Can you C the Respiratory Problem?

Wynnie Lau
Doctor of Pharmacy Student
University of British Columbia
November 15, 2012

Respiratory Tract Infections

- Responsible for 116 million physician office visits and 3 million ED visits annually in US

- Diagnostic uncertainties ↑ chances of inappropriate abx
  - conservative practices in face of ‘possible’ pneumonia

Wood. et al. Fam Pract 2007; 24:427-34.
IDSA guidelines on management of CAP 2007

Diagnosis

- IDSA recommends for diagnostic testing…
  - "In addition to ... clinical features, a demonstrable infiltrate by chest radiograph … is required for diagnosis of pneumonia"
- Pretest probability of pneumonia calculated with number of findings:
  - Absence of asthma
  - Temperature > 37.8
  - HR > 100 bpm
  - ↓ breath sounds
  - crackles
- all 5 sx only give 50% pretest probability

# of findings	Predicted probability
2	3%
3	10%
4	25%
5	50%

Heckerling et al. Ann Intern Med 1990; 113:664-70.
IDSA guidelines on management of CAP 2007

Other places in the world...

- In Sweden
  one study reported use of CRP test in 41% of all patients consulting a GP for respiratory tract infection

- 2011 Dutch College of General Practitioners:

  "... CRP measurements recommended for patients in whom CAP is suspected."

Dutch Working party on antibiotic policy/ Dutch association of Chest physicians. 2011.
Andre M et al. Scan J Infect Dis 2004; 36:192-7.

Background

- C-Reactive Protein (CRP)
  - Identified from observation of patients with pneumonia
  - protein reacted with pneumococcal c-polysaccharide in plasma during acute phase of pneumococcal pneumonia

Clyne B. J Emerg Med 1999; 17:1019-25.
Morley JJ. Ann N Y Acad Sci; 1982: 389; 406-18.

Point of Care CRP testing

- Quantitative measurement of CRP from finger-prick blood sample
- result available in < 3 mins
- reproducible & quantitative result within 8-160mg/L range
- In EU, machine costs ~ $2200 USD each test subsequently ~ $3-5 USD

http://www.nordia.ie/products/Health/Point_of_care_tests/QuikRead/QuikRead_CRP/ (Assessed 27Oct2012)
www.oriondiagnostica.com

Clinical Question

P	Adults presenting to MD offices with symptoms (fever, cough) of LRTI
I	Point of Care C- Reactive Protein testing
C	CXR or Standard of care
O	Primary: 1) Reduce Mortality 2) Prevent complications or hospitalizations Secondary 3) Diagnose CAP 4) Guide appropriate antibiotic prescribing

Search Strategy

Databases	Medline, Google Scholar, PubMed, EMBASE, Google
Search Terms	CRP, respiratory infection, primary care, diagnosis
Limits	English, Adults
Results	3 SR 4 RCT 15 PC

C- reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies

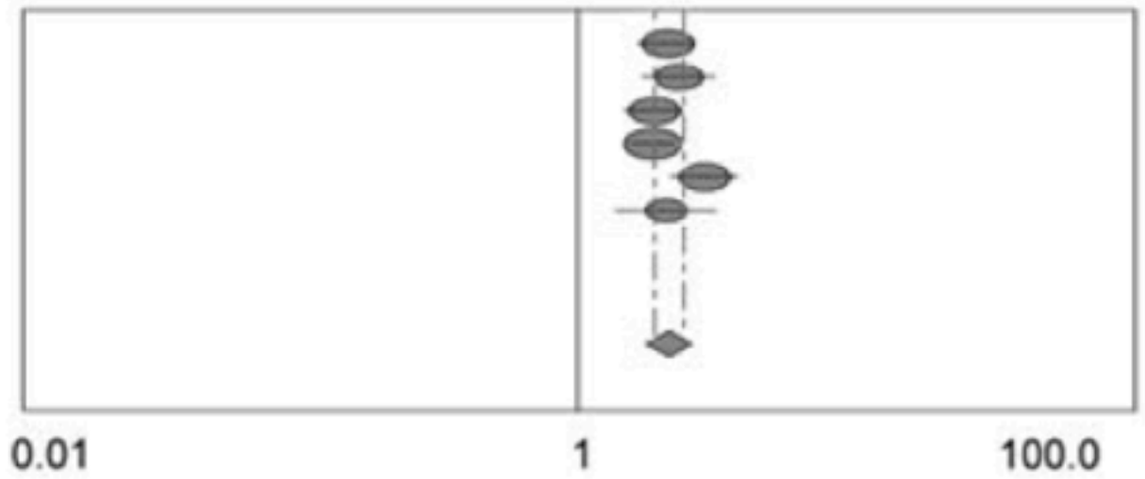
Gavin Falk and Tom Fahey Family Practice 2009; 26:10-21

