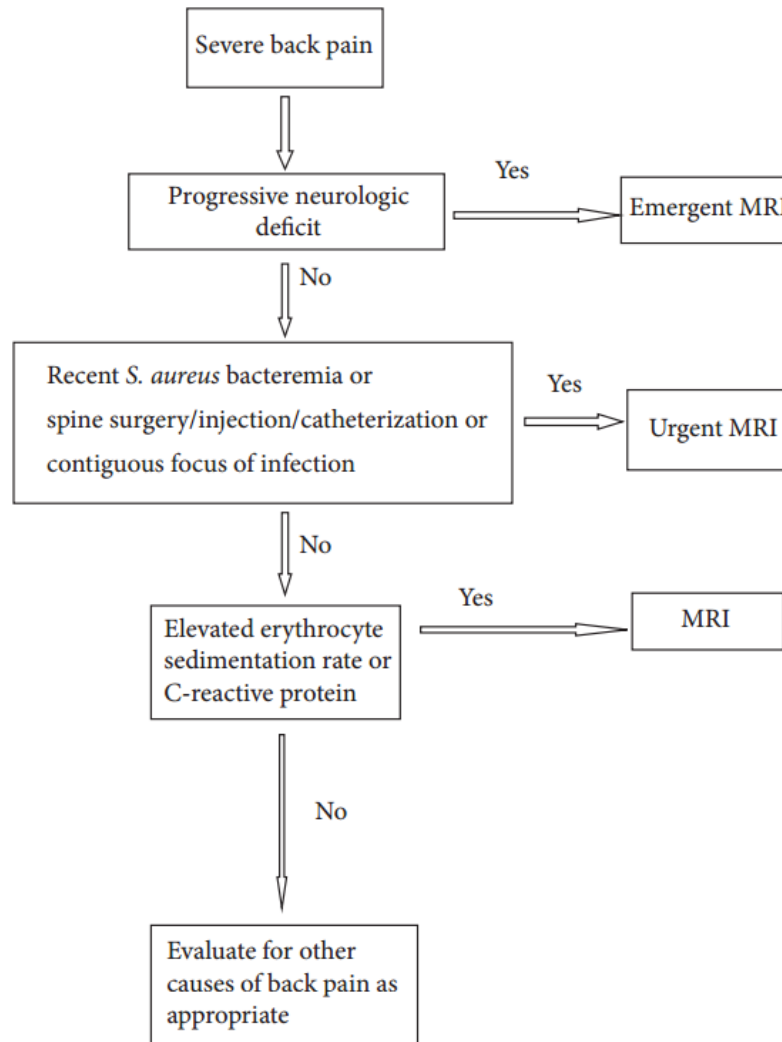
ESR: Normal Ranges

- Newborn 0-2 mm/hr
- Newborn to puberty 3-13 mm/hr
- Women 0-29 mm/hr (goes up during pregnancy)
- Men 0-22 mm/hr
- 1951 study, 20-30yo mean 8.3 mm/hr, 70-80yo mean 18.3 mm/hr

