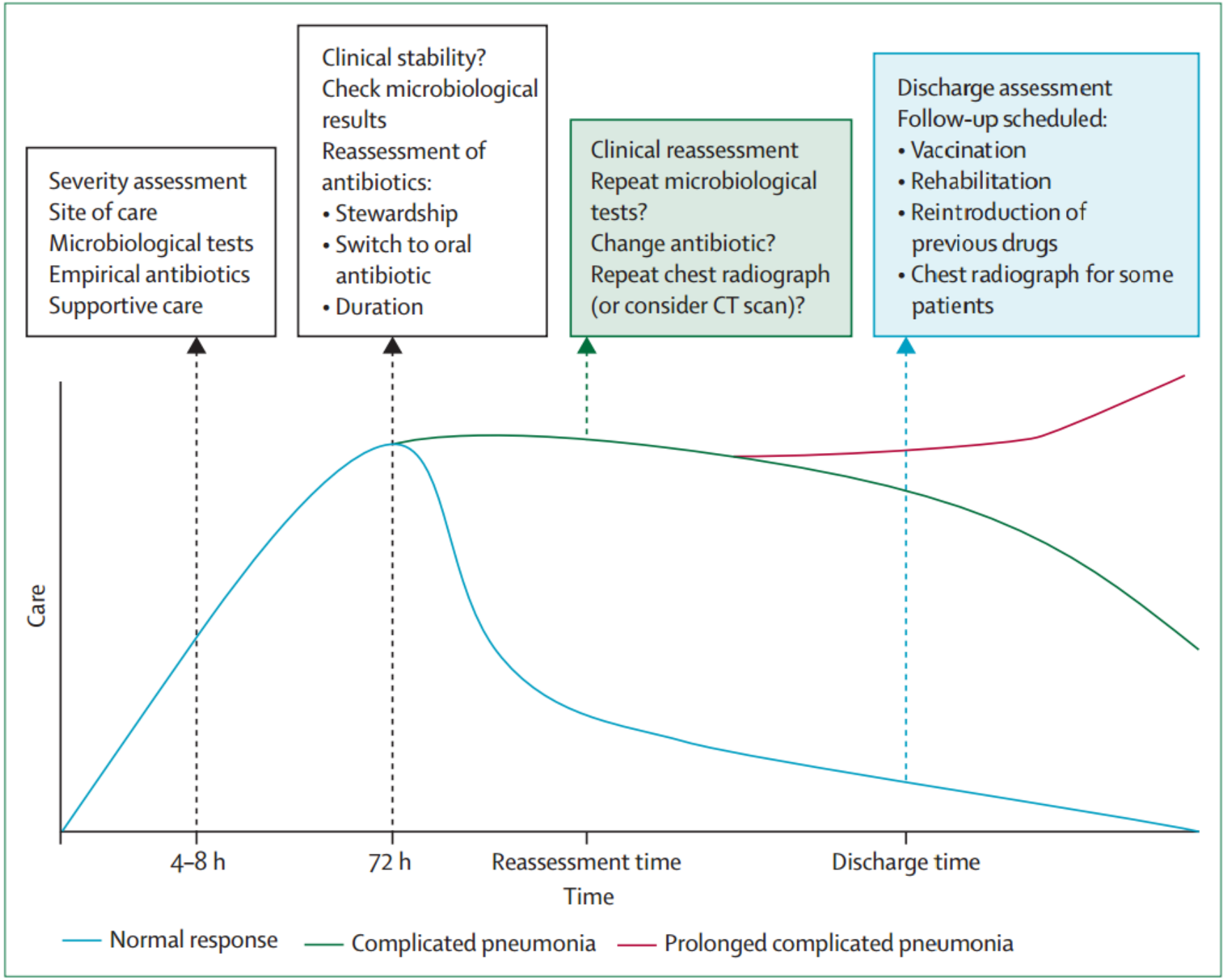
UWTASP

tele-antimicrobial stewardship program

June 25, 2019

Agenda

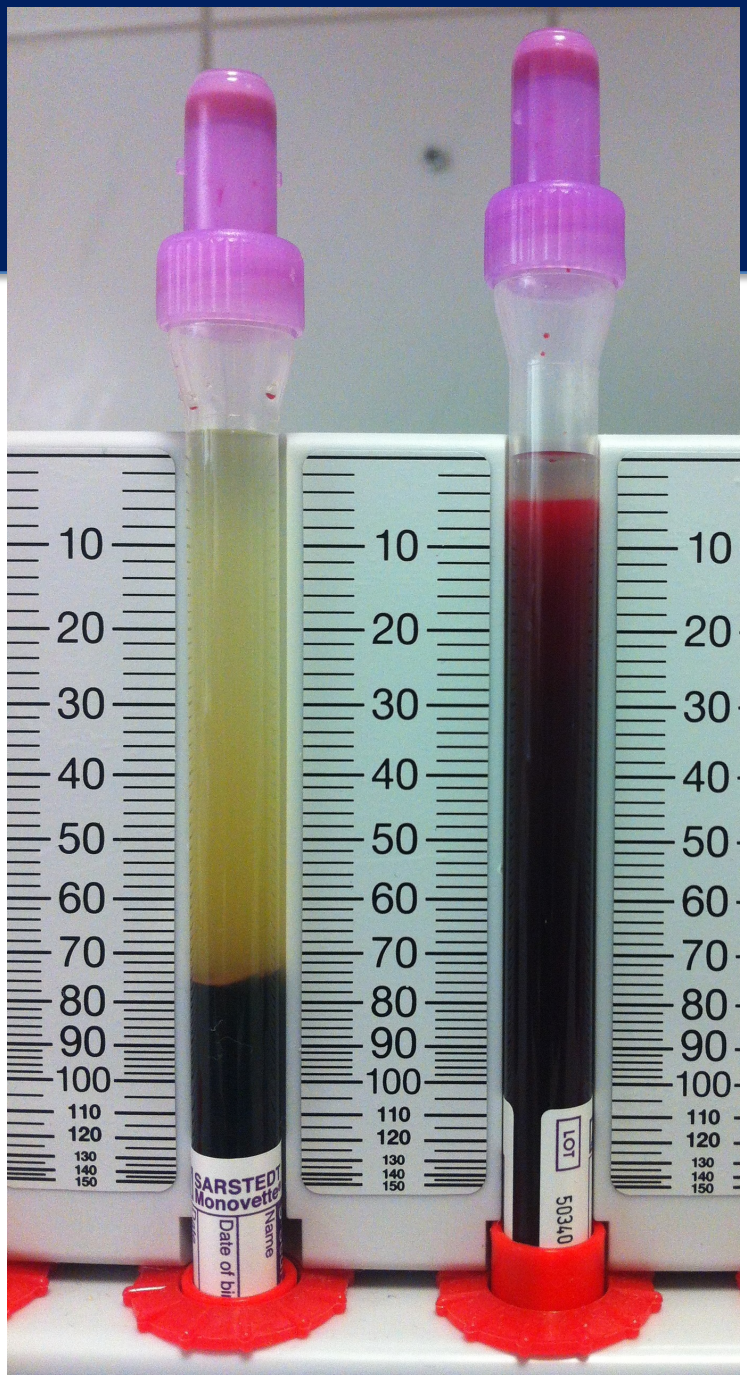
- Announcements
- Markers of Infection: CRP, ESR and Procalcitonin
- Case Discussions
- Open Discussion



Prina, Lancet, 2015

Erythrocyte Sedimentation Rate (ESR)

- A non-specific marker of *inflammation*
  - including Autoimmune disorders (PMR, SLE)
  - some cancers (multiple myeloma)
- Measures the rate at which RBCs fall in a test tube
  - Reported in mm/hr
- Surrogate marker – changes with elevation in globulins and/or fibrinogen, also RBC size



- Abdullah Sarhan, commons.wikimedia.org

What conditions can affect the ESR?