Falk et al. 2009

Design	Search PUBMED 1966-Sept 2008; EMBASE Jan 1980-Sept 2008 8 studies (all observational studies)
P	n=2194, community, primary care or ambulatory care pt w/ symptoms suggestive of acute respiratory infection Excluded - non-english studies
I	C- reactive protein
C	CXR
O	Diagnostic accuracy of CRP in diagnosing CAP using 3 different cut points of CRP (≤20, ≤50, >100 mg/L)

Results

(1) Cut point ≤ 20mg/L



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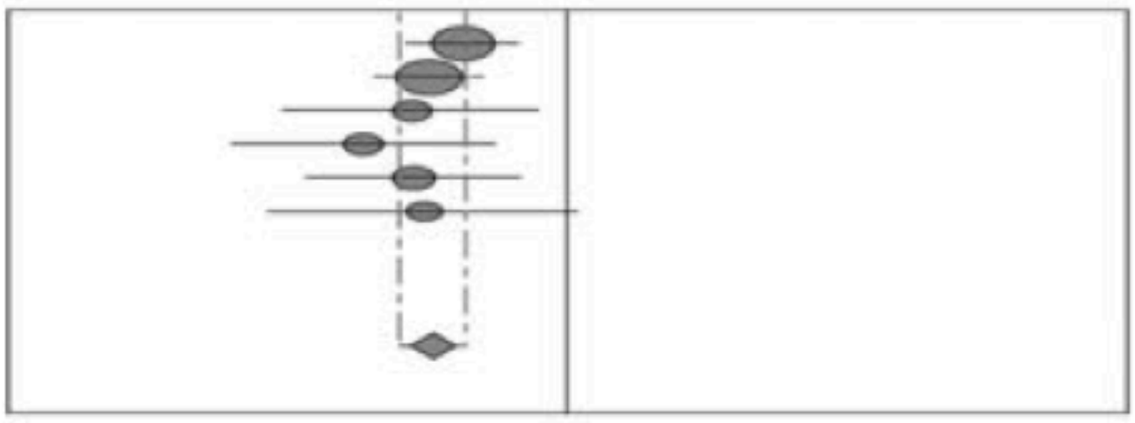
Random Effects Model
Pooled Positive LR = 2.10 (1.84 to 2.40)
Cochran-Q = 7.97; df = 5 (p = 0.1581)
Inconsistency (I-square) = 37.2 %
Tau-squared = 0.0100



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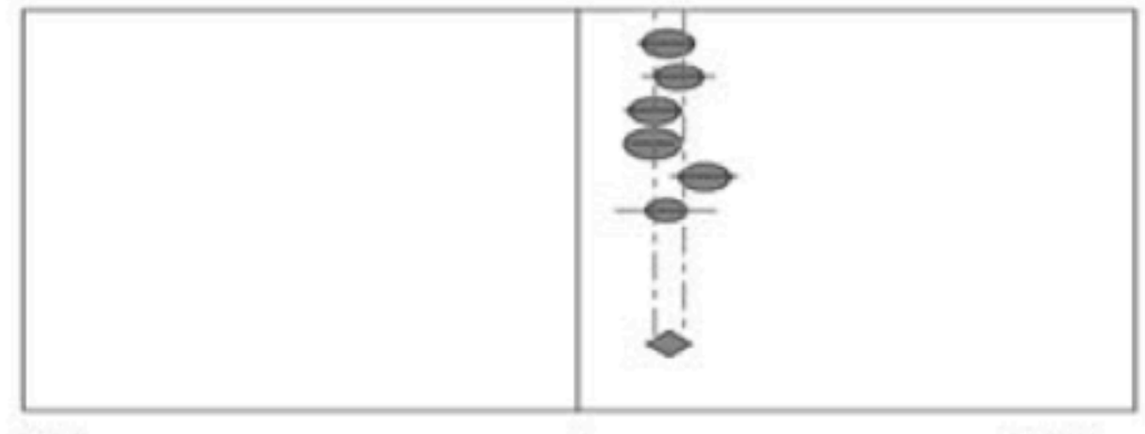