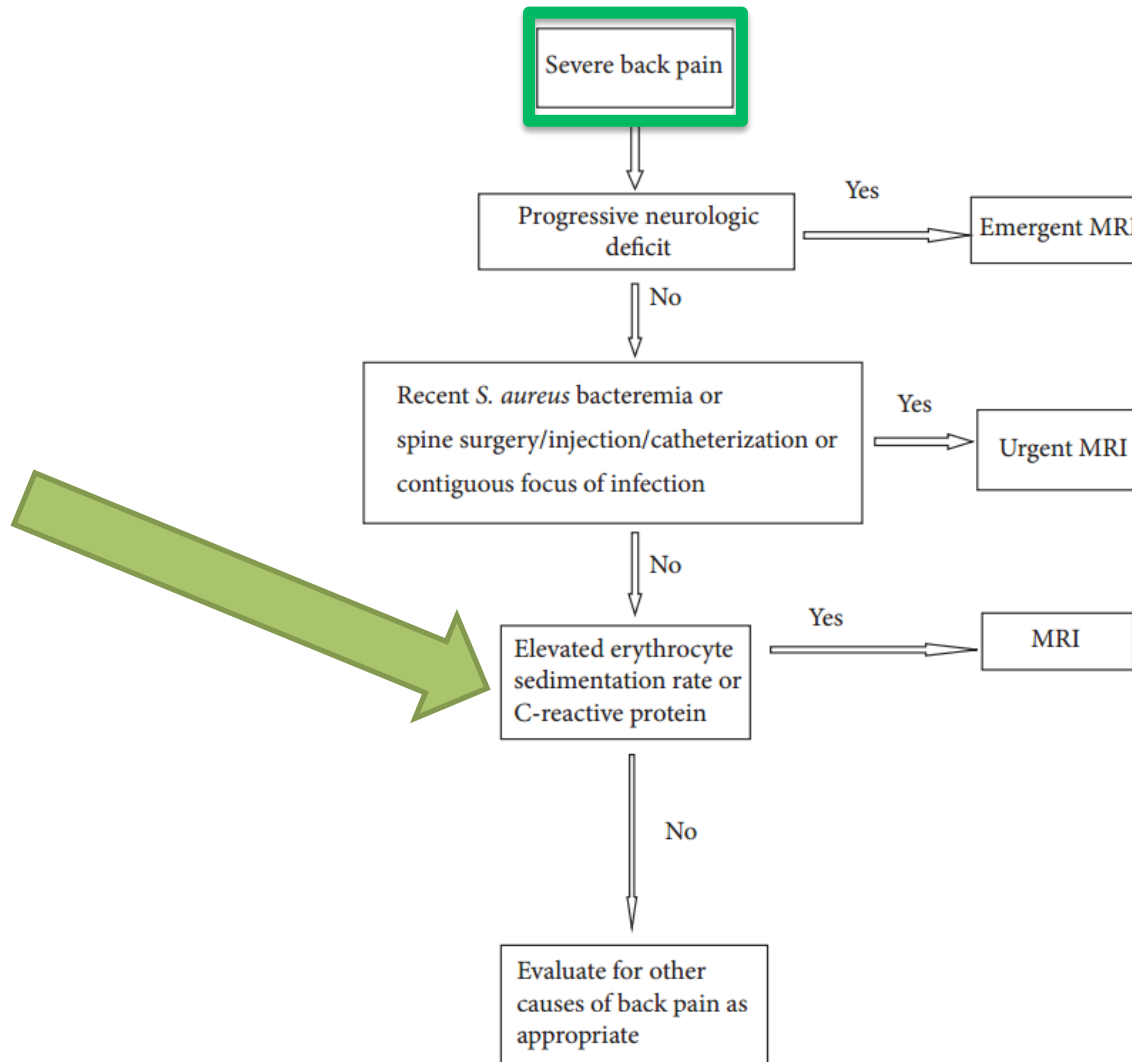
ESR in Use

- Child refusing to weight a leg
 - Significant elevation (>40 mm/h) helpful
 - But better when combined with fever, sx's, CRP, leukocytosis
- Children with ESR ≥ 100 mm/hr
 - 49.5% infection
 - 26.3% connective tissue disease
 - 12.1% malignancy
 - 8.1% renal disease
- Cannot be used to rule-out a disease

