Antimicrobial Stewarship Tools: Computerized prescribing, biomarkers

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Skopje, Macedonia

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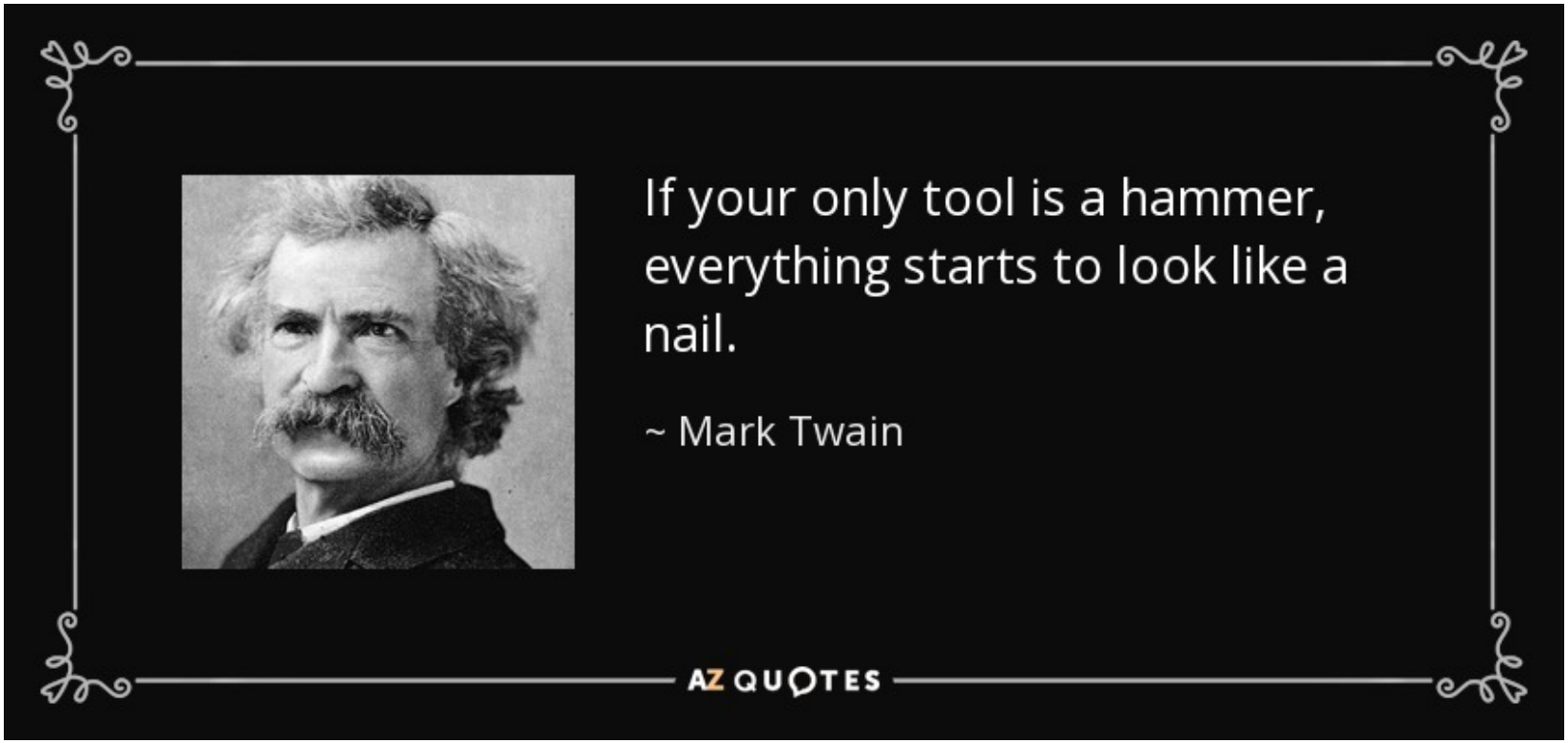
Tools


If your only tool is a hammer, everything starts to look like a nail.
~ Mark Twain
AZ QUOTES

The problem : When to start / When to stop

- Diagnosis are difficult & Mistakes are costly !
- Bacterial vs. viral ; Cancer ; Embolism ...
- Cure is very difficult to assess :
  - A patient may be cure if no relapse occurs in absence of antibiotics after a certain duration (may be years for bone infections !)
- In other words, we don't know much ...
- $\Rightarrow$ Need of surrogates for diagnosis of infection and cure :
  - Computer surrogates$\leftrightarrow$ Computerized decision support system
  - Biological surrogates$\leftrightarrow$ Biomarkers