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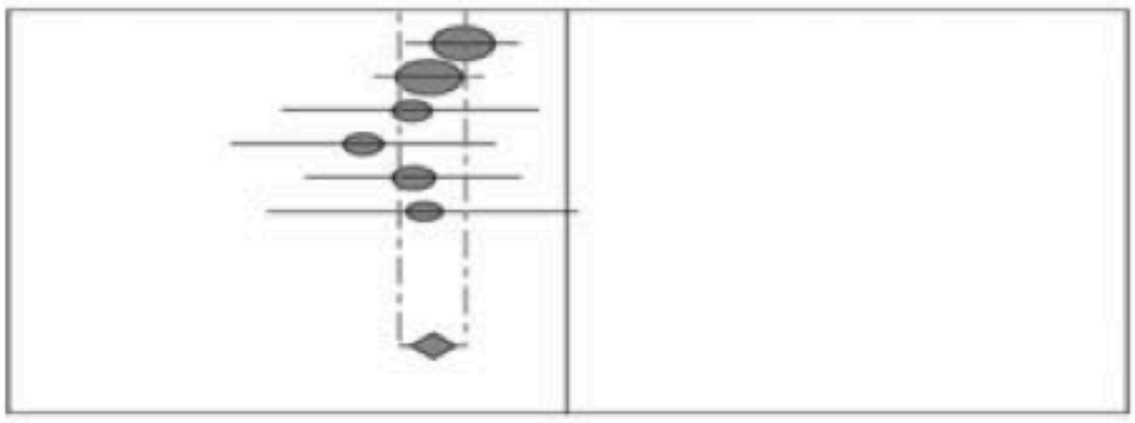

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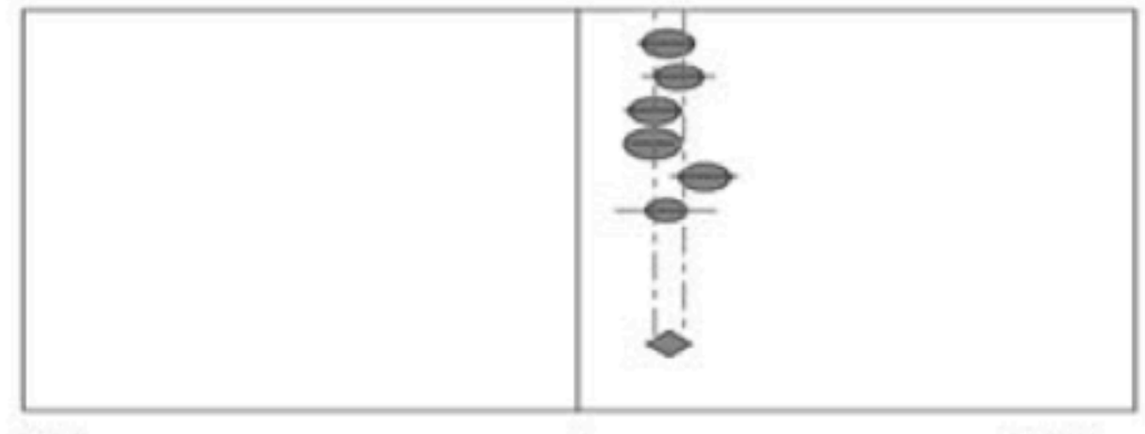