A Proposed Algorithm for Spinal Epidural Abscess



A Proposed Algorithm for Spinal Epidural Abscess

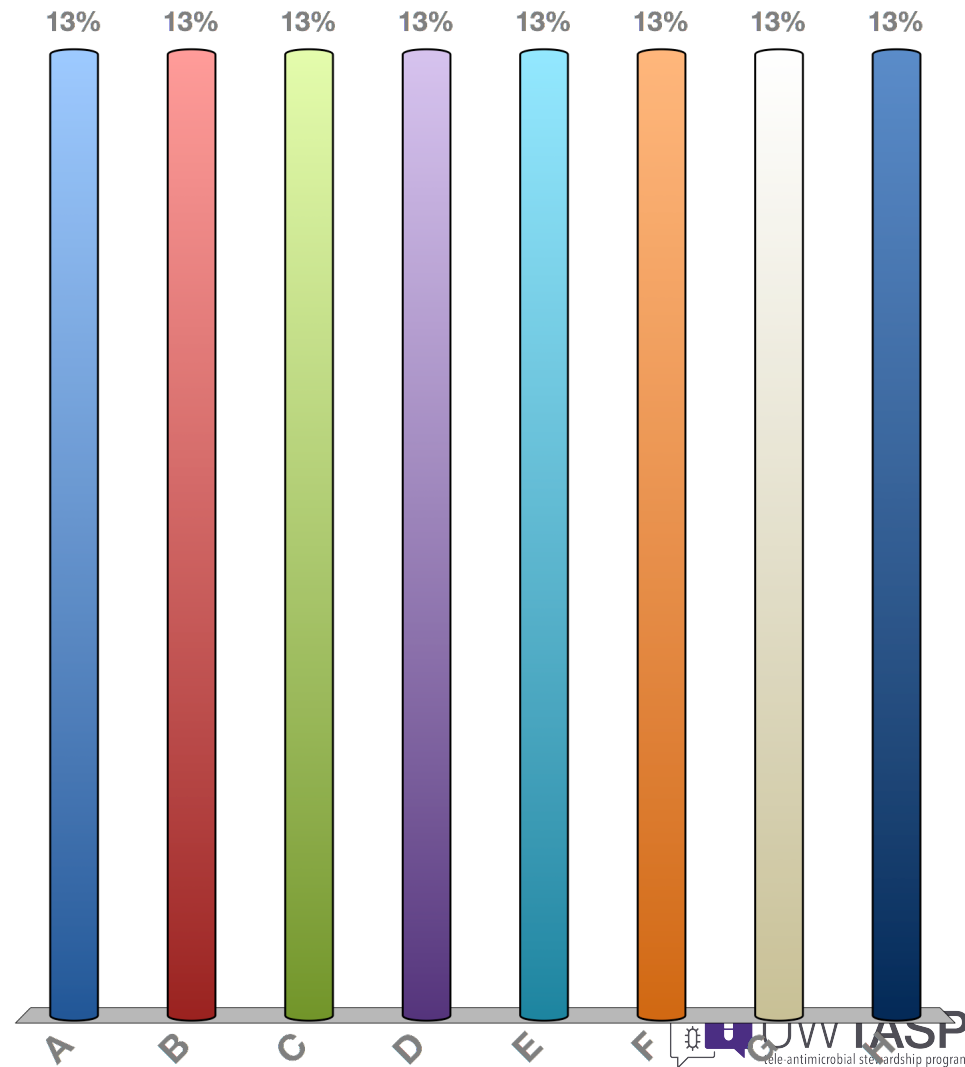


C-reactive Protein (CRP)

- A specific protein (pentraxin family)
- More direct measure of inflammation
- Made in liver in response to IL1 beta, IL-6 and TNF-alpha
- In turn, activates neutrophils, NK cells and adhesins
- Exists as pentameric and monomeric forms
- Measured in a variety of ways, including analyzers, ELISA, and lateral flow assays

CRP is Elevated in Which of The Following?

- A. Cardiovascular disease
- B. Pneumonia
- C. Trauma
- D. Viral infections
- E. Systemic lupus erythematosus
- F. Post-operative setting
- G. Only A, B and E
- H. All of the above



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CRP Levels

Normal CRP <3 mg/dL (some assays can go lower)

Clinical setting	CRP concentration increase (mg/L)
Mild inflammation and viral infections	~10-50
Active inflammation and bacterial infection	50-200
Severe infections and trauma	> 200

CRP as Predictor of CAP Mortality

Supplementary Table 7 Performance characteristics of C-reactive protein for predicting mortality in community-acquired pneumonia