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

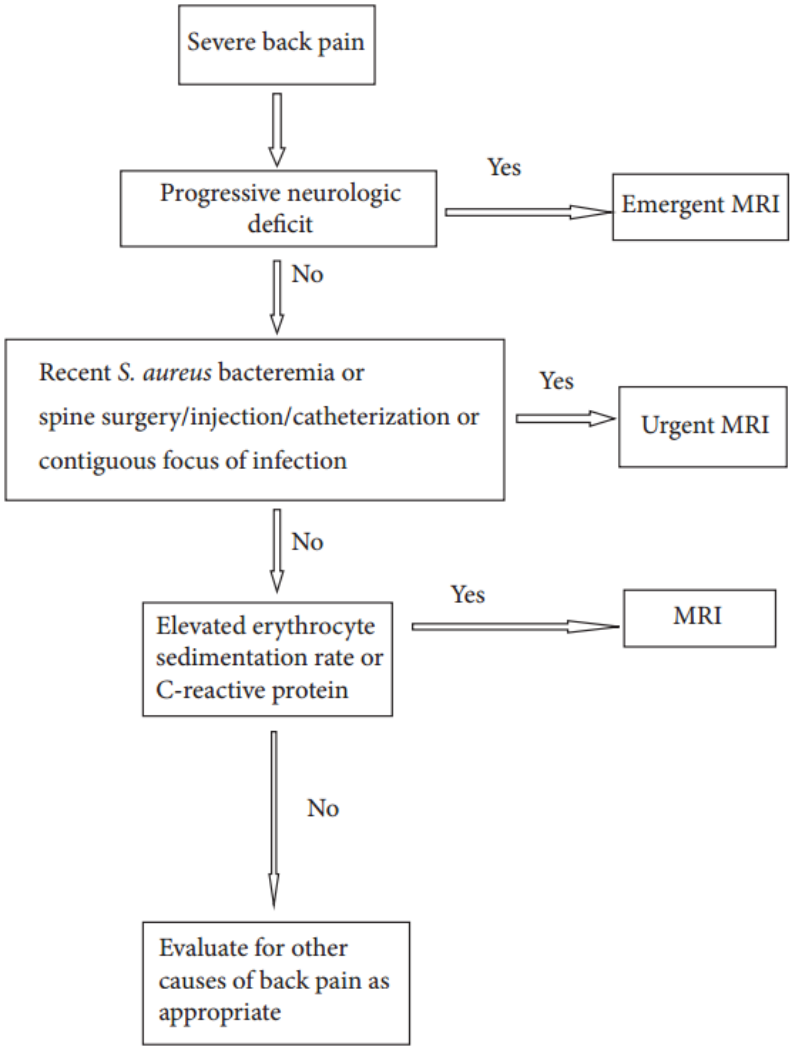
ESR: Normal Ranges

- 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

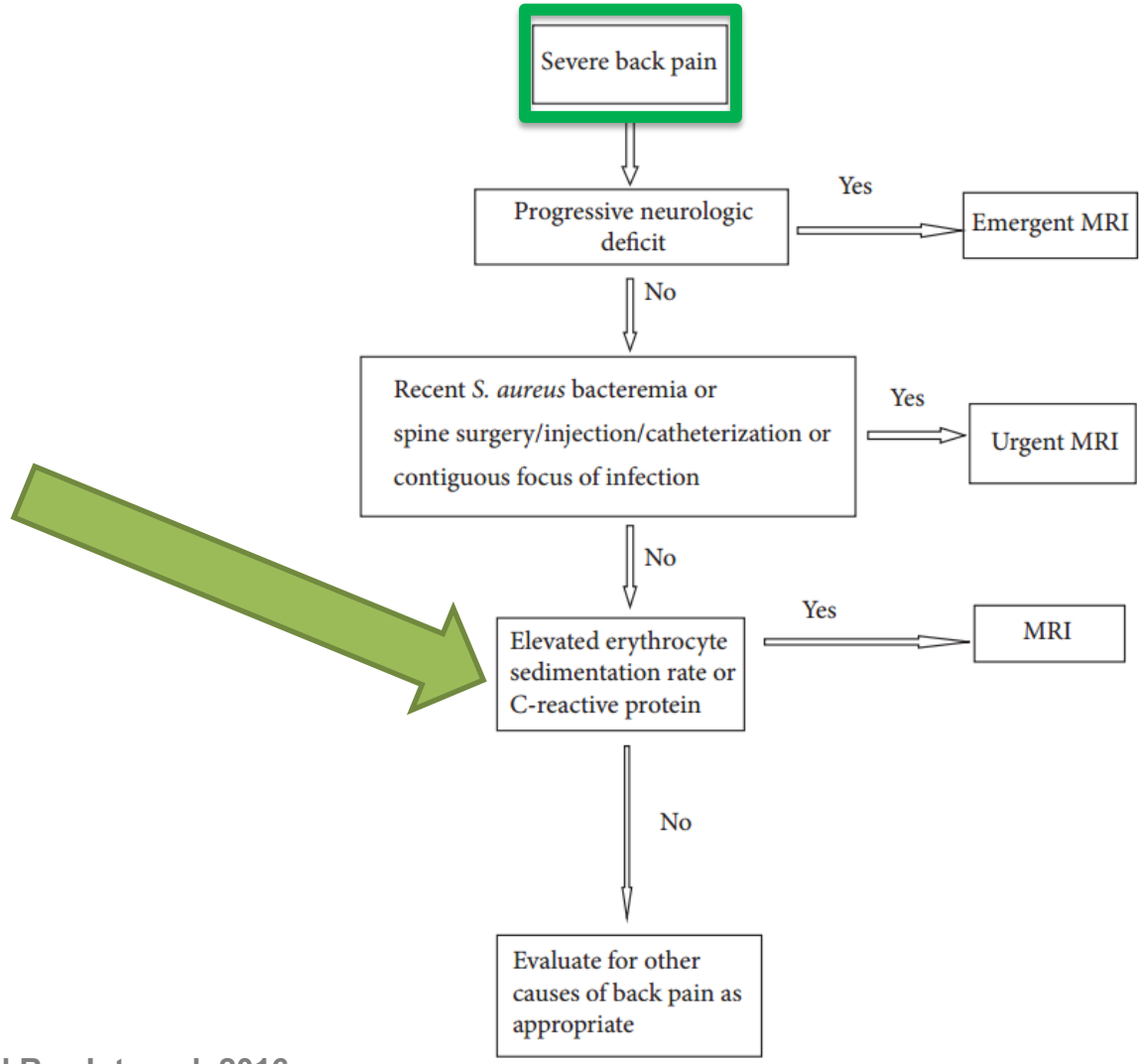
- Child refusing to weight a leg
  - Significant elevation (>40 mm/h) helpful
  - But better when combined with fever, sxs, CRP, leukocytosis
- Children with ESR ≥100 mm/hr
  - 49.5% infection
  - 26.3% connective tissue disease
  - 12.1% malignancy
  - 8.1% renal disease
- Cannot be used to rule-out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

