Can biomarkers improve the rational use of antibiotics?

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OBJECTIVES

- To describe the problem of antibiotic overuse and bacterial resistance in hospitalized patients
- To present the evidence regarding the potential role of biomarkers to guide antibiotic use for adult and pediatric patients

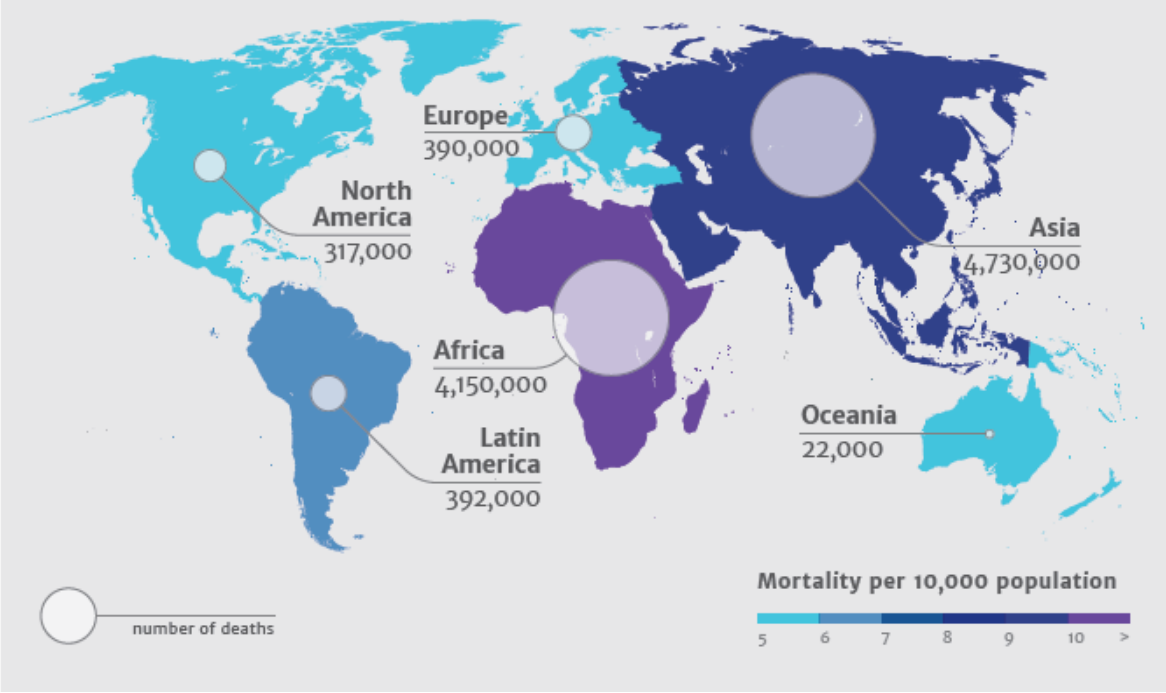
DISCLOSURES

- I have no potential conflict of interest to disclose

Antibiotic overuse and bacterial resistance

Bacterial resistance

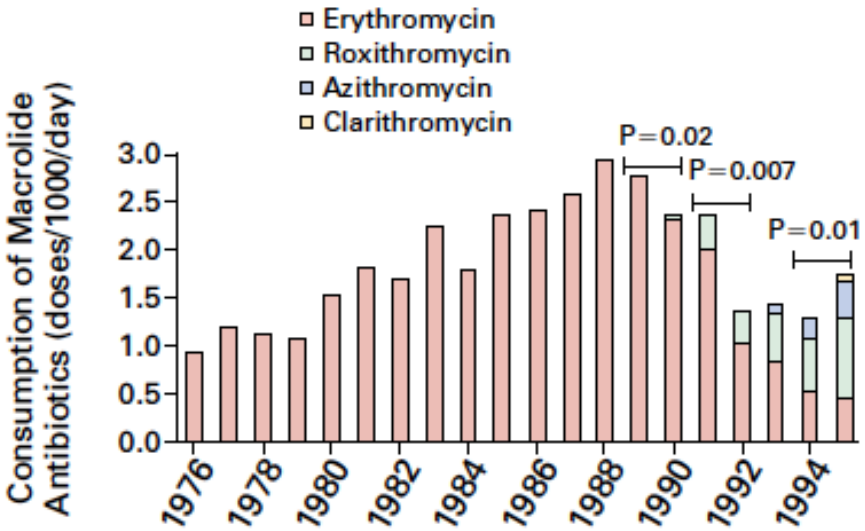
- **Antibiotic resistance is a major problem worldwide**
  - Currently: 700 000 deaths/year
  - 2050: 10 million deaths/year (US$ 60-100 trillion/year)

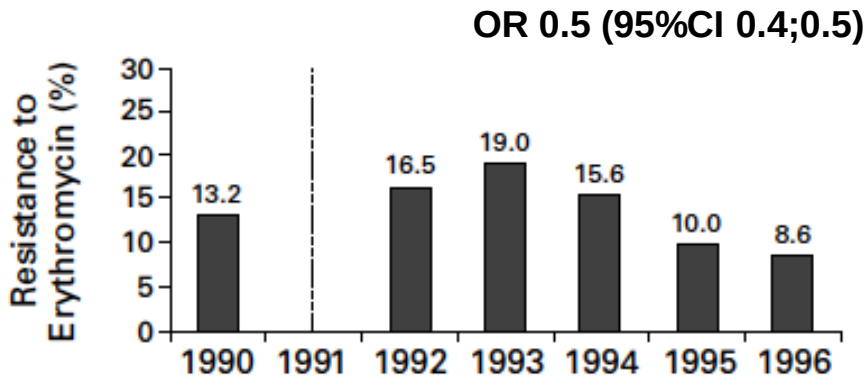


O'Neill J et al. Review on antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014
Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance. 2016. (http://www.cdc.gov/drugresistance/about.html.)

Bacterial resistance and antibiotic use

- **Seppälä H et al. (N Engl J Med 1997)**
  - Finland, 1988-1996
  - Resistance to erythromycin among Group A Streptococcal isolates from throat swabs and pus cultures





Seppälä HJ et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A Streptococci in Finland. N Engl J Med 1997;337:441-6.