Section 1

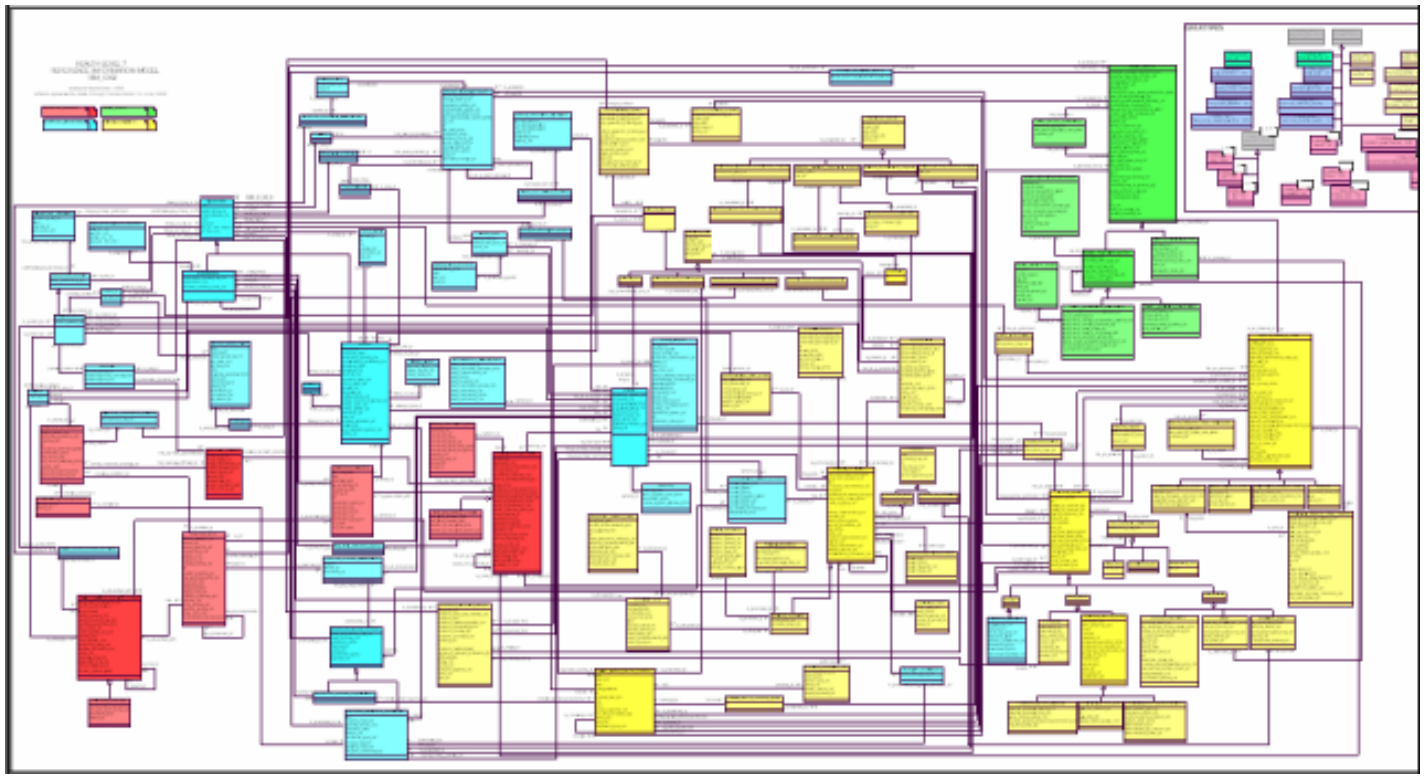
Computerized decision support system

What is it

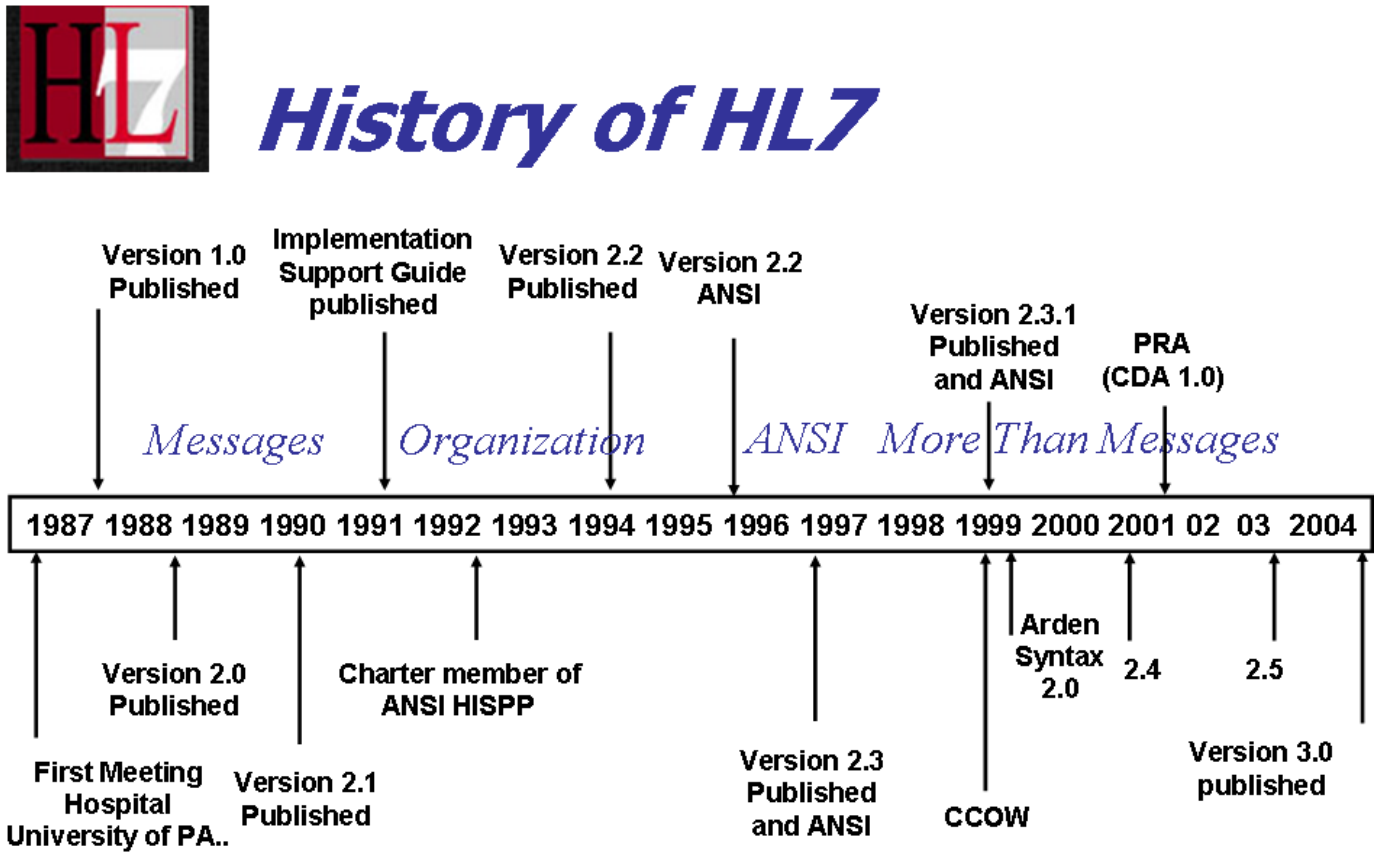
- A program that generates diagnostic and therapeutic recommendations from patient specific information that was input about the suspected diagnosis, such as the presence or absence of specific signs and symptoms
- "Medical artificial intelligence"
- A system that links all the information available in various databases (clinical files, laboratory results, pharmacist...)

Problem

- Many different systems operating in parallel in hospital
- Not standardized
- Not communicating



Toward a common language for interoperability : HL7



Not that recent

- Electronically identified interventions [1]
- LDS Hospital in Salt Lake City, Utah
- 545 patients in a 12-beds ICU over 1 year
- Outcomes compared to 2 previous years
- $\searrow$ in inappropriate ATB doses, ATB related drug events and total cost of care ...

1. Evans RS. NEJM 1998

Effective even if basic

IHC ANTIBIOTIC ASSISTANT & ORDER PROGRAM

00000000 Doe, John Q. E615 77yr M Dx:PANCREATITIS
Max 24hr WBC=26.3 ↑ (21.1) **Admit:06/21/96.17.50** Max 24hr Temp=38.3 ↑ (37.8)
RENAL FUNCTION: Impaired, CrCl= 28, Max 24hr Cr=2.0 ↓ (2.2) IBW: 77kg
Patient's Diff shows a left shift, Max 24hr Bands = 20 ↑ (8)
ANTIBIOTIC ALLERGIES: Ofloxacin
CURRENT ANTIBIOTICS:
1. 07/14/96.17:23 AMPHOTERICIN B, VIAL 45 Q 24hrs
2. 07/18/96.12:19 VANCOMYCIN (VANCOCIN), VIAL 1000 Q 72hrs
Total amphotericin given = 181mg

IDENTIFIED PATHOGENS	SITE	COLLECTED
Enterococcus	T-Tube	07/17/96.10:57
Staphylococcus aureus	Blood	07/17/96.10:28
Candida albicans	Abdomen	07/14/96.06:23

ABX SUGGESTION	DOSAGE	ROUTE	INTERVAL	
Vancomycin	*1000mg	IV	*q72h	(infuse over 1hr)
Amphotericin B	45mg	IV	q24h	(infuse over 2-4hr)

Suggested Antibiotic Duration: 28 days
*** Adjusted based on patient's renal function**
<1>Micro, <2>OrganismSuscept, <3>Drug Info, <4>ExplainLogic, <5>Empiric Abx
<6>Abx Hx, <7>ID Rnds, <8>Lab/Abx Levels, <9>Xray, <+ or F12>Change Patient
<Esc>EXIT, <F1>Help, <0>User Input, <.>OutpatientModels
ORDERS: <*>Suggested Abx, <Enter>Abx List, </>D/C Abx, <->Modify Abx

- 14 minutes vs. 3.5 seconds [2]
- Decreased cost [3]
- Appropriate antibiotic choice [4]
- Fewer antibiotic doses [5]
- Shorter LOS [6]
- Decreased adverse events [7]
- Decreased mortality [8]

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2. Evans RS. NEJM 1998
3. Evans RS. *NEJM* 1998, Barenfanger J *J Clin Microbiol* 2001, Jozefiak ET *Am J Health Syst Pharm* 1995, McGregor JC *J Am Med Inform Assoc* 2006, Paul M *JAC* 2006, Pestotnik SL *Ann Intern Med* 1996, Schentag JJ *Diagn Microbiol Infec Dis* 1993
4. Paul M *JAC* 2006, Samore MH JAMA 2005, Thursky KA Int J Qual Health care 2006
5. Evans RS. NEJM 1998, Pestotnik SL *Ann Intern Med* 1996
6. Evans RS. NEJM 1998, Paul M *JAC* 2006
7. Evans RS. NEJM 1998, Pestotnik SL *Ann Intern Med* 1996
8. Pestotnik SL *Ann Intern Med* 1996

Commercial systems with antimicrobial stewardship options

Product Name	Company (also known as)	City, State	Infection Prevention Capabilities
360 Care Insights	Truven	Ann Arbor, MI	Yes
ABX Alert	ICNet	Warrensville, IN	Yes
Antibiotic Assistant	Hospira (Theradoc)	Salt Lake City, UT	Yes
Dynamic Monitoring Suite	Vigilanz	Minneapolis, MN	Yes
Epiquest Live	Epiquest Live	Boca Raton,FL	Yes
Medici	Asolva Inc	Pasadena, CA	Yes
Patient Event Advisor	Care Fusion (Medmined)	Birmingham, AL	Yes
QC Pathfinder	Vecna	Cambridge, MA	Yes
Safety Advisor	Premier	Charlotte, NC	Yes
Sentri 7	Wolters Kluwer (Pharmacy One Source)	Bellevue, WA	Yes