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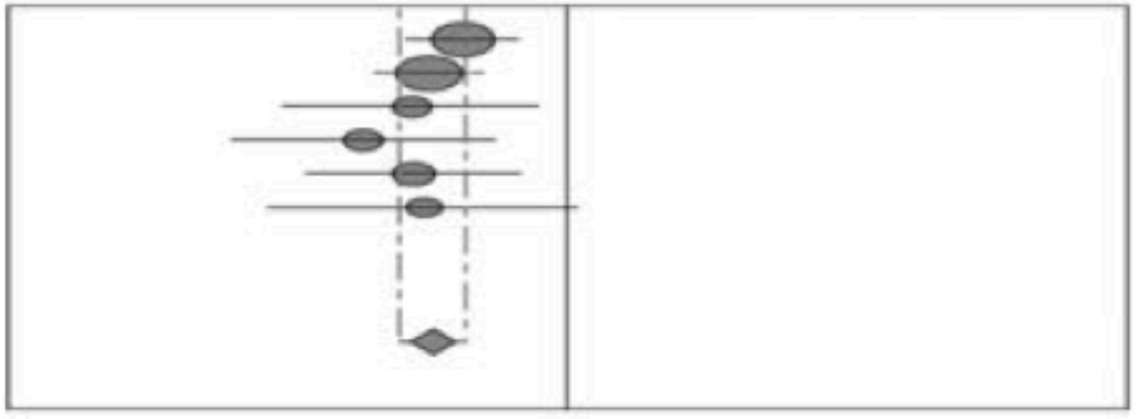

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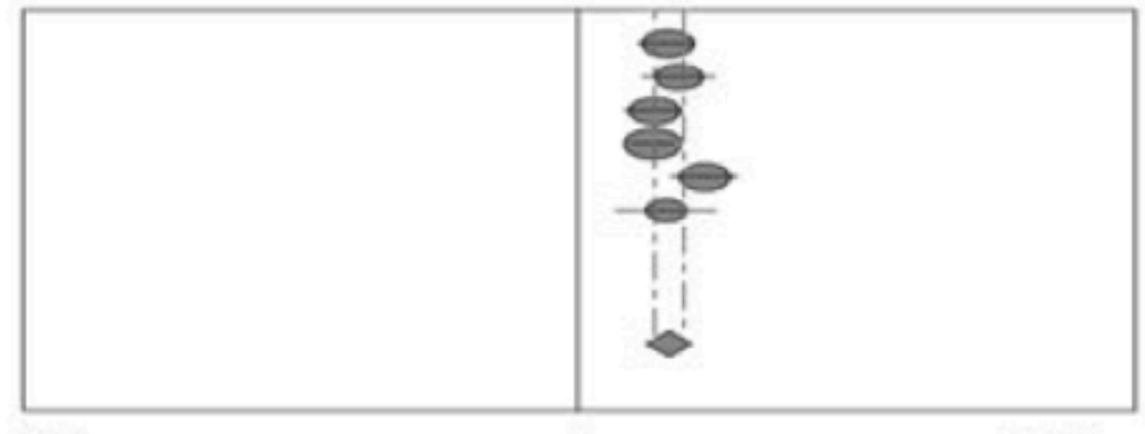

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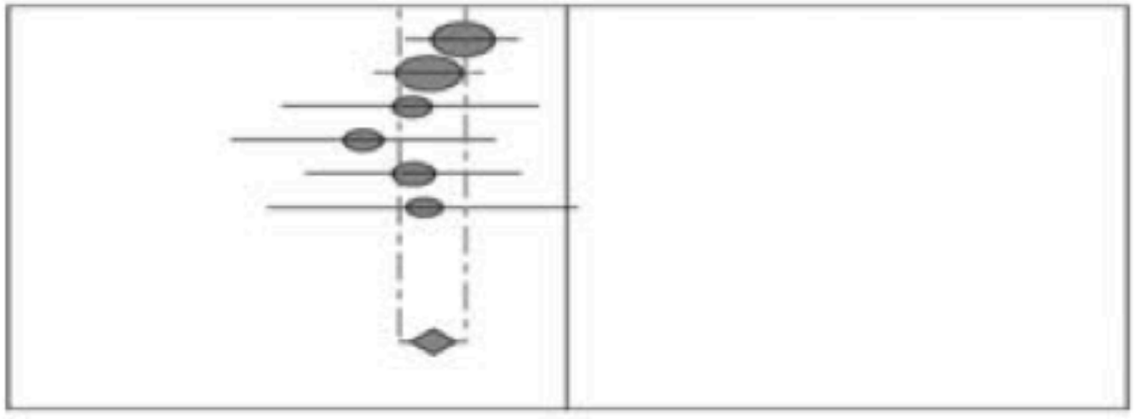