Bacterial resistance and duration of antibiotic treatment

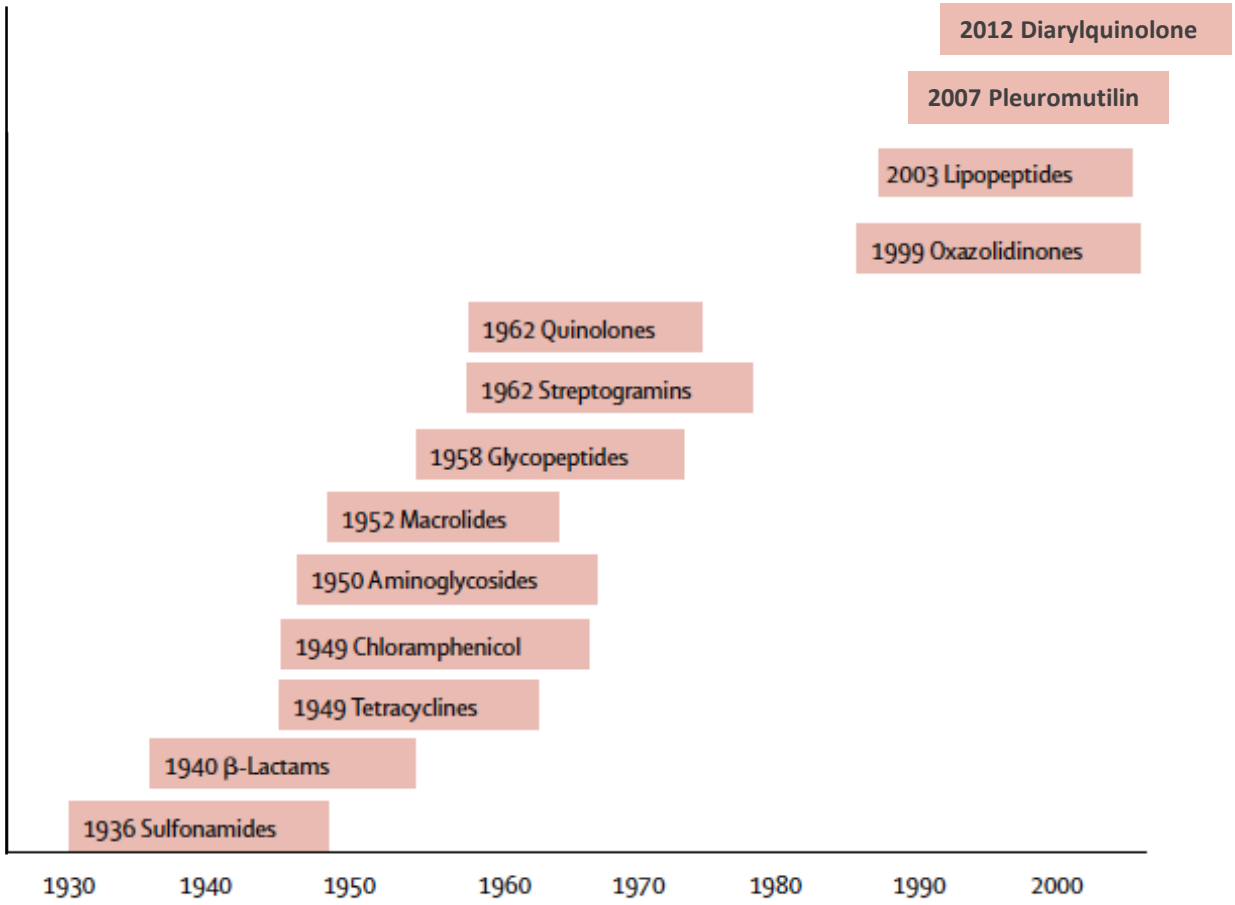
- **Guillemot D et al. (JAMA 1998)**
  - Prospective cohort study
  - 941 children 3-6 years
  - Pharyngeal carriage of penicillin-resistance *S. pneumoniae*
    - Duration of beta-lactam treatments >5 days: OR 3.5 (95%CI 1.3-9.8)

- **Chastre J et al. (JAMA 2003)**
  - RCT
  - 197 mechanically ventilated patients – VAP
  - 8 vs.15 days of antibiotic treatment
  - Results:
    - Recurrent infection caused by resistant bacteria: 42% vs. 62% (p 0.04)
    - Infection recurrence: 2.9% (90%CI -3.2;9.1)
    - Mortality: 1.6% (90%CI -3.7;6.9)

Chastre J et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588-98.
Guillemot D et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA 1998;279:365-70.

Antibiotic development

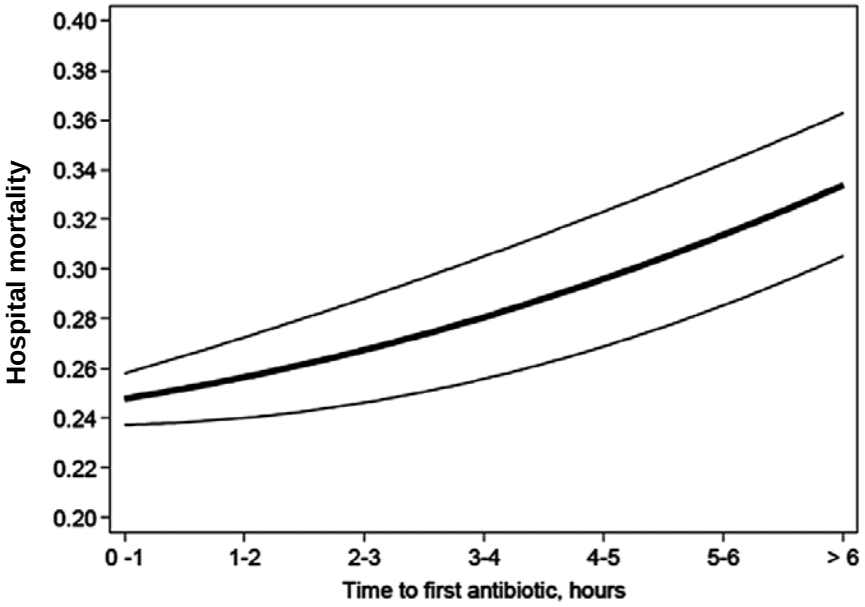
- **The pipeline is running dry**

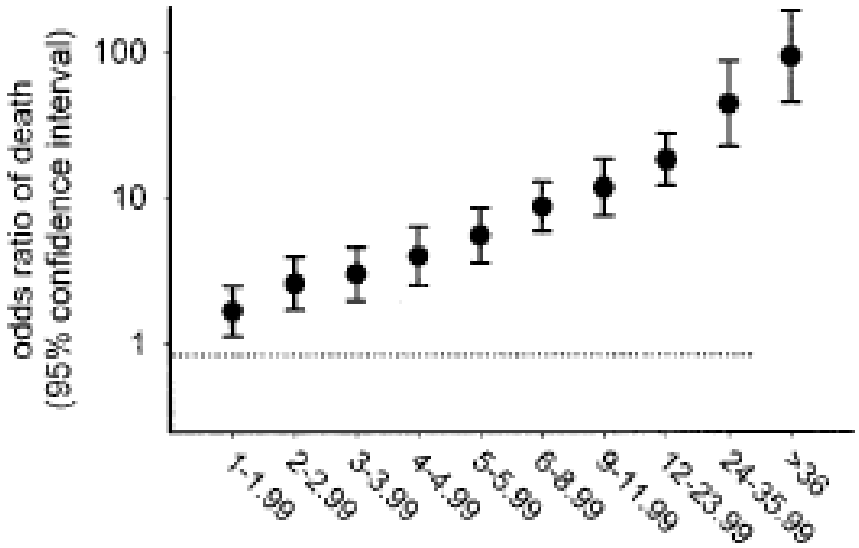


Norrby SR et al. Lack of development of new antimicrobial drugs: a potential serious threat to public health. Lancet Infect Dis 2005;5:115-9.