Common alerts for infectious diseases

- Bug-Drug mismatch
- Positive culture but no antibiotic
- Antibiotic but no positive culture
- IV to PO
- Duration of therapy alerts
- Duplicate antibiotic therapy
- Dose adjustments to renal/liver function
- Target specific antibiotics (carbapenem, costly ATB ...)
- Target organism (MDRO)

Practical examples

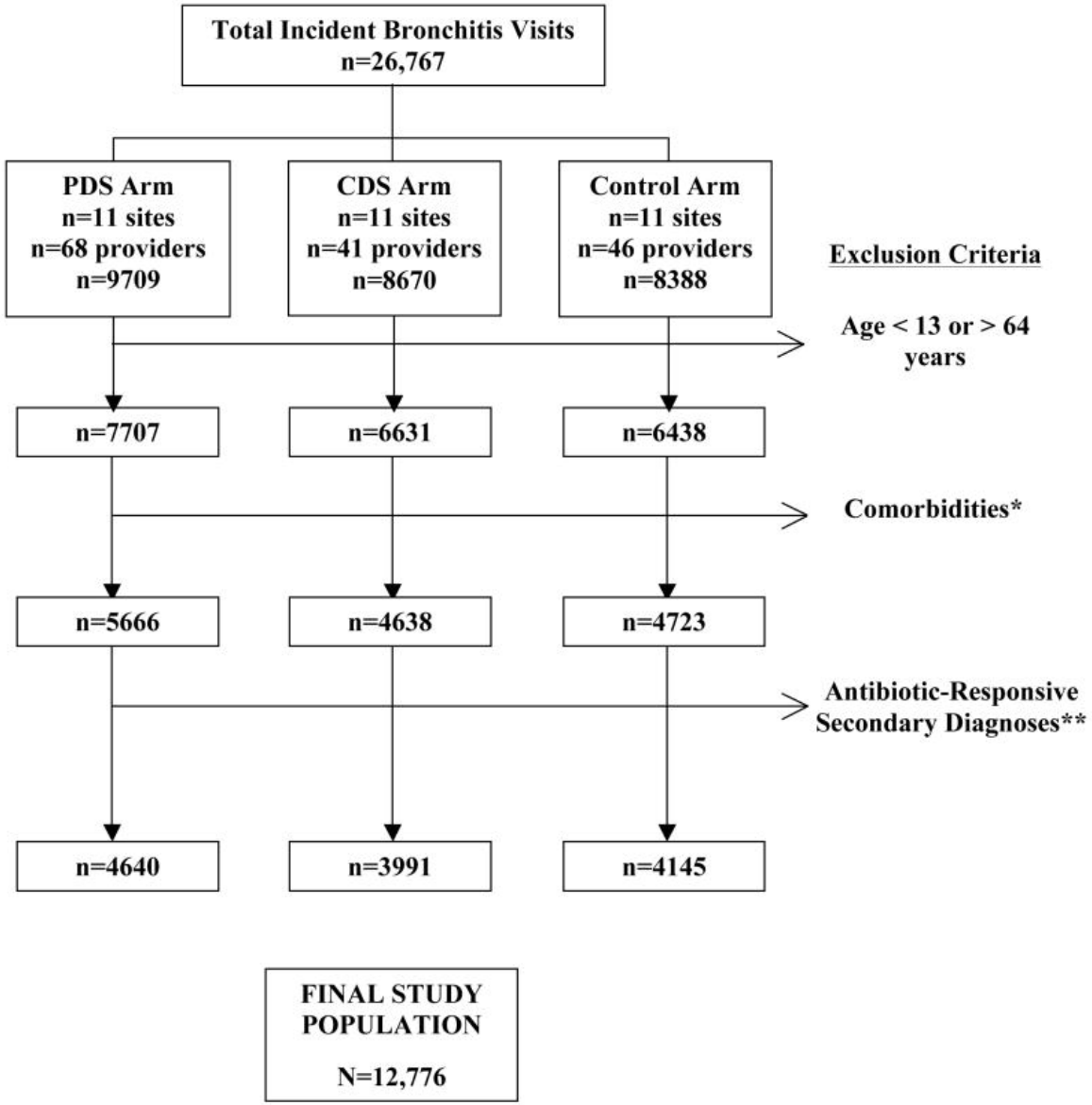
- Patients under Vancomycin >72h without positive culture
- Patients receiving Piperacillin/Tazobactam and Metronidazole
- Patients eligible for conversion from IV to PO linezolid
- Levofloxacin at full dose with renal insufficiency
- Positive blood culture for C. albicans and no antifungal treatment

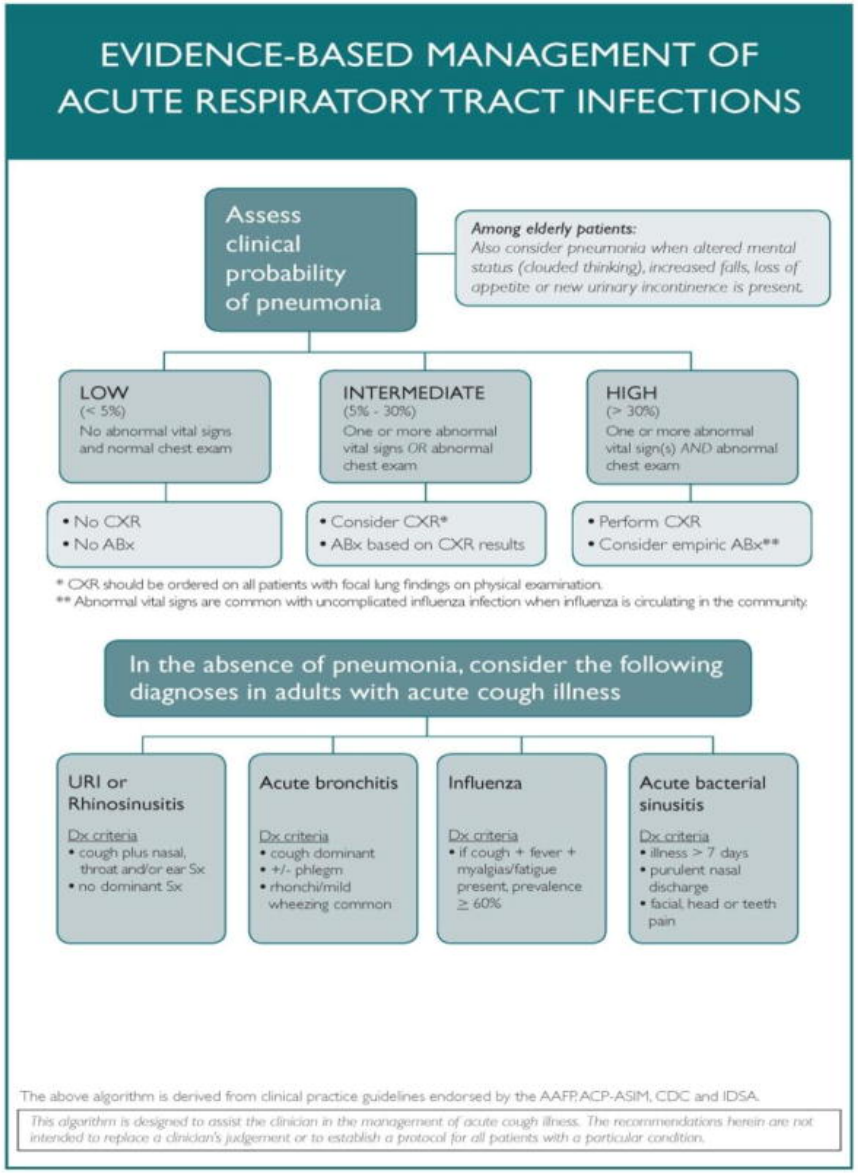
But it is also beneficial for non ID-related problems (anticoagulation...)