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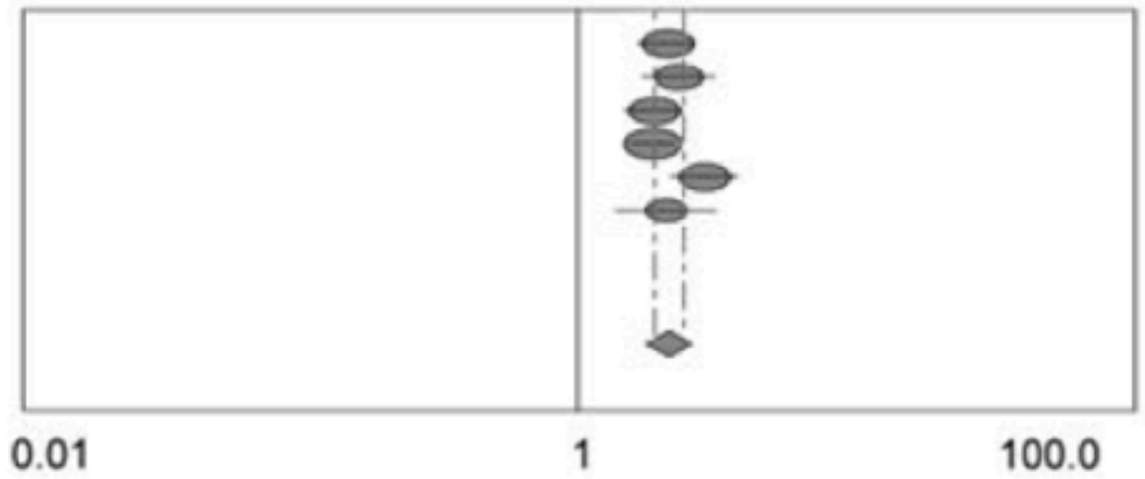

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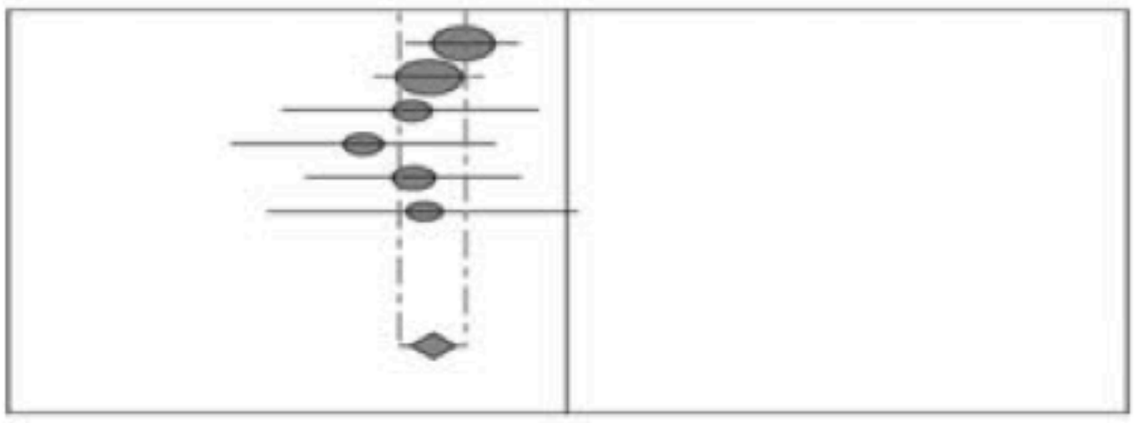

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Thinking it through...

# of findings	Predicted probability
2	3%
3	10%
4	25%
5	50%

Thinking it through...