Professional Society	Infection	Recommendation about ATB duration	Level of evidence
Society of Critical Care Medicine and the European Society of Intensive Care Medicine, 2012 IDSA (endorsed)	sepsis	Adults: 7-10 days Children: no recommendation	2C (well done observation studies with control RCTs AND inconsistency of results)
IDSA, 2017	meningitis	10-21 days "The duration of antimicrobial therapy in patients with bacterial meningitis has often been based more on tradition than on evidence-based data" (2004)	confidence in an estimate of effect across the recommendations: low
Canadian Pediatric Society (CPS), 2014	meningitis	5-21 days "The recommended length of treatment varies with the pathogen and the clinical course of infection"	not provided
IDSA, 2011 American Academy of Pediatrics (endorsed)	community-acquired pneumonia	"The courses of 10 days have been studied, although shorter courses may be as just effective"	moderate quality
CPS, 2011	pneumonia	7-10 days "Pneumonia complicated by empyema or abscess formation requires longer duration of therapy as determined by clinical course"	not provided
IDSA, 2010	complicated intra-abdominal infection	4-7 days	moderate evidence - evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

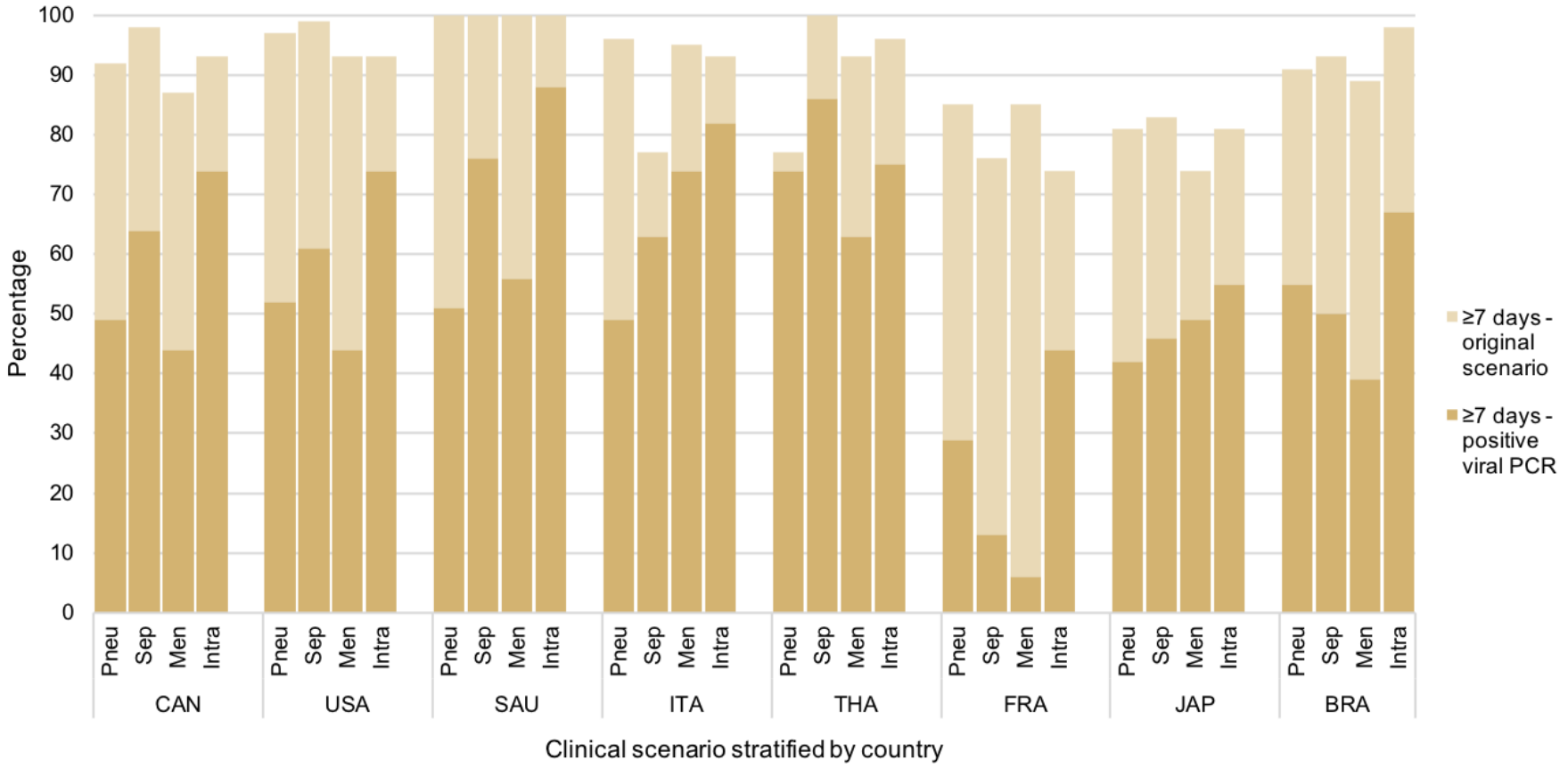
Antibiotic treatment delay and mortality