Outpatient example

- Three arm cluster randomized trial[9]
- 33 primary care practices in Pennsylvania, USA
- Acute uncomplicated bronchitis
- Control vs. Print Based vs. Decision support

9. Gonzales R JAMA Int Med 2013


Total Incident Bronchitis Visits
n=26,767
PDS Arm
n=11 sites
n=68 providers
n=9709
CDS Arm
n=11 sites
n=41 providers
n=8670
Control Arm
n=11 sites
n=46 providers
n=8388
Exclusion Criteria
Age < 13 or > 64 years
n=7707
n=6631
n=6438
Comorbidities*
n=5666
n=4638
n=4723
Antibiotic-Responsive Secondary Diagnoses**
n=4640
n=3991
n=4145
FINAL STUDY POPULATION
N=12,776



EVIDENCE-BASED MANAGEMENT OF ACUTE RESPIRATORY TRACT INFECTIONS

Assess clinical probability of pneumonia

Among elderly patients: *Also consider pneumonia when altered mental status (clouded thinking), increased falls, loss of appetite or new urinary incontinence is present.*

LOW (< 5%)
No abnormal vital signs and normal chest exam
- No CXR
- No ABx

INTERMEDIATE (5% - 30%)
One or more abnormal vital signs *OR* abnormal chest exam
- Consider CXR*
- ABx based on CXR results

HIGH (> 30%)
One or more abnormal vital sign(s) *AND* abnormal chest exam
- Perform CXR
- Consider empiric ABx**

* CXR should be ordered on all patients with focal lung findings on physical examination.
** Abnormal vital signs are common with uncomplicated influenza infection when influenza is circulating in the community.

In the absence of pneumonia, consider the following diagnoses in adults with acute cough illness

URI or Rhinosinusitis
Dx criteria
- cough plus nasal, throat and/or ear Sx
- no dominant Sx

Acute bronchitis
Dx criteria
- cough dominant
- +/- phlegm
- rhonchi/mild wheezing common

Influenza
Dx criteria
- if cough + fever + myalgias/fatigue present, prevalence ≥ 60%

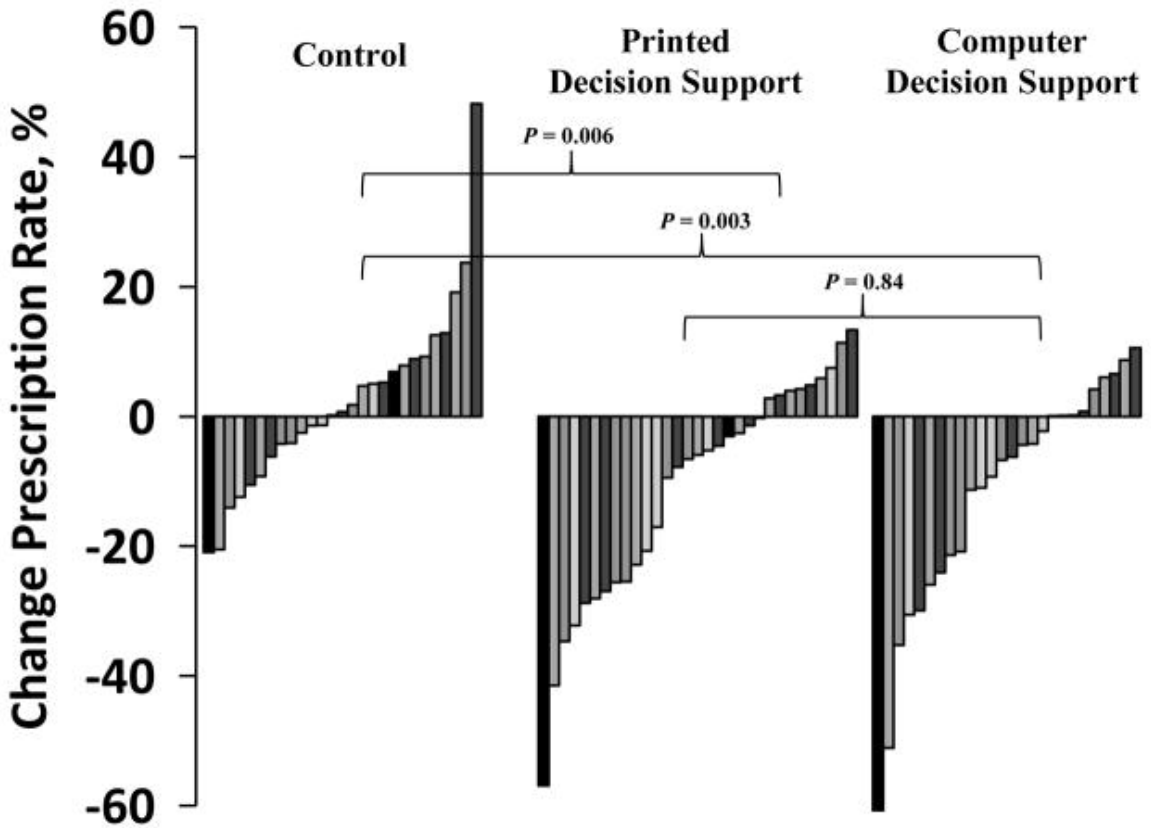
Acute bacterial sinusitis
Dx criteria
- illness > 7 days
- purulent nasal discharge
- facial, head or teeth pain

The above algorithm is derived from clinical practice guidelines endorsed by the AAFP, ACP-ASIM, CDC and IDSA.

This algorithm is designed to assist the clinician in the management of acute cough illness. The recommendations herein are not intended to replace a clinician's judgement or to establish a protocol for all patients with a particular condition.

Results on antibiotic prescribing

- Control arm : $\nearrow$ (72.5%$\rightarrow$74.3%)
- Print-based arm : $\searrow$ (80%$\rightarrow$68.3%)
- Computerized decision support arm : $\searrow\searrow$ (74.0%$\rightarrow$60.7%)


Control
Printed Decision Support
Computer Decision Support
P = 0.006
P = 0.003
P = 0.84
Change Prescription Rate, %
60
40
20
0
-20
-40
-60

Additional benefits with CDSS

CDSS similarly efficient to printed-based support, but

- Reports can be edited easily
- A general tool that can be easily adapted for many situation, according to new guidelines, new intervention ...
- Adherence can be measured (useful to justify your AMS Team)

Section 2

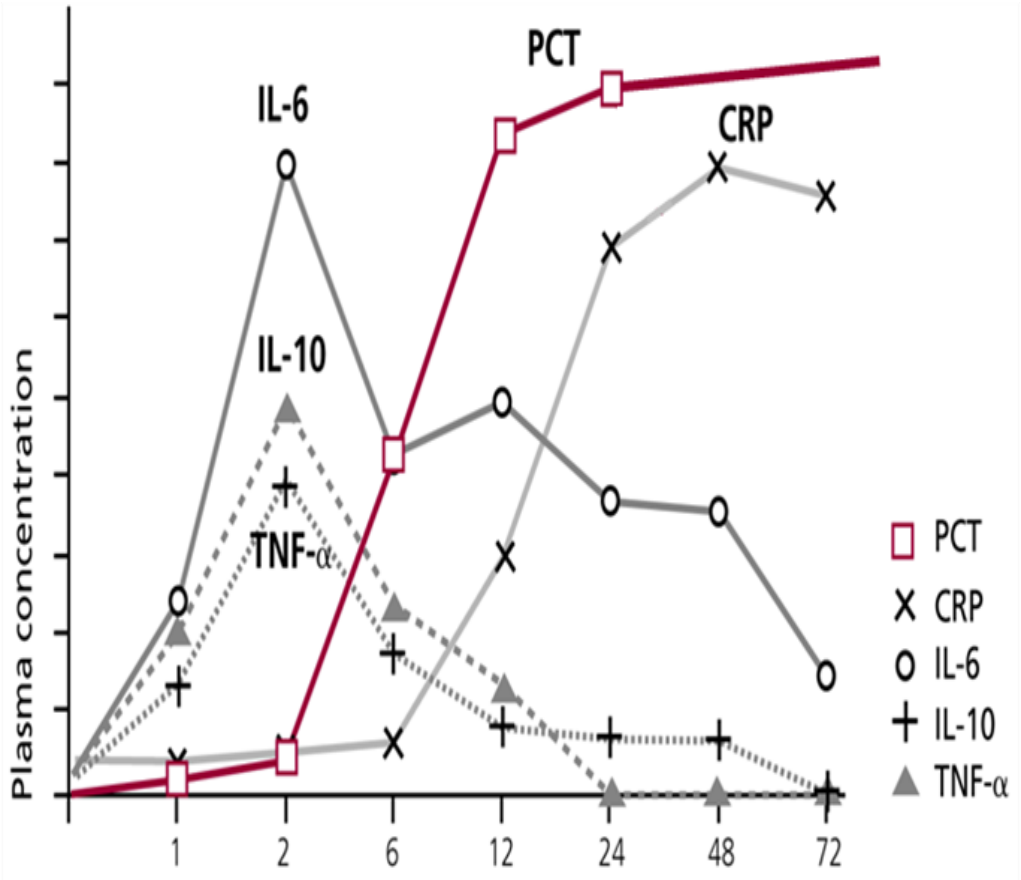
Biomarkers

Biomarkers

- Many potential biomarkers
  - White blood cells
  - Eosinophils
  - Fibrinogen
  - ESR
  - CRP
  - **Procalcitonin**
  - IL-6
  - S-TREM-1
  - Endothelial biomarkers
  - ...
- But Procalcitonin-guided strategies have been proven successful in clinical trials