A Proposed Algorithm for Spinal Epidural Abscess



Bond, Biomed Res Internal, 2016

A Proposed Algorithm for Spinal Epidural Abscess



Bond, Biomed Res Internal, 2016

C-reactive Protein (CRP)

- A specific protein, involved in innate immunity
- More direct measure of inflammation
- Made in liver in reponse to IL1 beta, IL-6 and TNF-alpha
- In turn, activates neutrophils, NK cells and adhesins
- Measured in a variety of ways, including analyzers, ELISA, and lateral flow assays
- No standard reporting unit (some labs use mg/dL, others mg/L)

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. All of the above

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

De Carvalho, Acta Rheum Port, 2007

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)
Kolditz et al.	2010	181	58	10·3	4	31	21	2	0·67(0·22-0·96)	0·40(0·27-0·55)
Courtais et al.	2013	102·4	109	8·2	5	32	68	4	0·56(0·21-0·86)	0·68(0·58-0·77)
Horie et al.	2012	284·4	102	8·8	6	9	84	3	0·67(0·30-0·93)	0·90(0·82-0·95)
Kim et al.	2011	143	424	13·6	35	137	229	23	0·60(0·47-0·73)	0·63(0·57-0·68)
Salluh et al.	2011	214	90	15·5	7	18	58	7	0·50(0·23-0·77)	0·76(0·65-0·85)
Lacoma et al.	2011	109·7	75	8	5	30	39	1	0·83(0·36-1·00)	0·57(0·44-0·68)
de Jager et al.	2012	46	395	5·8	10	74	298	13	0·58(0·51-0·65)	0·60(0·57-0·62)
ProCAP		114	302	12·5	26	140	124	12	0·68(0·51-0·82)	0·47(0·41-0·53)
ProHOSP		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.

Viasus, J Infection, 2016

CRP: Pros and Cons

- Strong predictor of abx rx for RTIs
- 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?

- ESR
  - Rises in 24-48 hrs
  - Slower decline may correlate with complete resolution
  - Better for some autoimmune conditions, ex. SLE
- 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