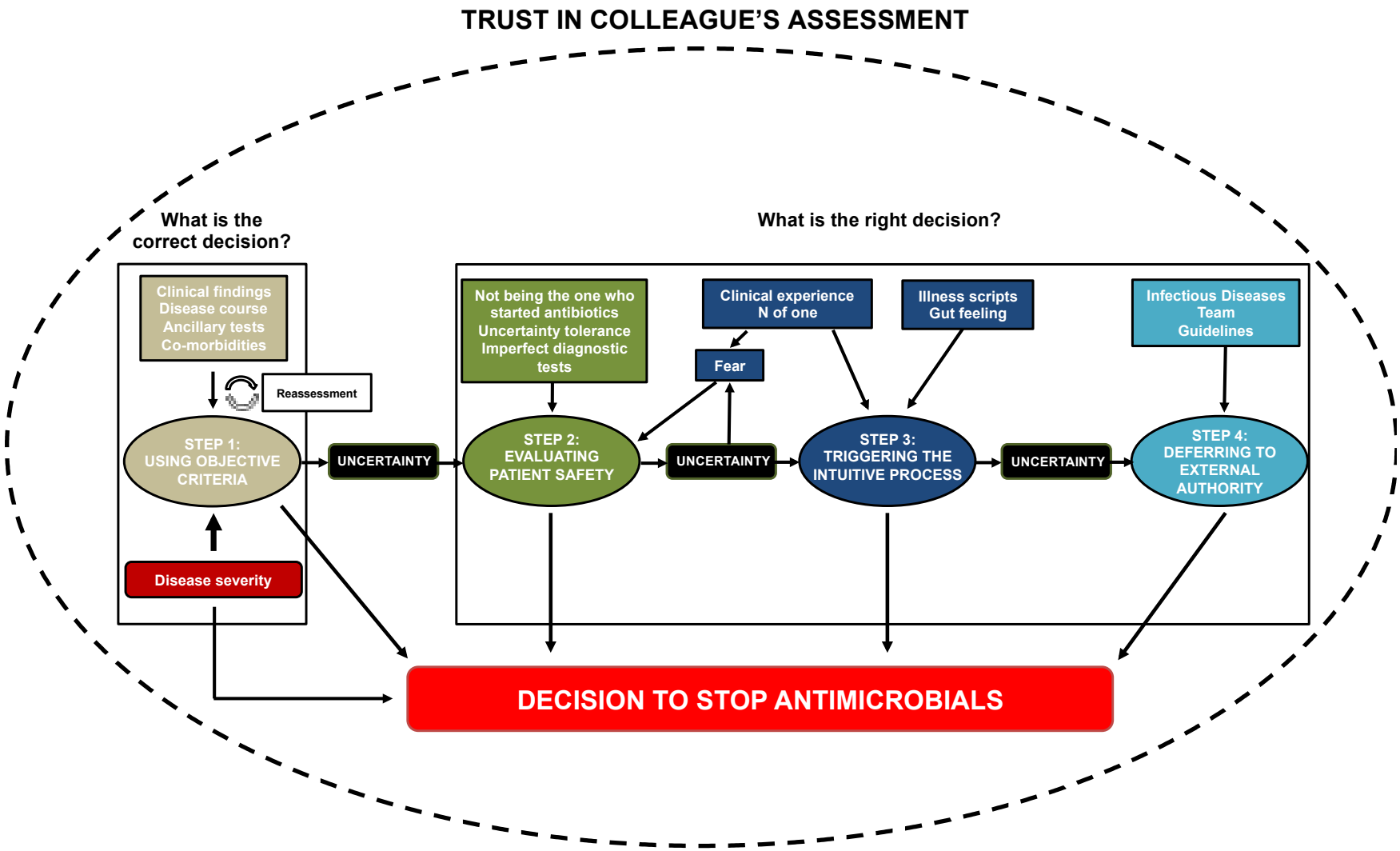
Ferrer R et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749-55.
Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.

Clinical utility of viral PCR



Fontela PS et al. Determinants of antibiotic tailoring in pediatric intensive care: an international survey. 2019.

Decision-making process to stop antimicrobial treatment



Fontela PS et al. Clinical reasoning behind antimicrobial use in pediatric intensive care units: a qualitative study. 2019.

Use of infection biomarkers to guide antimicrobial use

Ideal biomarker

- **Appropriate behaviour**
  - High levels at the beginning of ATB treatment
  - Progressive decline with appropriate treatment
  - Increase in levels if the infection relapses or a superimposed bacterial infection occurs
- **Readily available**
- **Fast turnaround time**
- **Cost**

Benefit: to personalize antibiotic treatment decisions

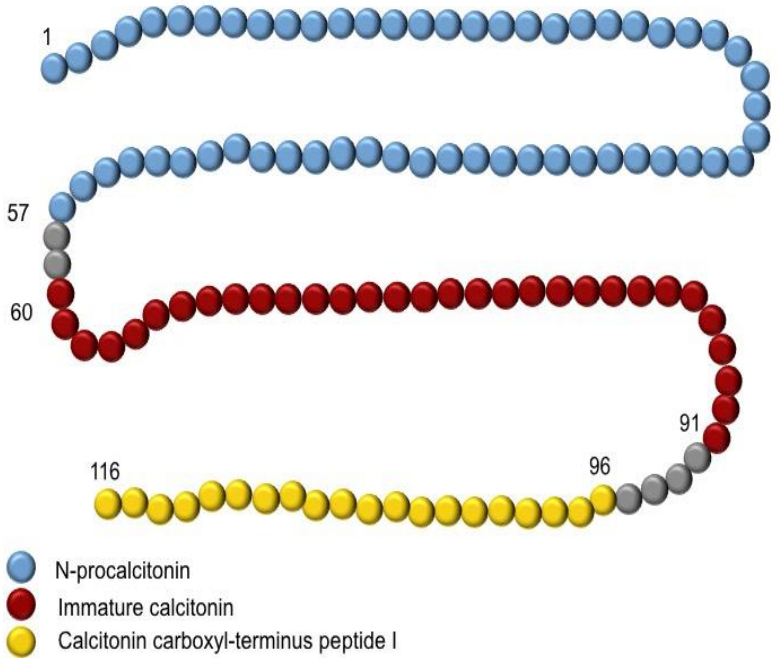
Infection biomarkers

- **Good quality evidence**
  - Procalcitonin
  - C-reactive protein
- **More evidence needed**
  - CD64 neutrophil
  - Serum amyloid A protein
- **Future**
  - Molecular biology
    - Proteomics, transcriptomics and metabolomics

Fontela PS et al. Can biomarkers improve the rational use of antibiotics? Curr Opin Infect Dis 2018;31(4):347-352
Fontela PS, Papenburg J. Procalcitonin and antibiotic use: imperfect, yet effective. Lancet Infect Dis 2018;18(1):11-13.

Procalcitonin

- 116-AA polypeptide precursor of the hormone calcitonin
- Practically undetectable in healthy individuals
- Surrogate biomarker of bacterial infection and “poor prognosis” vs. role in the inflammatory response
- Initial increase 2.5-4 h after infectious stimulus with peak levels in 6-13.5 h
- Half-life 22.5 h
- Cut-offs:
  - Initiation: 0.25 to 0.5 ng/mL
  - Stopping: 0.1 to 1 ng/mL or drop ≥ 80-90% of peak value



Fontela PS, Lacroix J. *Procalcitonin: is this the promised biomarker for critically ill patients?* J Pediatr Intensive Care 2016; 5(4):162-171.