Procalcitonin kinetic

Peak at 6-12h (Half-life≈24h) [10]



10. Meisner, J.Lab. Med., 1999

Procalcitonin can be produced anywhere

Low level when infection is localized, high level when infection extends [11]

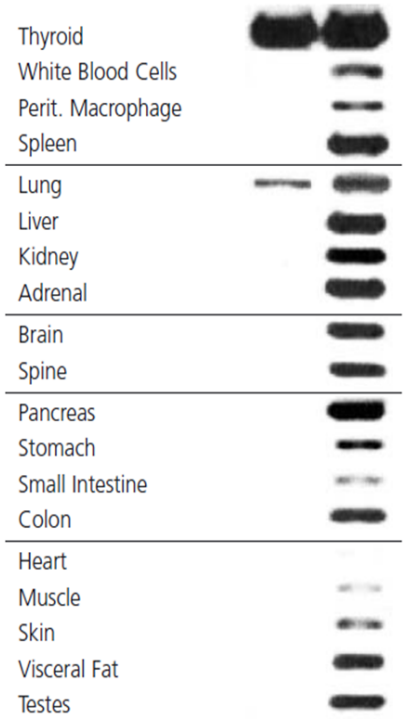


Figure: PCT in healthy subjects vs. bacterial infection

11. Müller JCEM 2001

What for ?

- Reduction of unnecessary antibiotic
  - Primary or secondarily through reduction of treatment duration
- Five validated situations [12] :
  - Acute pancreatitis
  - Lower respiratory tract infection (LRTI)
  - Meningitis
  - Sepsis in the ICU
  - Sepsis in neonates (materno-foetal infection)

12. Quenot et al. Annals of Intensive Care 2013

ICU algorithm

Use of procalcitonin on admission to the ICU				
PCT range	**PCT <0.25 µg/l**	**PCT <0.5 µg/l**	**PCT ≥0.5 µg/l**	**PCT >1.0 µg/l**
Recommendation on antibiotics	Empirical antibiotics strongly recommended in all patients with suspected infection			
Comments	Low PCT makes bacterial sepsis unlikely; consider alternative diagnosis; clinical reassessment and re-measurement of PCT every 1-2 days			
Use of procalcitonin during follow up in the ICU (every 1-2 days)				
PCT range	**PCT <0.25 µg/l or drop by >90%**	**PCT <0.5 µg/l or drop by >80%**	**PCT ≥0.5 µg/l**	**PCT >1.0 µg/l**
Recommendation on antibiotics	Stop of antibiotics strongly recommended if patients show clinical recovery strongly encouraged	Stop of antibiotics recommended if patients show clinical recovery strongly encouraged	Stop of antibiotics discouraged	Stop of antibiotics strongly discouraged
Over-ruling the algorithm	Consider continuation of antibiotics if patients are clinically not stable			
Comments			Consider treatment failure if PCT does not decrease adequately	

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13. Schuetz, Curr Opin Crit Care 2012

PROHOSP (When to start)

Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections : the ProHOSP randomized controlled trial [14]

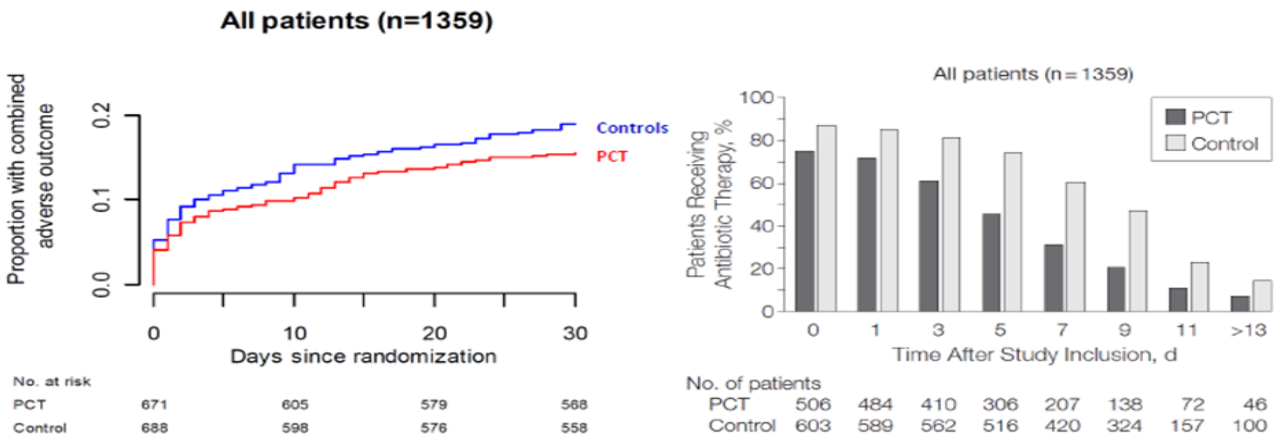


Table 2. Rates of Combined Adverse Outcomes and Mortality by Randomization Group

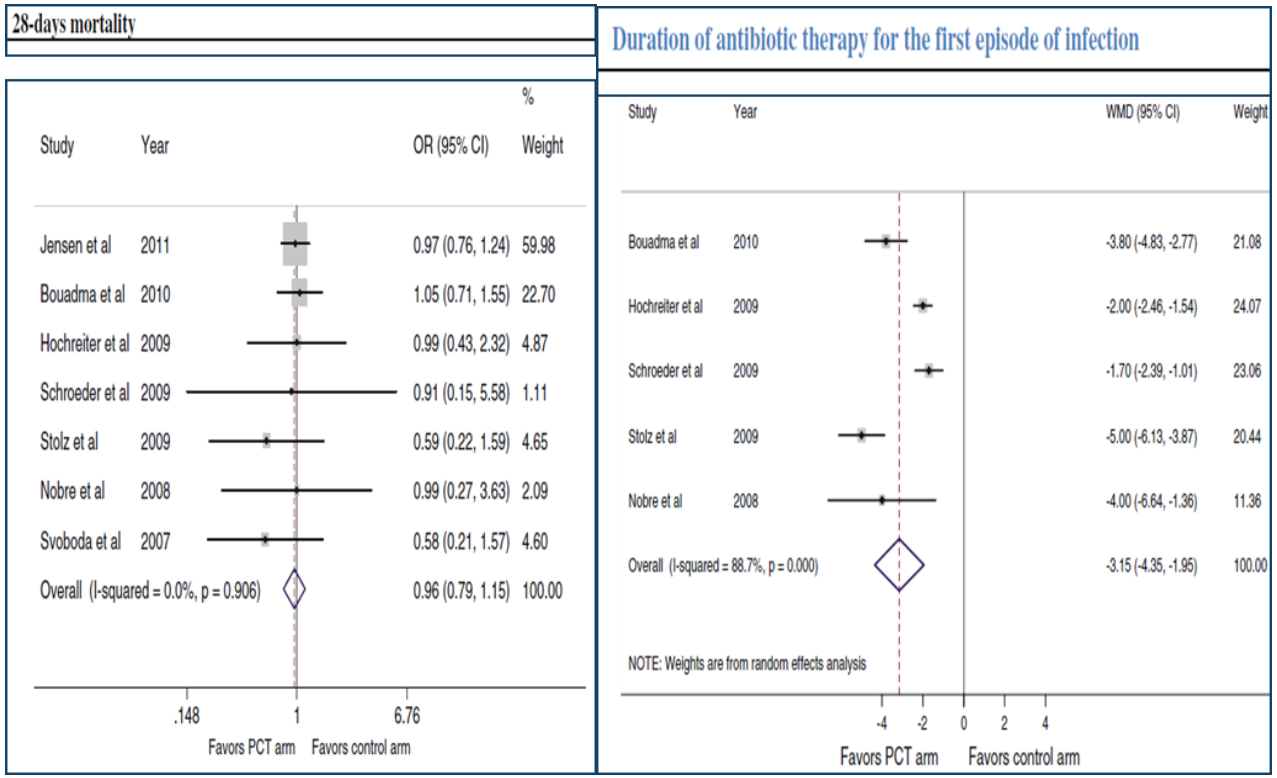
	No. (%) of Patients		
	PCT Group	Control Group	Risk Difference, % (95% CI)
All patients (intention-to-treat)[a]	(n = 671)	(n = 688)	
Overall adverse outcome	103 (15.4)	130 (18.9)	−3.5 (−7.6 to 0.4)
Death	34 (5.1)	33 (4.8)	0.3 (−2.1 to 2.5)
ICU admission	43 (6.4)	60 (8.7)	−2.3 (−5.2 to 0.4)
Recurrence/rehospitalization	25 (3.7)	45 (6.5)	−2.8 (−5.1 to −0.4)
Disease-specific complication	17 (2.5)	14 (2.0)	0.5 (−1.1 to 2.0)