Author	Year	Cut-off (mg/L)	n	Mortality (%)	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
<u>Kolditz et al.</u>	2010	181	58	10.3	4	31	21	2	0.67(0.22-0.96)	0.40(0.27-0.55)
<u>Courtais et al.</u>	2013	102.4	109	8.2	5	32	68	4	0.56(0.21-0.86)	0.68(0.58-0.77)
<u>Horie et al.</u>	2012	284.4	102	8.8	6	9	84	3	0.67(0.30-0.93)	0.90(0.82-0.95)
<u>Kim et al.</u>	2011	143	424	13.6	35	137	229	23	0.60(0.47-0.73)	0.63(0.57-0.68)
<u>Salluh et al.</u>	2011	214	90	15.5	7	18	58	7	0.50(0.23-0.77)	0.76(0.65-0.85)
<u>Lacoma et al.</u>	2011	109.7	75	8	5	30	39	1	0.83(0.36-1.00)	0.57(0.44-0.68)
<u>de Jager et al.</u>	2012	46	395	5.8	10	74	298	13	0.58(0.51-0.65)	0.60(0.57-0.62)
<u>ProCAP</u>		114	302	12.5	26	140	124	12	0.68(0.51-0.82)	0.47(0.41-0.53)
<u>ProHOSP</u>		153	925	5.4	27	446	429	24	0.53(0.38-0.67)	0.49(0.46-0.52)

Abbreviations: CI, confidence interval; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

CRP as Predictor of CAP Mortality

Effects of C-reactive protein for predicting mortality in community-acquired pneumonia

Mortality (%)	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
10.3	4	31	21	2	0.67(0.22-0.96)	0.40(0.27-0.55)
8.2	5	32	68	4	0.56(0.21-0.86)	0.68(0.58-0.77)
8.8	6	9	84	3	0.67(0.30-0.93)	0.90(0.82-0.95)
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TP, true positive; FP, false positive; TN, true negative; FN, false negative.

CRP: Pros and Cons

- Strong predictor of abx rx for RTIs
- No difference in POC CRP use and clinical recovery
- Maybe a link between CRP and reduction in abx use?
- Cannot differentiate between bacterial and viral lower RTIs in children
- Cannot determine the microbial agent in acute bronchitis in adults
- Some evidence that high CRP is associated with severe RTI (pneumonia)

Why Order an ESR *and* a CRP?

- CRP
 - Direct measure of protein in the blood
 - Rises acutely (4-6 hrs of onset)
 - Falls quickly (w/in 24-48 hrs)
 - Tighter correlation with acute inflammation
- ESR
 - Rises in 24-48 hrs
 - Slower decline may correlate with complete resolution
 - Better for some autoimmune conditions, ex. SLE

Procalcitonin

- Procalcitonin is the peptide precursor of calcitonin
- Normally undetectable in serum
- Detectable levels associated with a variety of conditions, but higher levels associated with immune response to bacterial bioburden, i.e. infection
- Driven down by IFN-gamma, so low in viral infections

Procalcitonin and Differentiation

- Community-acquired pneumonia
 - 545 ED pts, 372 classified as PNA
 - PCT >0.1 ng/mL, Sn 90%, Sp 59%
 - PCT >1 ng/mL, Sn 43%, Sp 96%
 - As accurate as ED physicians and CRP(?)
- ICU patients and pneumonia
 - 78 ICU pts with SIRS, 60 confirmed infected
 - PCT 1.1, Sn 97%, Sp 78%

Procalcitonin and Antimicrobial Duration

- Five randomized ICU-based trials
- Nobre study:
 - Antibiotics stopped when PCT level dropped >90% from baseline, after at least 3 or 5 days
 - Antibiotic duration and exposure decreased in PCT-guided groups
 - Mortality, relapse and hospital LOS similar
 - ICU LOS in PCT group shortened by 2 days
- Use of PCT as guide = reduced costs