Procalcitonin meta-analyses

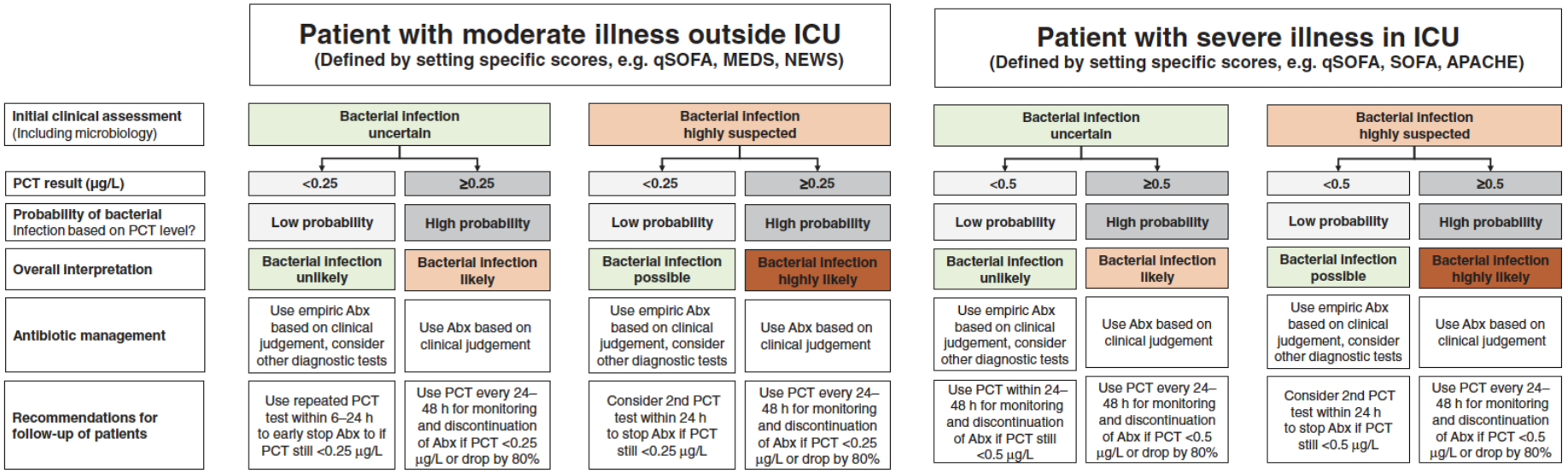
Author	N	Infection type	Antibiotic duration (95%CI; days)	Mortality (%)	ICU LOS (95%CI; days)	Hospital LOS (95%CI; days)
Schuetz 2018 (IPD)	26 RCTs (6,708)	acute respiratory infection	Treatment initiation: OR 0.27 (0.24,0.32) Treatment duration: MD -2.43 (-2.71;-2.15)	30-day mortality: OR 0.83 (95%CI 0.70;0.99)	MD 0.39 (-0.81;1.58)	MD -0.19 (-0.96;0.58)
Soni 2013	5 RCTs	suspected severe bacterial infection	MD -2.05 (-2.59;-1.52)	Hospital + 28-day mortality: MD 0.00 (95%CI -0.06;0.05)	MD 0.33 (-1.88;2.53)	-
Prkno 2013	7 RCTs	severe sepsis and septic shock	HR 1.27 (1.01;1.53)	28-day mortality: RR 1.02 (95%CI 0.85-1.23)	HR 1.05 (0.82;1.29)	HR 1.03 (0.82;1.24)
Schuetz 2012	5 RCTs	acute respiratory infection	MD -3.17 (-4.28;-2.06)	30-day mortality: OR 0.79 (95%CI 0.53;1.17)	MD 1.01 (-1.26;3.28)	MD -1.36 (-4.55;1.77)
Mattahaiou 2012	7 RCTs	severe bacterial infection	MD -3.15 (-4.35;-1.95)	28-day mortality: OR 0.95 (95%CI 0.79;1.16)	MD -0.36 (-1.97;1.26)	MD -0.12 (-1.09;0.85)
Heyland 2011	5 RCTs	severe bacterial infection	MD -2.14 (-2.51;-1.78)	hospital mortality: OR 1.06 (95%CI 0.86;1.30)	-	-
Kopterides 2010	5 RCTs	severe bacterial infection	MD -2.36 (-3.11;-1.61)	28-day mortality: OR 0.93 (95%CI 0.69;1.26)	MD -0.57 (-1.90;0.76)	MD -0.13 (-1.10;0.84)

RCT = randomized controlled trials; OR = odds ration; MD = mean difference; HR = hazard ratio; RR = relative risk; 95%CI = 95%confidence interval

Reduction of antibiotic use without increasing mortality

Procalcitonin guidelines

- **Acute infections, non-immunosupressed adult patients**



Real world: trends not always available because procalcitonin is infrequently measured

Schuetz P et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use.Clin Chem Lab Med 2019.

Procalcitonin use in children and newborns

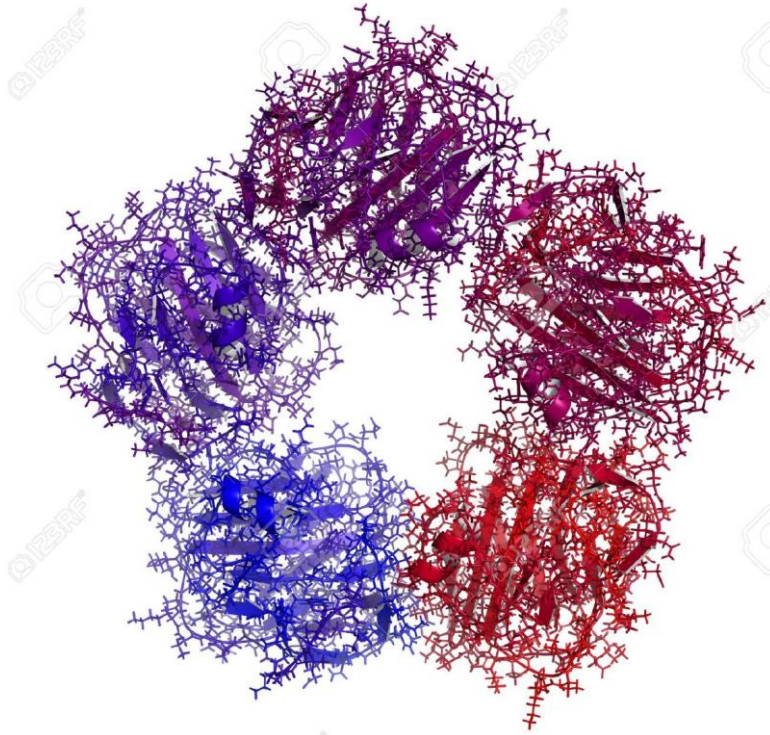
Author	N	Age range	Infection	PCT use	Antibiotic use
Esposito 2011	319	1 mo-14 y	community-acquired pneumonia	initiation and cessation	5.4 vs. 11 days
Baer 2013	337	1 mo-18 y	LRTI	initiation and cessation	***LRTI*** 4.5 vs. 6.3 days (-1.8 days; 95%CI -3.1, -0.5) ***Pneumonia*** 5.7 vs. 9.1 days (-3.4 days; 95%CI -4.9, -1.7)
Stocker 2017 (NeoPINS)	1710	GA 34 weeks and older	Early-onset sepsis	cessation	55·1 vs. 65·0 hours ($p < 0.0001$)

LRTI: lower respiratory tract infection

- **Treatment initiation cut-offs: > or ≥ 0.25 ng/mL**
- **Treatment stopping cut-offs: ≤ or >0.25 ng/mL**

C-reactive protein

- Pentraxin with 206 AA residues
- Median serum concentrations in healthy adults were reported to be 1.5 mg/L
- Released in response to cytokines
- Important role in defense against pathogens
- Biomarker for chronic inflammatory diseases
- Initial increase 6-8 h after infectious stimulus with peak levels in 30-50 h
- Half-life 19 h