# of findings	Predicted probability	+ LR	- LR
2	3%	6%	1%
3	10%	19%	4%
4	25%	41%	10%
5	50%	68%	25%

Authors' conclusion

"CRP ≤ 20mg/L may be valuable for ruling out CAP when pretest probability is ≥ 10%"

Limitations

- high CAP prevalence in studies, median 16% (5-89%)
- although compared to CXR, definitions of it varied in studies
- did not explain how the 3 different cut points were derived
- excluded non-English studies

Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review

Madelon F Engel, F P Paling, A I M Hoepelman, V van der Meer and JJ Oosterheert
Family Practice 2012; 29:383-393

Engel et al. 2012

Design	Searched from January 1975- July 2010, published literature only 9 studies (4 RCT, 5 PC), excluding studies with QUADAS validity scores <50%
P	≥ 16 years old consult GP for probable LRTI <u>Exclude:</u> immunocompromised, confirmed PNA/bronchitis, hospital population
I	CRP measurement
C	Standard of care
O	1. POC CRP testing to reduce antibiotic prescription 2. Predicting etiology (bacterial vs viral) 3. Does CRP level in LRTI pt have prognostic value? 4. Can CRP predict radiographically confirmed pneumonia?

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Results - abx prescription Δ

Author	Study	Outcome	RR (95% CI)	ARR
Cals (2009)	Cluster RCT (n=431)	@ index consult % abx	0.6* (0.5-0.7)*	22.1%**
		@ 28d % abx	N/A	13.4%**
Cals (2010)	RCT (n=258)	@ 28d % abx total	0.8* (0.6-0.9)*	12.4%**
		@ 28d % abx prescription in 0-20 mg/L CRP group	0.53 (0.3-0.85)	23.3%**
Diederichsen (2000)	RCT (n=812)	@ index consult % abx	0.8* (0.5-1.2)*	3%**
Melbye (1995)	RCT (n=239)	@ index consult % abx	1.0 (0.8-1.2)*	N/A

* value calculated by article authors **calculated by WL

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Clinical recovery

Author	Mortality	Morbidity	Patient preference
Cals (2009)	no death or hospitalization	**NSS** (7 d recovery) **NSS** (avg days to full recovery)	**NSS** (pt satisfaction) **NSS** (future consultation intention)
Cals (2010)	no death or hospitalization	**NSS** (avg days to full recovery) **NSS** (median daily symptom)	**13.1% abs*** ↑ in satisfaction w CRP **13.8% abs*** ↑ would use same GP again w CRP
Diederichsen (2000)	N/A	**4% SS* abs** ↑ 7d morbidity in CRP	N/A

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Results - Diagnostic Accuracy

Author	Study	CRP cut pt (mg/L)	Sn	Sp	+ LR**	- LR**
Holm 2007	PC n=682	≥ 20	0.73	0.65	2.09	0.42
Hopstaken 2003	PC n=243	≥ 10	0.97*	0.31*	1.41	0.10*
		≥ 20	0.91*	0.51*	1.98	0.18
		≥ 50	0.88*	0.75*	3.52	0.16
Macfarlane 2001	PC n=289	≥ 50	0.66*	0.89*	6.00	0.38*

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Authors' conclusions

- Antibiotic prescription
  - "implementation leads to minimal reduction in abx prescription at expense of ↑ costs"
- Diagnostic value
  - when combined with clinical presentation, may have added value

Limitations

- study enrollment dependent on GP opinion - selection bias
- different methodologies
- all studies from western Europe population
- limited search and contradictory evidence

A decision aid to rule out pneumonia and reduce unnecessary prescriptions of antibiotics in primary care patients with cough and fever

Johann Steurer, Ulrike Held, Anne Spaar, Birke Bausch, Marco Zoller, Roger Hunziker, Lucas M Bachmann

BMC Medicine 2011; 9: 56-63.