Schuetz P, *et al.* JAMA. 2009;302:1059-66.

14. P. Schuetz JAMA 2009

Meta-analysis (When to stop)

PCT-based intervention in ICU : No risk and efficient to limit ATB duration in ICU [15]



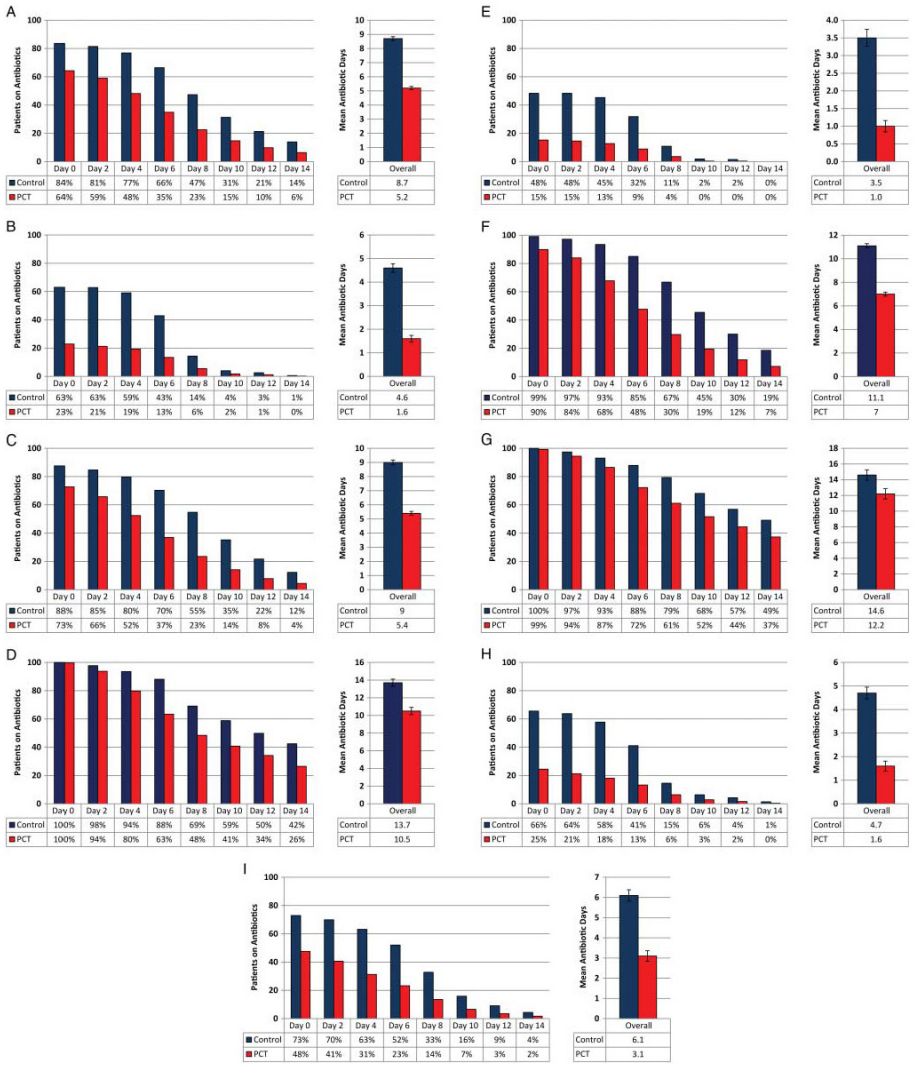
15. Matthaiou, Intens. Care Med. 2012

5 indications but which patients ?

- Procalcitonin to Guide Initiation and Duration of Antibiotic Treatment in Acute Respiratory Infections : An Individual Patient Data Meta-Analysis (4221 patients, 14 trials) [16]
  - Antibiotic use in all patients (n = 4221 ; A)
  - Primary-care patients (n = 1008 ; B)
  - Emergency-department patients (n = 2605 ; C)
  - Intensive-care patients (n = 598 ; D)
  - Patients with upper acute respiratory tract infections (n = 549 ; E)
  - Patients with community-acquired pneumonia (n = 2027 ; F)
  - Patients with ventilator-associated pneumonia (n = 242 ; G)
  - Patients with bronchitis (n = 531 ; H)
  - Patients with chronic obstructive pulmonary disease exacerbation (n = 584 ; I)

16. Schuetz P CID 2012

Less antibiotics with PCT, in every situation



And in real life ?

Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life" : an international, multicenter poststudy survey (ProREAL) [17]

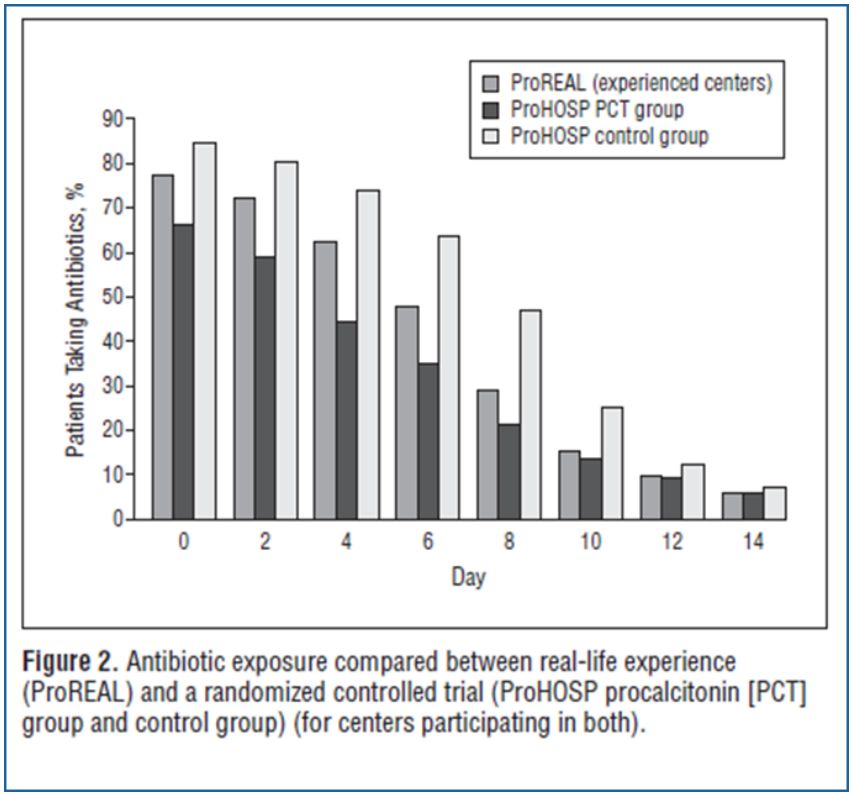


Figure 2. Antibiotic exposure compared between real-life experience (ProREAL) and a randomized controlled trial (ProHOSP procalcitonin [PCT] group and control group) (for centers participating in both).

17. Albrich W. Arch Intern Med. 2012

But how much ?