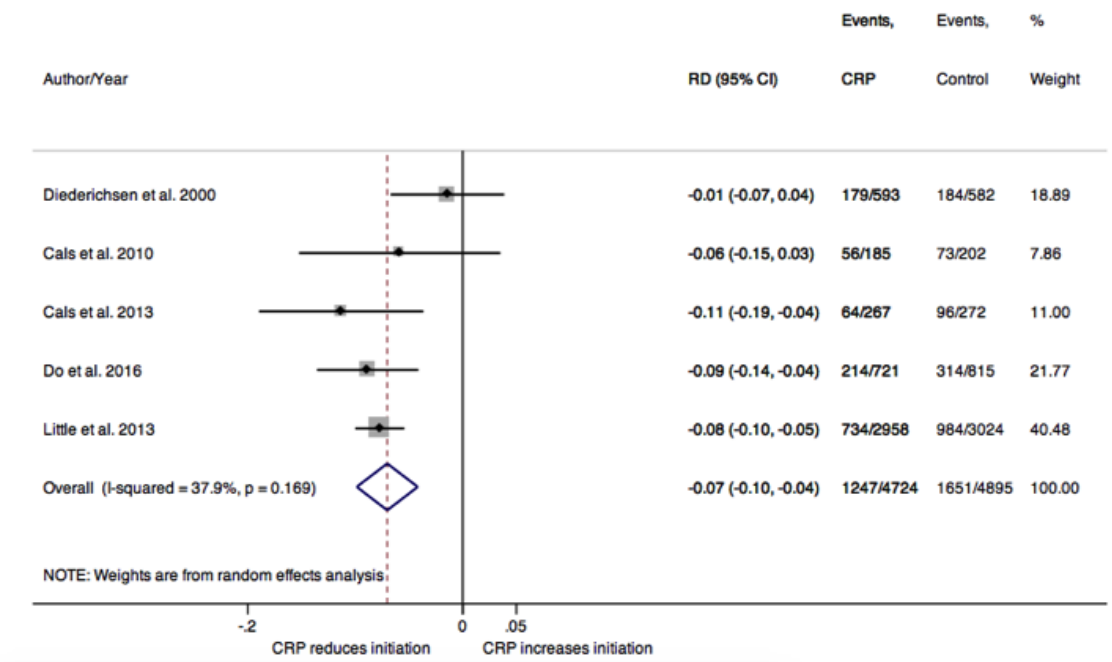
Fontela PS et al. Can biomarkers improve the rational use of antibiotics? Curr Opin Infect Dis 2018;31(4):347-352

CRP to guide antimicrobial use

- **Adults – initiation of treatment**

Recommended cut-offs:

- Withhold if < 20 mg/L
- Start if ≥ 100 mg/L



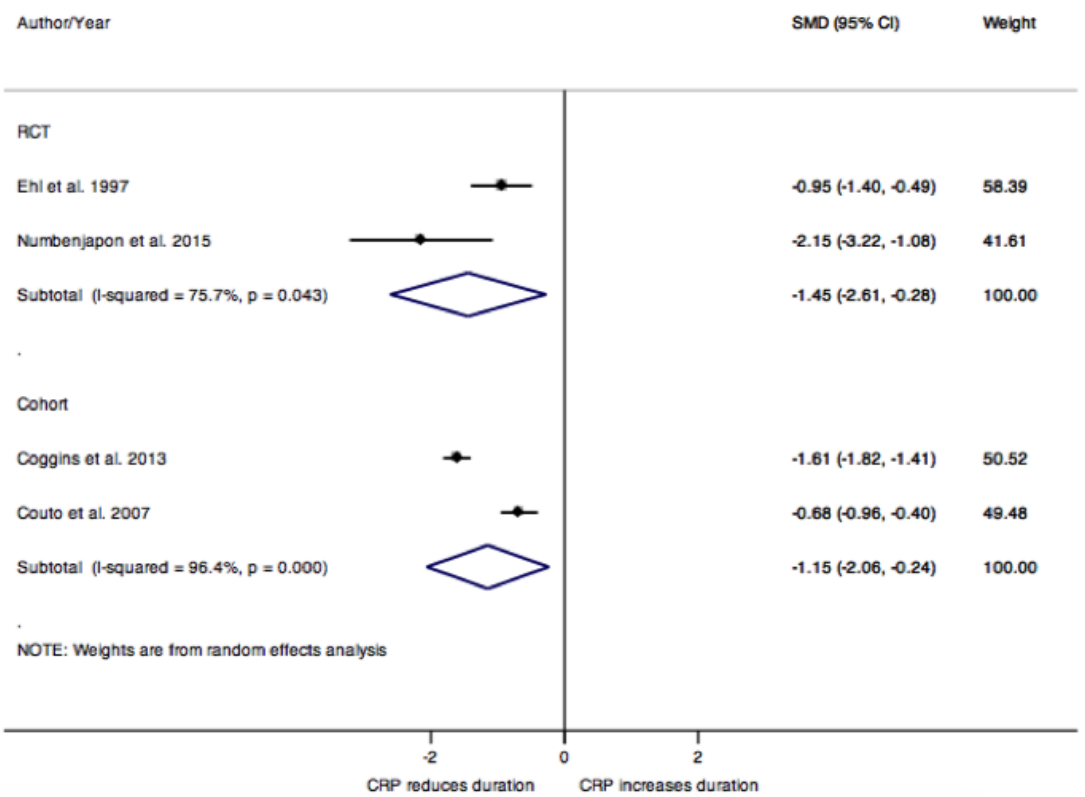
Petel D et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. BMJ Open 2018;8(12):e022133.

CRP to guide antimicrobial use

- **Neonates – treatment duration**

Recommended cut-off:

- Stop if < 10 mg/L

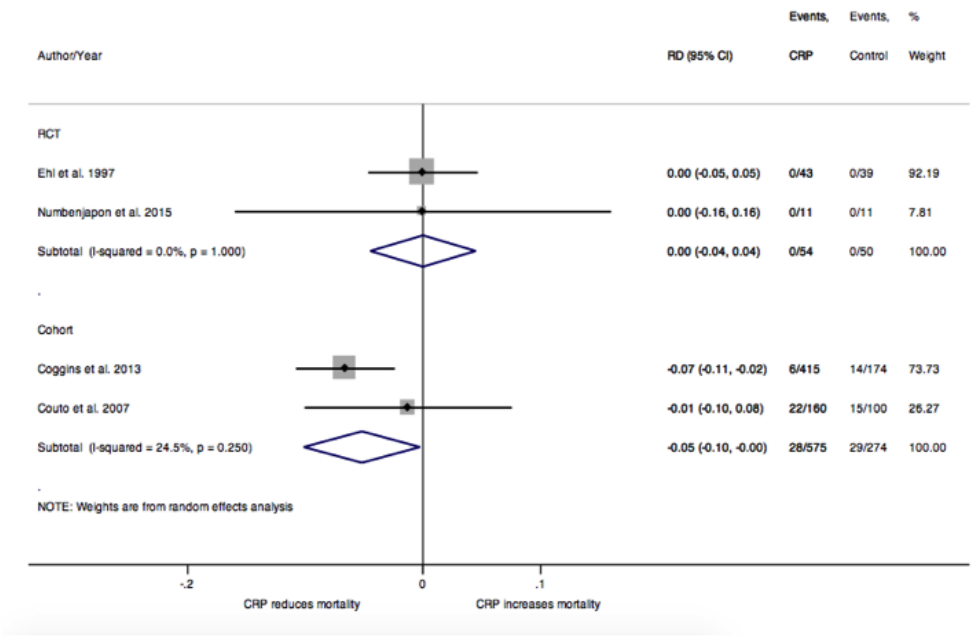


Petel D et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. BMJ Open 2018;8(12):e022133.

