Role of diagnostics in management of Healthcare Associated Infection (and related issues of antimicrobial resistance)

Professor Barry Cookson

Division of Infection and Immunity,
Univ. College London

Dept. of Health Policy,
London School of Hygiene & Tropical Medicine

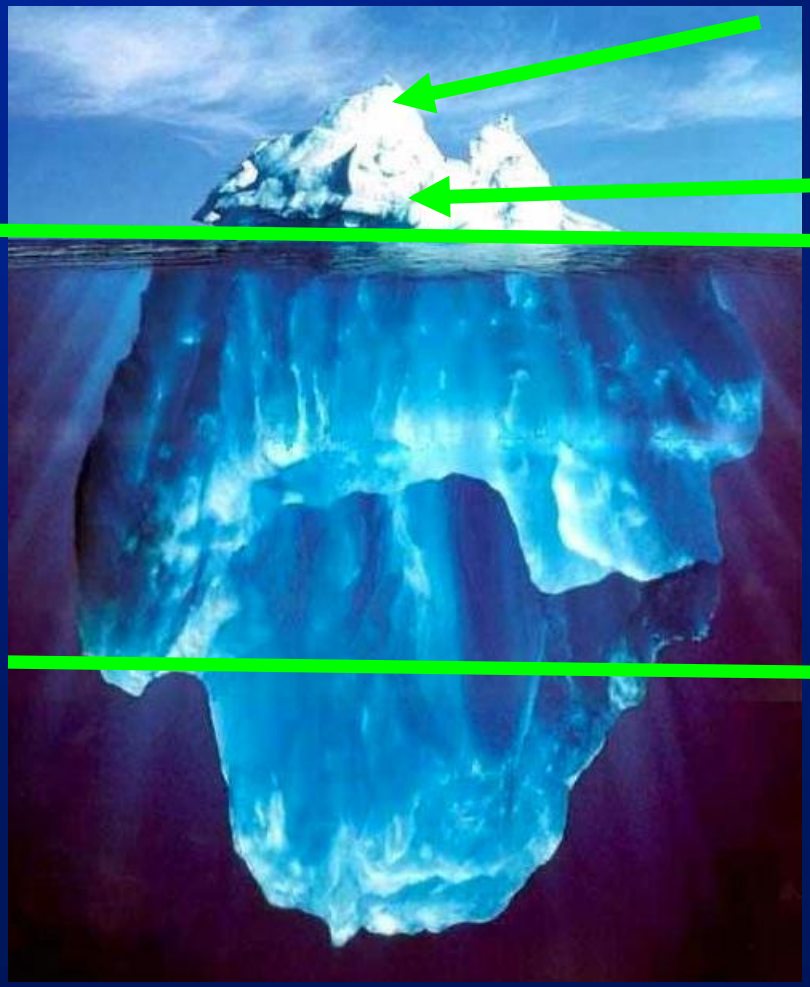
QIAGEN would like to thank our speaker, Prof. Barry Cookson, for his presentation.

Typical Healthcare Associated Infection (HAI) Pathogens
The Iceburg Phenomenon

Bloodstream Infections

Clinical specimens

Other Infections



Screening

Colonisation (>70%)

Undetected Colonisation

Management of HAI (and Antimicrobial Resistance)

- Correct diagnosis of sepsis and other infections
- Sensitive detection of patients carrying or infected with HAI pathogens
- Correct identification and typing to inform infection prevention and control (IPC) and antimicrobial stewardship (ASt) measures (NGS tracks does not type organisms: TAT very long at present)

Important HAI Pathogens covered in another session

Molecular targeting for:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- *Clostridium difficile* (*C. diff*)
- Extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Vancomycin-resistant enterococci (VRE)
- ISSUES OF PREDICTING PHENOTYPE

HAI IPC and ASt Management

Rapid molecular and Other microbiological tests

Clinical decision support

Typing needed to interpret results e.g. is it an outbreak, Are interventions working?