Medico-economic simulation of PCT impact : Less ATB & and not more expensive [18]

Table 4. Model results. The costs per patient with sepsis at the ICU, split up for each of the aspects of the treatment. Overall costs are shown both per patient and for the estimated yearly number of ICU patients with sepsis in the Netherlands ($n = 13\,000$)[32]. Numbers may not add up due to rounding.

Parameter	Value		Difference
	Without PCT	With PCT	
Hospital stay	€31,214	€28,083	−€3132
General ward	€5666	€4555	−€1112
ICU admission and stay	€25,548	€23,528	−€2020
Treatment	€4672	€4637	−€35
Antibiotics	€1465	€1248	−€218
Mechanical ventilation	€2974	€3157	€182
Dialysis therapy	€232	€232	€0
Laboratory analyses	€2030	€1694	−€336
Blood cultures	€1392	€1063	−€329
PCT	€0	€75	€75
Other laboratory tests	€638	€556	−€82
Total costs per patient	€37,917	€34,414	−€3503
Total costs in the Netherlands ($n = 13\,000$)	€492,916,869	€447,379,610	−€45,537,259

18. Kip, J of Med Eco 2015

Neonatal sepsis

- Rare but severe
  - Proven infection : 1-4/1000 birth
  - Probable infection : 3-4/1000 birth
- Mortality 2-10%, but 10-30% for premature neonates
- Clinical criteria : 80% of suspicion...
- Classical criteria : CRP & gastric liquid microbiological sample : Costly, invasive& and not perfect

Umbilical cord blood Procalcitonin

	All newborns n=2154		Preterm newborns n=812		Term newborns n=1342	
Sensitivity	0.923	(0.734-0.986)	1.000	(0.771-1.00)	0.778	(0.402 - 961)
Specificity	0.971	(0.963-0.977)	0.951	(0.933-0.964)	0.983	(0.974 - 0.989)
Negative predicting value	0.999	(0.996-1.000)	1.000	(0.994-1.000)	0.998	(0.994 - 1.000)
Positive predictive value	0.279	(0.190-0.388)	0.304	(0.192-0.443)	0.233	(0.106 - 0.427)
Positive likelihood ratio	**31.7**	(24.2-41.7)	20.4	(15.0-28.7)	45.1	(26.4 - 76.9)
Negative likelihood ratio	**0.08**	(0.02-0.30)	0.00	(0.00 – NA)	22.6	(0.07 - 0.77)

19

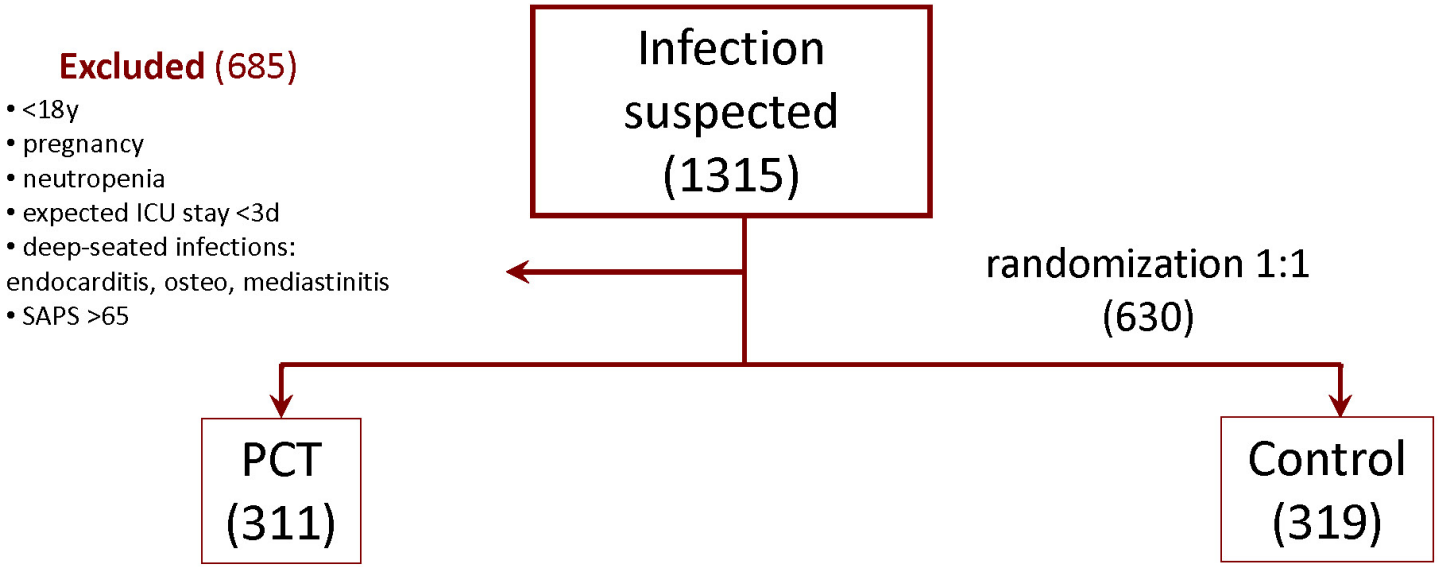
19. Joram N EJCMID

Just a tool. . .

- Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial) : a multicentre randomised controlled trial [20]
- RCT in ICU with infected patients (suspicion)
- Intervention : availability of serial procalcitonin levels/algorithm
- Antimicrobial decisions (agent, dose & duration) made by clinician
- Outcome : Antimicrobial use (superiority) & mortality (non-inferiority ; δ 10%)

20. Bouadma L JAMA 2010

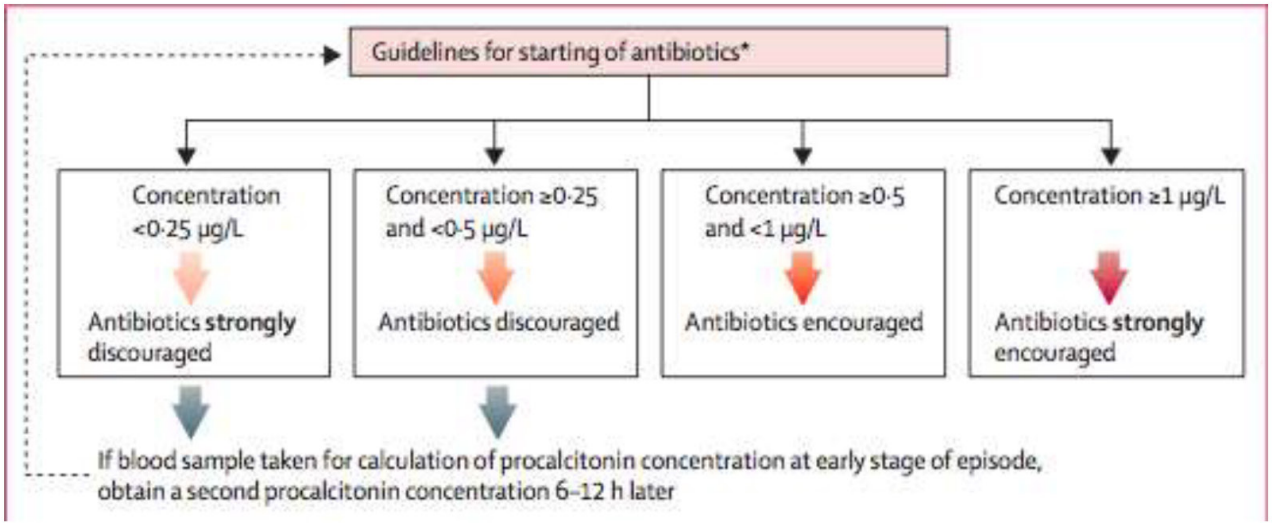
Just a tool. . .