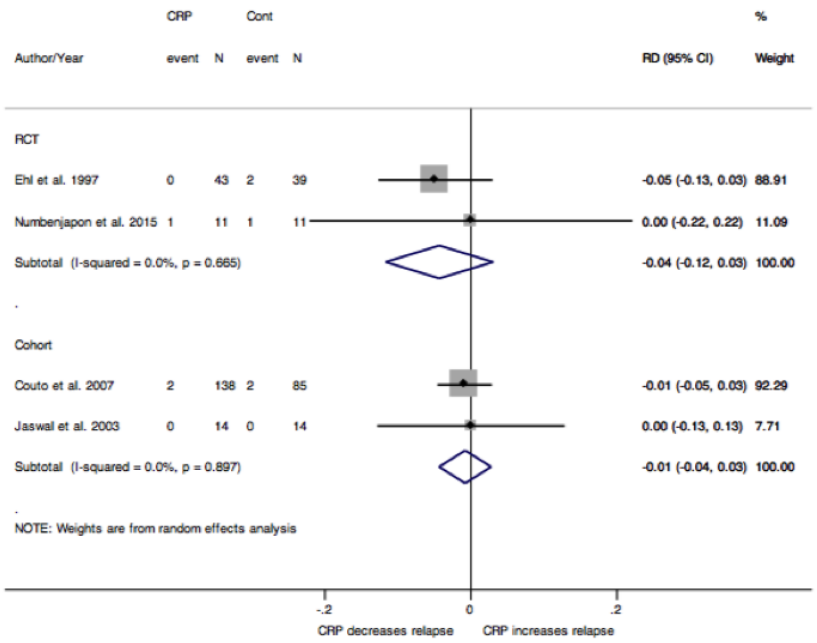
CRP to guide antimicrobial use

- **Neonates**

Mortality risk



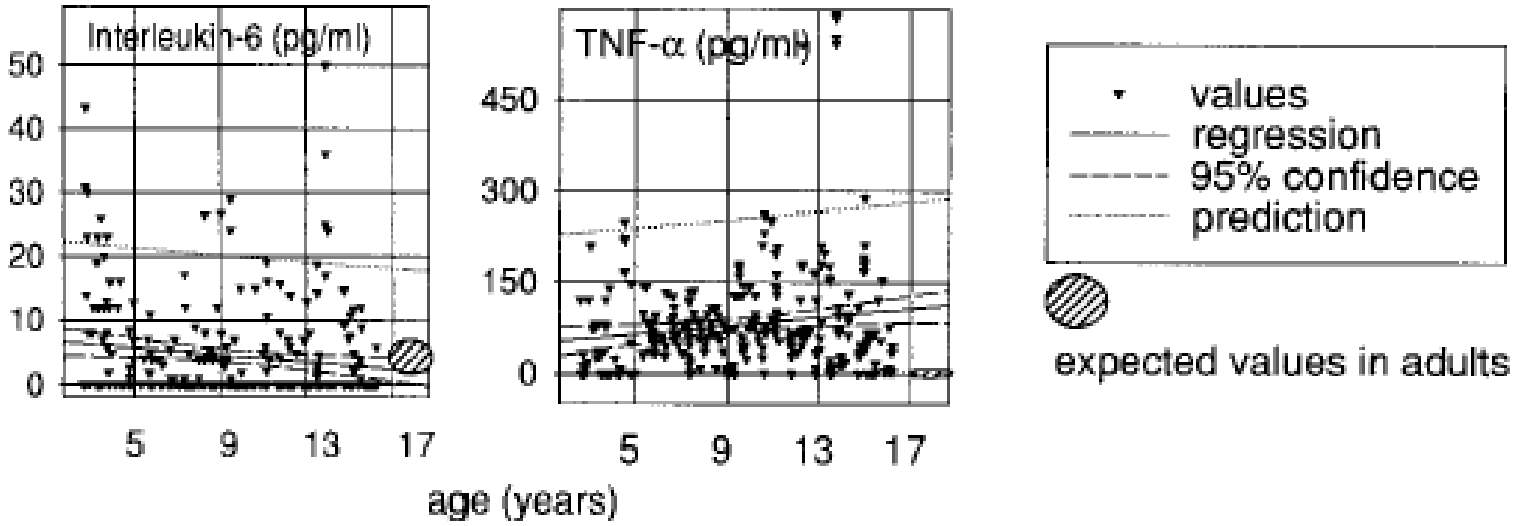
Infection relapse



Petel D et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. BMJ Open 2018;8(12):e022133.

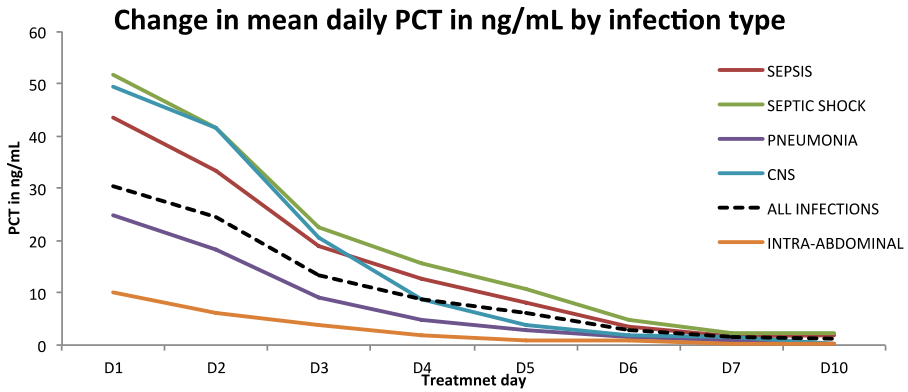
Inflammatory response in healthy children

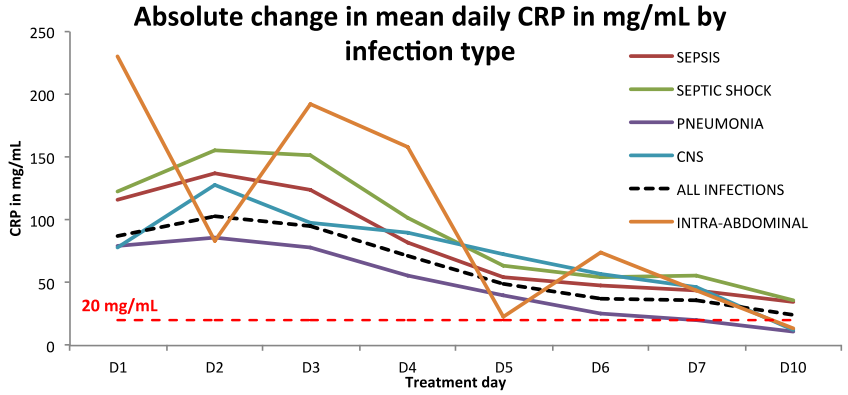
- **Sack U et al. (Clin Diagn Lab Immunol 1998)**
  - Prospective cohort study
  - 275 healthy children