Ramsay, Arch Dis Child Educ Prac Ed, 2015

UW TASP tele-antimicrobial stewardship program

Procalcitonin

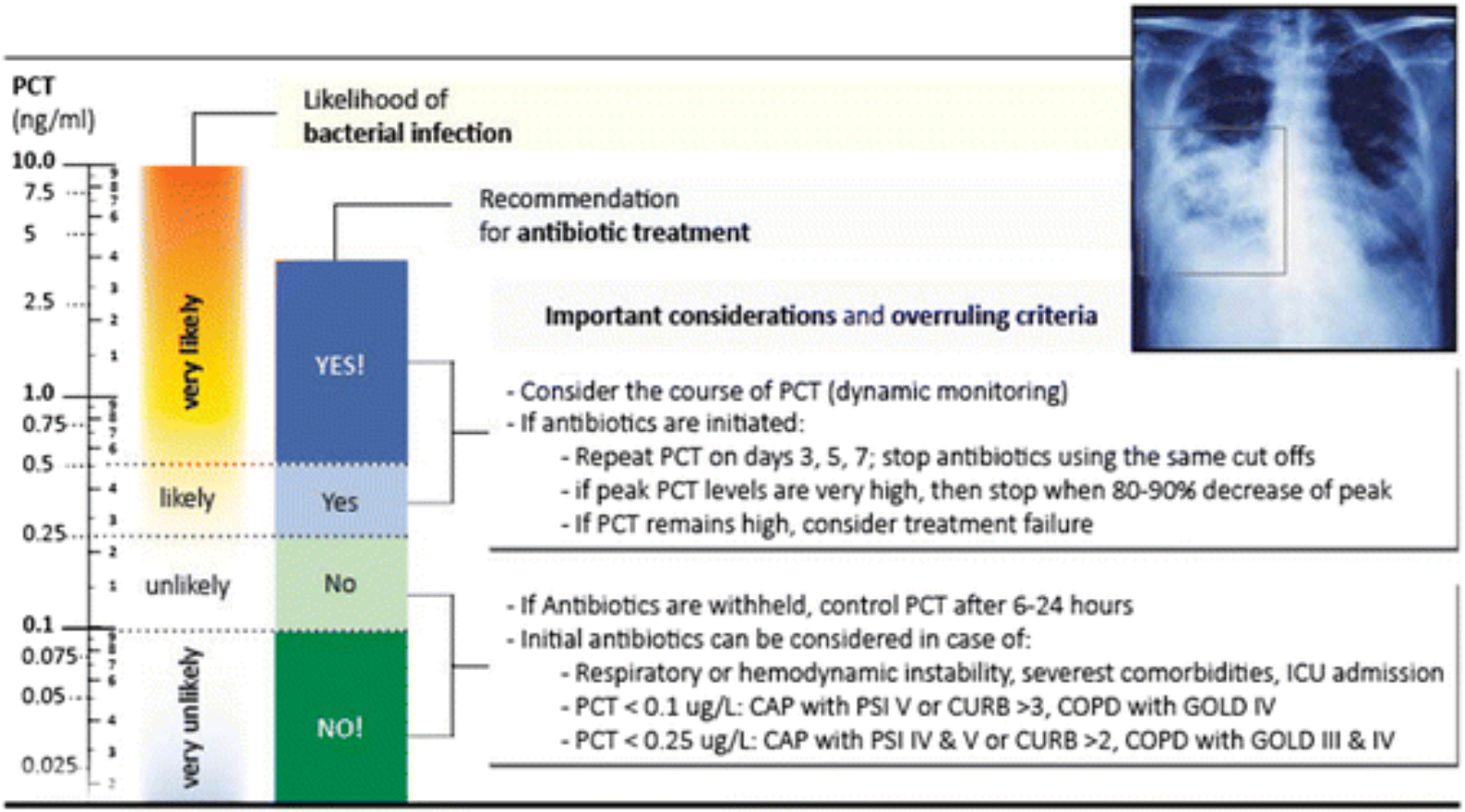
- Procalcitonin is the precursor of calcitonin
- Normally undetectable in serum
- Detectable levels associated with a variety of conditions, but higher levels associated with immune response to bacterial bioburden
- Driven down by IFN-gamma, so low in viral infections

Procalcitonin and ARI

- Patient level meta-analysis, 26 RCTs
  - CAP in 40%, most in ED or ICU
  - Recs to initiate or continue abx based on cut-off PCT value
- Outcomes:
  - 30 day mortality:
    - 9% in PCT vs. 10% controls*
  - Reduced abx days: 2.4*
  - Reduced abx AEs: OR 0.68*
- Limitations:
  - 1/26 studies done in the US

Schuetz, Lancet, 2018

PCT Algorithm



Sager, BMC Medicine, 2017

Procalcitonin In Reality

- ProACT trial showed limited utility in US hospitals without algorithm
- Are we really just testing algorithms in care?
- Some hints at decreased abx days in sepsis with equivalent outcomes
- $$$$
- Difficulties validating certain assays
  - (UW not using Diazyme)

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