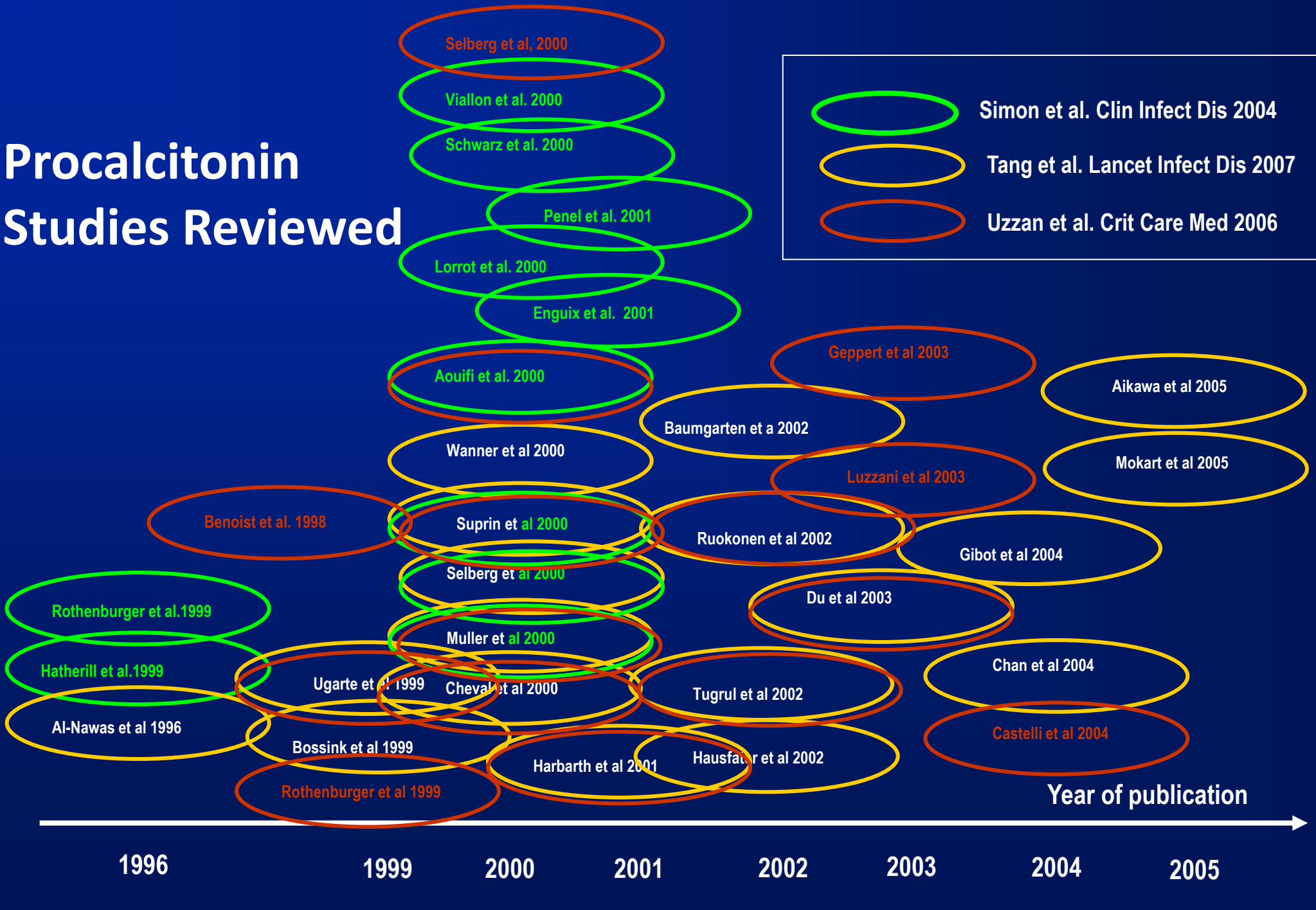
Biomarkers & Procalcitonin

Agenda

- Biomarkers & Procalcitonin (PCT):
  Findings from recently published RCTs and possible impact on antibiotic prescribing practices

- Update on rapid (molecular) diagnostic tools for diagnosis of severe infections and informing IPC and ASt