Steurer et al. 2011

Design	P, Cohort, Switzerland, Nov 2006 Dec 2009
P	n=621 patient from 86 physicians, 47 yo, 50% male <u>Incl:</u> ≥ 18yo with new/worsened cough (≥ 24hrs) & subjective/ measured fever, consecutive <u>Excl:</u> chronic lung disease, developed cough/fever during hospital stay, HIV+, steroids w/in last month, active chemotherapy, hx of organ transplant, pregnancy, mental disorder/incapable of reading study leaflet and /or giving consent
I	25-item questionnaire, CRP and CXR for all patients
O	Develop a tool to rule out PNA in primary care where med hx and physical exam are inconclusive for diagnosis

Variate	All patients (n=621)	without PNA (n=494)	with PNA (n=127)
Age	46.7 (SD16.3)	46.6 (16.1)	46.8 (SD 17.2)
Gender (male)	308 (50%)	247 (50%)	61 (48%)
New onset/worsened cough duration (days)	7.0 (SD 9.6)	6.7 (SD 6.4)	8.4 (SD 17)
Daily fever	350 (56%)	266 (54%)	84 (66%)
Dyspnea	223 (36%)	165 (33%)	58 (46%)
Respiratory Rate (# /min)	17 (SD 6)	16.6 (SD 5.7)	18.6 (SD 5.9)
Pleural Friction rub	18 (3%)	7 (1%)	11 (9%)
Abnormal CXR in single locus	140 (23%)	84 (17%)	56 (44%)
CRP 0 to 10	108 (17%)	108 (22%)	0 (0%)
CRP 11 to 50	265 (43%)	240 (49%)	25 (20%)
CRP 51 to 100	106 (17%)	78 (16%)	28 (22%)
CRP > 100	134 (22%)	61 (12%)	73 (57%)

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Steurer et al.

- using Classification and Regression Trees to determine easy to use rule out criterion
  - selected 6 variables
    - Chronic cough
    - Daily fever
    - Dyspnea
    - Respiratory rate
    - Pleural friction rub
    - C-Reactive Protein

Steurer et al.