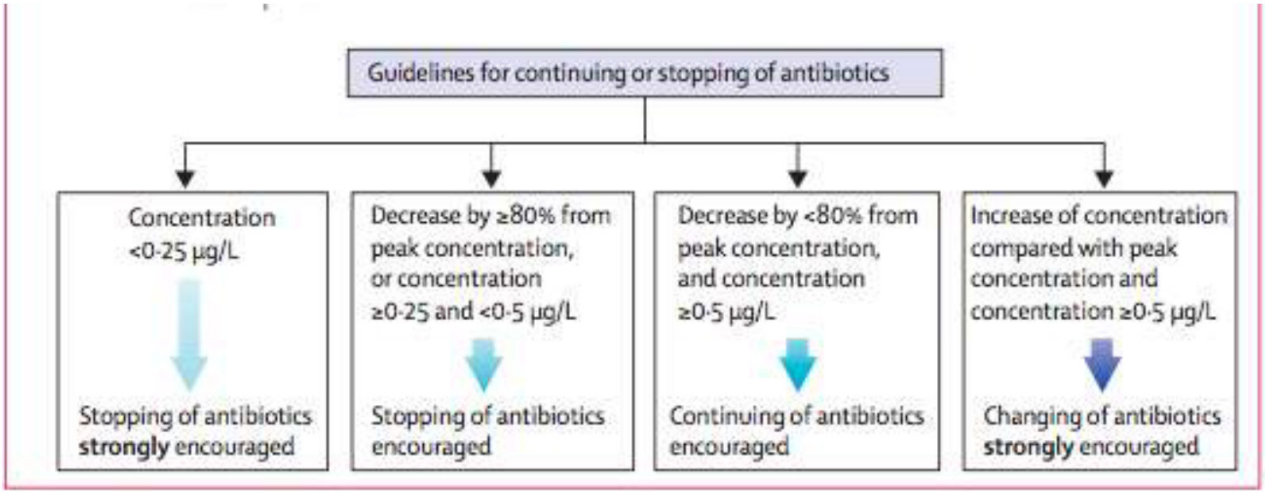


- Guidelines for starting of ABX
  - If no ABX: repeat PCT 6-12h later
- Guidelines for continuing/stopping ABX
  - daily PCT until withdrawal
- Guidelines for ABX re-start

- Standard of care

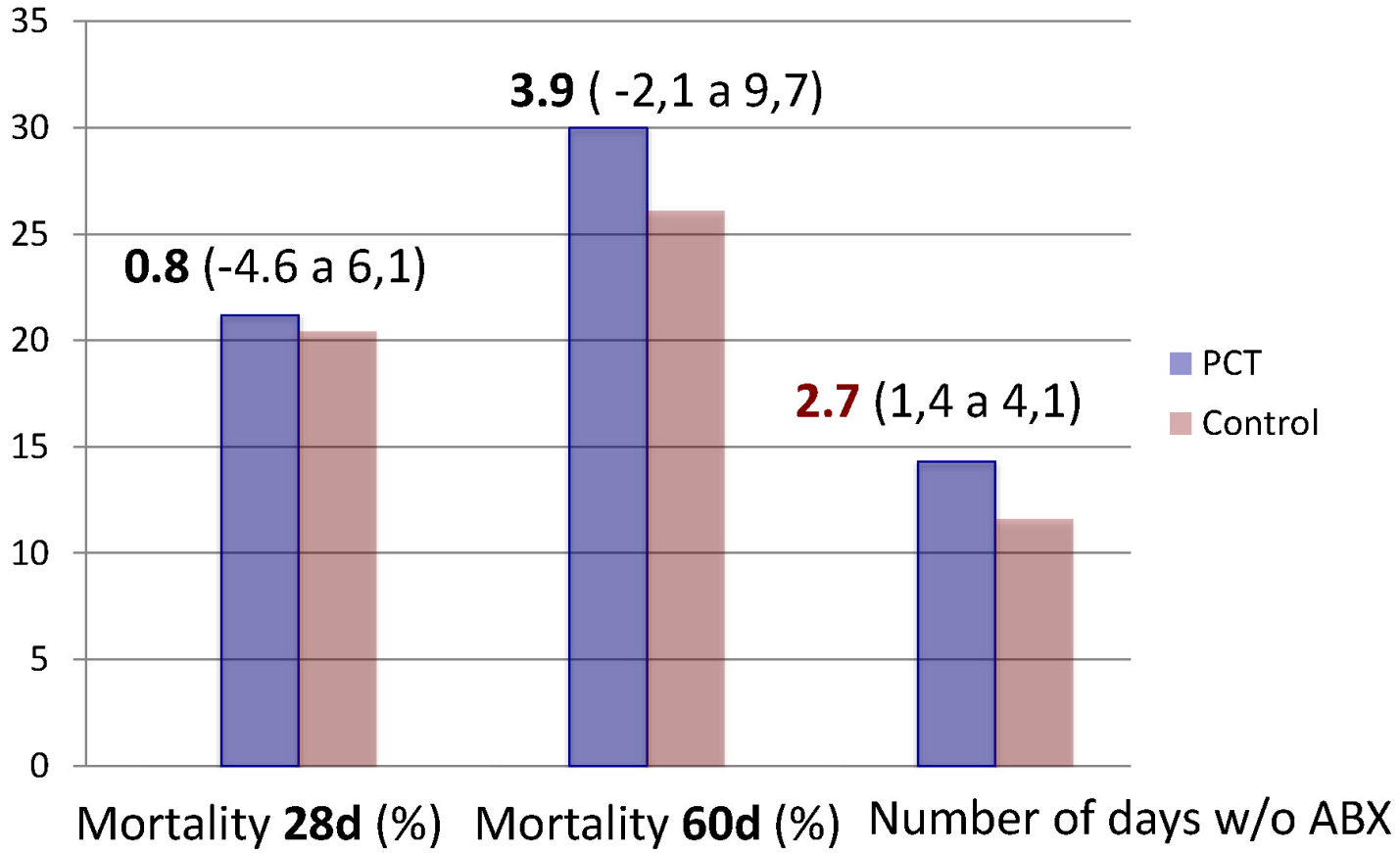
Just a tool. . .


Guidelines for starting of antibiotics*
Concentration <0·25 µg/L
Antibiotics strongly discouraged
Concentration ≥0·25 and <0·5 µg/L
Antibiotics discouraged
Concentration ≥0·5 and <1 µg/L
Antibiotics encouraged
Concentration ≥1 µg/L
Antibiotics strongly encouraged
If blood sample taken for calculation of procalcitonin concentration at early stage of episode, obtain a second procalcitonin concentration 6–12 h later


Guidelines for continuing or stopping of antibiotics
Concentration <0·25 µg/L
Stopping of antibiotics strongly encouraged
Decrease by ≥80% from peak concentration, or concentration ≥0·25 and <0·5 µg/L
Stopping of antibiotics encouraged
Decrease by <80% from peak concentration, and concentration ≥0·5 µg/L
Continuing of antibiotics encouraged
Increase of concentration compared with peak concentration and concentration ≥0·5 µg/L
Changing of antibiotics strongly encouraged

Just a tool. . .

Variable	PCT (%)	Control (%)
Age	61 a	62.5 a
SAPSII	43.8 pt	43.4 pt
SOFA	7.4 pt	7.2 pt
Septic shock	45	41
Lactate >2	37	38
Community acquired	50	55
Microbiologically documented infections	69	71
Clinically documented infections	12	17
Possible infection	4	2
NO infection	15	11
Pulmonary infection	71	74
Urinary tract infection	9	6
Intrabdominal infection	5	7
CNS	3	2
Catheter	2	1
Others	4	3
PCT	12 mcg	12 mcg



Days of antibiotic exposure/1000 inpatient days:653 vs 812 (-19.5%)

PCT acted as a guide not as a rule

PCT guidelines were not followed in 219 episodes (53%)

- 65 patients did receive ATB despite PCT$<$0.5
- 4 patients did not received despite PCT$>$0.5
- In 39 patients, ATB were discontinued despite PCT$>$0.5
- In 79 patients, ATB were continued despite PCT$<$0.5

Conclusion : Why PCT ?

- If diagnosis uncertainty
- Early biomarker for non-viral infection
- Better than clinical examination alone
- Better than CRP
- Better use of ATB
  - Individualized treatment
  - Decrease ATB duration
- Only biomarker with 15 intervention studies, with positive results
- >3000 publications... Even in Nature : "Devices that quickly identify bacterial infections would benefit health and slow the spread of resistance". Nature 2014
- Now Point-of-care PCT : 20 min

Remember

Useful situations :

- Acute pancreatitis
- Lower respiratory tract infection (LRTI)
- Meningitis
- Sepsis in the ICU
- Sepsis for the neonates

And now Point of Care PCT ! !

- Portable (2.4kg)
- Easy to use and fast (20 min)
- Total blood
- Very precise (CV<15%)

Thank you for your attention

Figure: Questions ? Coffee ? Ice-cream ?