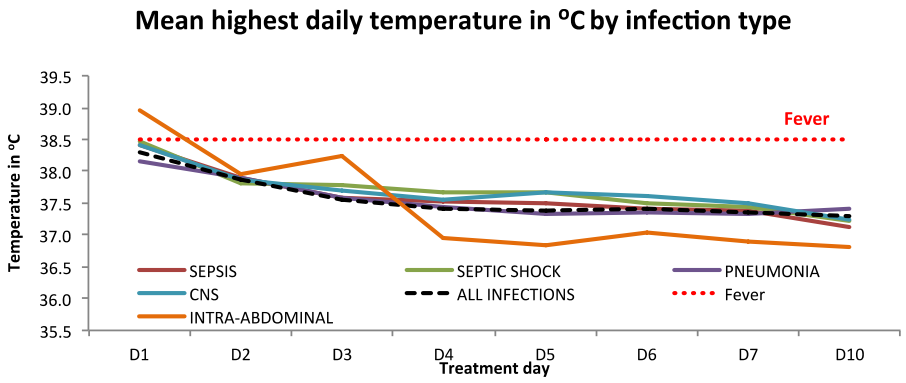


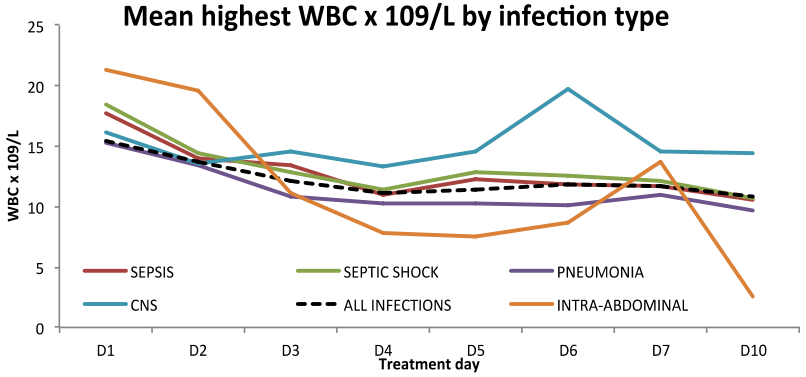
Sack U et al. Age-dependent levels of select immunological mediators in sera of healthy children. Clin Diagn Lab Immunol 1998;5:28-32.

Evolution of biomarker levels during antimicrobial treatment









Fontela PS et al. Infection markers to tailor antibiotic use in pediatric intensive care units. Preliminary data; 2019.

CONCLUSIONS

- The burden of bacterial resistance and antimicrobial overuse cannot be underestimated
- Antimicrobial-related decisions are complex and strongly influenced by subjective criteria and contextual variables
- There is an urgent need for the development of more objective criteria to guide antimicrobial-related decisions
- The use of infection biomarkers such as procalcitonin and CRP was shown to be safe and effective to reduce antimicrobial use in adult patients
- More evidence is needed before implementing the use of biomarkers to guide antimicrobial use in pediatric and neonatal patients

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- GFRUP

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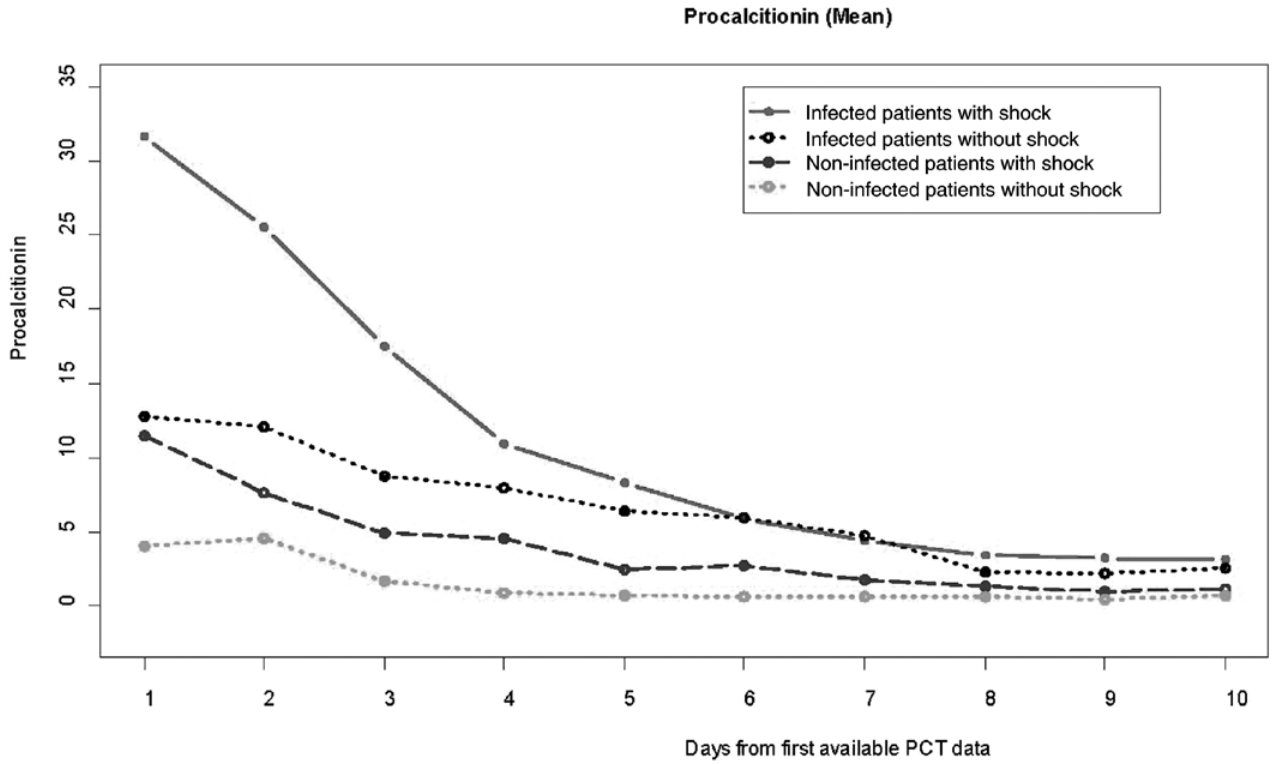
Procalcitonin kinetics

- **Reynolds et al. (Crit Care Med 2012)**
  - Prospective cohort study
  - 598 adult ICU patients



Reynolds SC et al. Longitudinal changes in procalcitonin in a heterogeneous group of critically ill patients. Crit Care Med 2012; 40:2781–87.