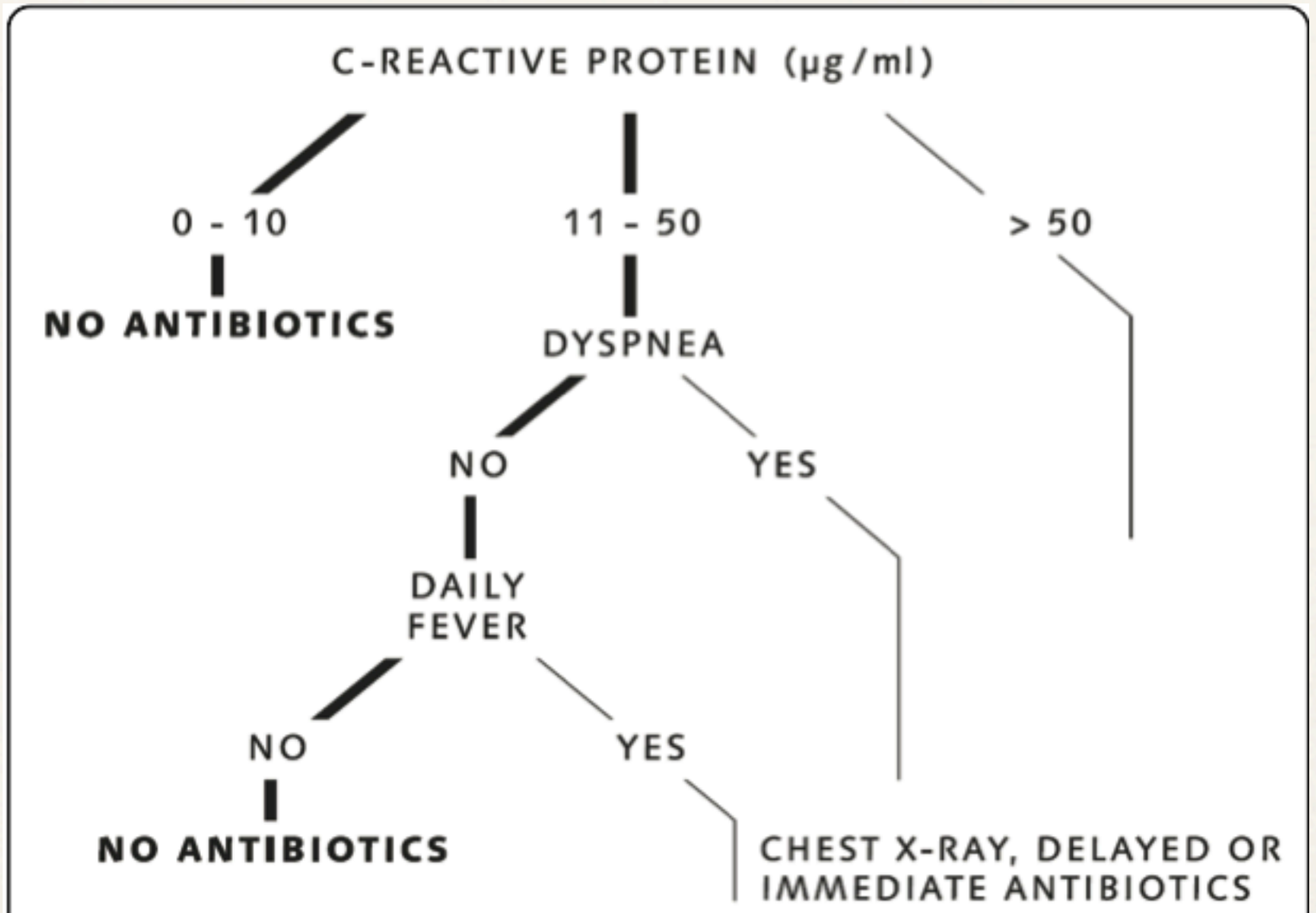

Figure 1 Decision tree to rule out pneumonia. C-reactive protein measured in µg/ml.

Steurer et al.

- Using developed tool - assessed abx prescribing in study cohort
  - “tested whether difference of two sample proportions of antibiotic prescription with and without tool was different from zero”
    - overall potential abx ↓ 9.1 % (95% CI: 6.4 -11.8; $p < 0.001$)

Authors' conclusions

"After taking history and physical

and in doubt about pneumonia and indication of abx…

measuring CRP and using decision rule may…

help identify group of patient where PNA is very unlikely

and CXR and abx are unnecessary"

Limitations

- high prevalence of pneumonia in cohort
- requires validation in a new set of patients for external validation
- no mention of # of patients turned away with specified inclusion criteria

Summary

- Adult with symptoms of LRTI, if after Hx and Physical, still uncertain...
  - Give abx
  - CRP - @ a cost of $3-5USD possible ARR 10-13%
  - Delayed abx -- in LRTI no Δ in abx use - delayed abx by 3 days
  - Communicate -- 25% ARR of abx use @ 28d compared to standard
  - CXR or Pro-calcitonin -- not available as POCT

Francis NA et al. Br J Gen Pract 2012 Sept; 62(602):e639-46
Cals et al. BMJ 2009; 338:b1374.

My Recommendation

- CRP instead of CXR or standard of care..
  - Mortality?
  - Morbidity? Hospitalization, Side Effects?
  - Diagnostic accuracy?
  - Guide antibiotic prescribing?

    Remembering that this will COST money ~ $3-5 each test

    Not recommend using CRP to replace CXR or standard of care

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Questions are guaranteed in life; Answers aren't.

Applicability

- 9 primary care in 9 cities included 80 clinicians and 121 patients interviewed

	Advantages	Disadvantages
Clinician	-manage pt expectations (persuasion/education) - Desirable to pt (pt satisfaction/reassure by technology) - Clinican decision making (help with process/confidence) - improved management/tx (targeted/reduce abx/↓ reconsult)	- Test performance (sensitivity/specificity/reliability) - "value" of result (cut points/interpretation/confounder) - Clinician factors (challenges' own reasoning/treating test not pt/ oversimplify) - Finances and Time (cost of test/↑ workload/ equipment) - Patient factors (stigmas to demand test/ pt may not want it)

Wood F et al. Family Practice 2011; 28:661-9.

Applicability

	Advantages	Disadvantages
Patient	-useful tool (better dx/tx/faster) - Help establish if abx needed (match abx to illness/avoid unnecessary prescribing) - Trust in test & doctor (trust test is necessary/results) - Saving money & time (save rx costs/ fewer reconsults)	- anxiety (waiting for result/needle phobia) - Feasibility (time/costs) - Safety (of information/ hygiene) - Clinician factors (interpretation/treat test not patient) - Commercialism (unnecessary tests)

Wood F et al. Family Practice 2011; 28:661-9.