PCT as COPD Biomarker

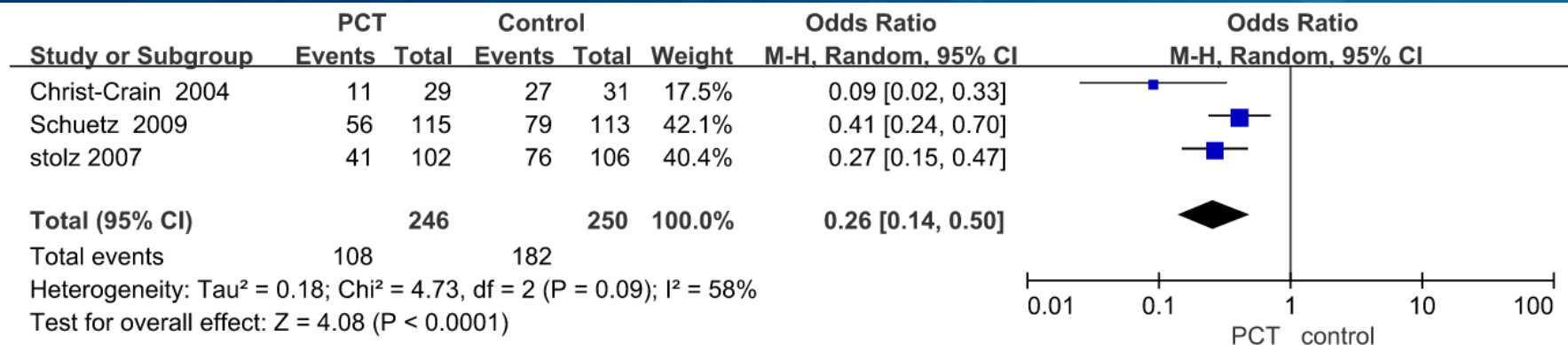


FIGURE 3 PCT-guided treatment on antibiotic prescriptions in patients with AECOPD

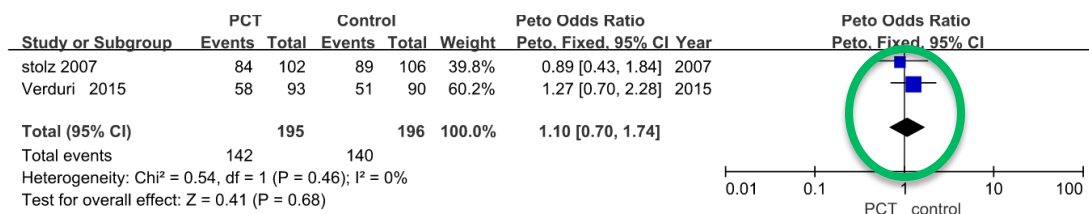


FIGURE 4 PCT-guided treatment on mortality in patients with AECOPD

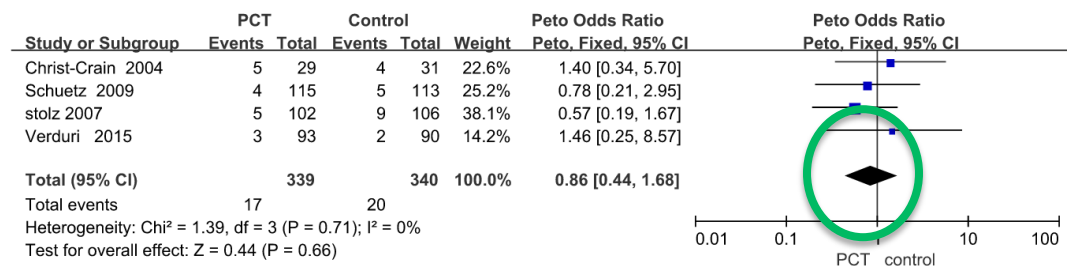


FIGURE 5 PCT-guided treatment on clinical success in patients with AECOPD

Other Serum Biomarkers

- Complement
- Ferritin
- Fibrinogen
- Serum amyloid A
- Plasma viscosity
- Alpha-defensin
- Human beta-defensin-2 and -3
- Leukocyte esterase
- Cathelicidin LL-37
- Albumin (goes down with inflammation)