Procalcitonin Studies Reviewed



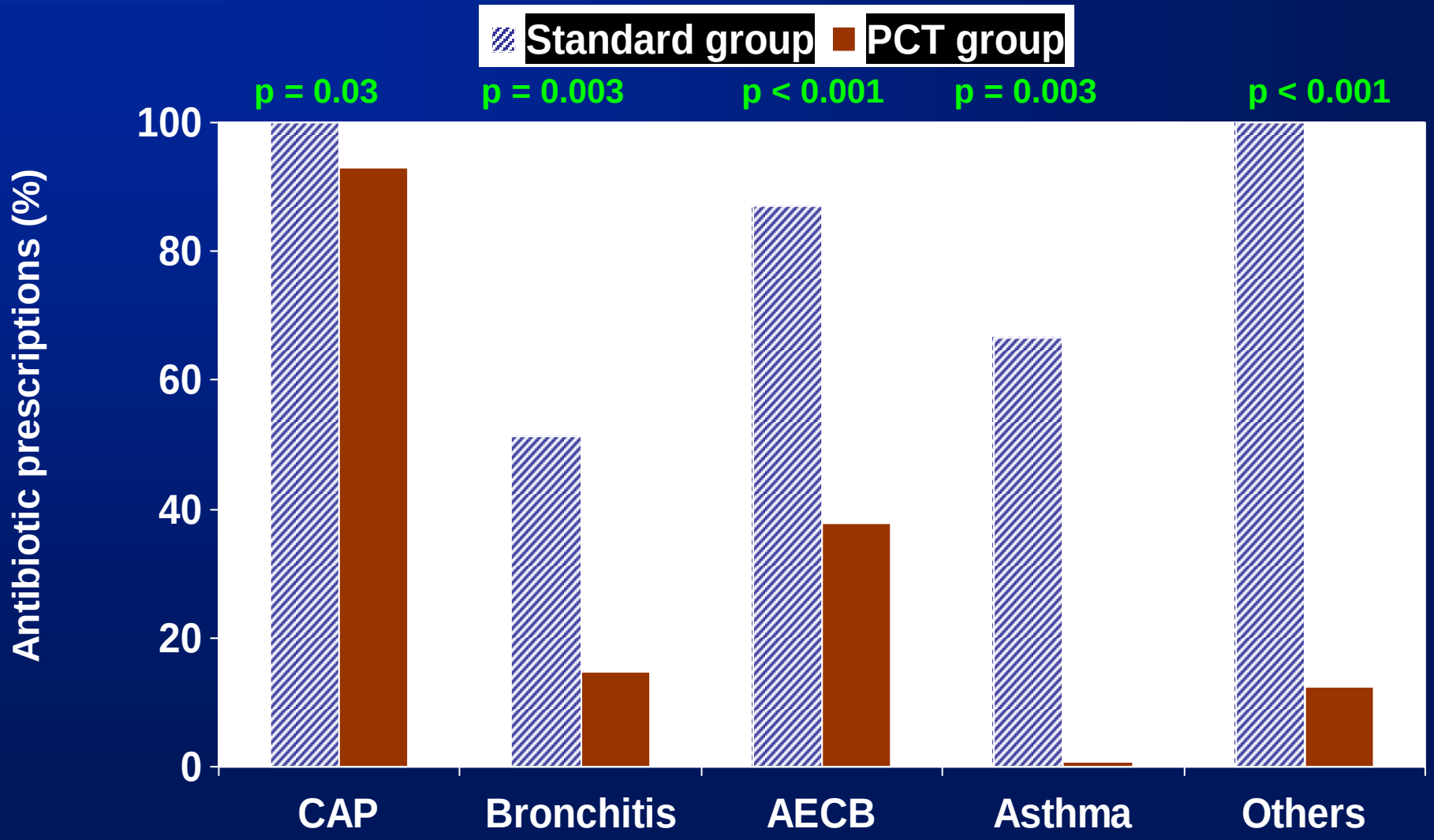
Reasons for discrepant conclusions on PCT as a marker of infection

- **Different assays: no gold standard**
- **Cut-off range depends on:**
  - **Clinical setting**
  - **Pretest probabilities e.g. organism spectrum**
- **Poor design of many studies**
- **Single PCT measurement of limited value**
- **False positives & negatives (≈10%): useful lists**
- **Heterogeneous study populations & Clinical Settings**

Schuetz P et al. Swiss Med Weekly 2009; 139: 318-26

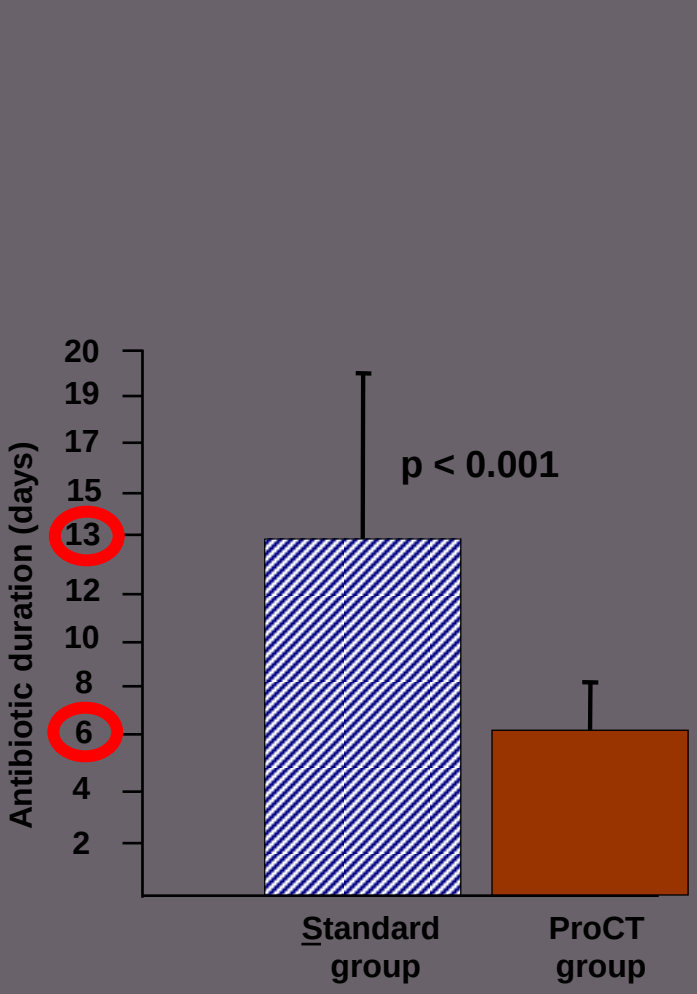
Christ-Crain M & Muller B, Swiss Med Wkly 05; 135: 451-60

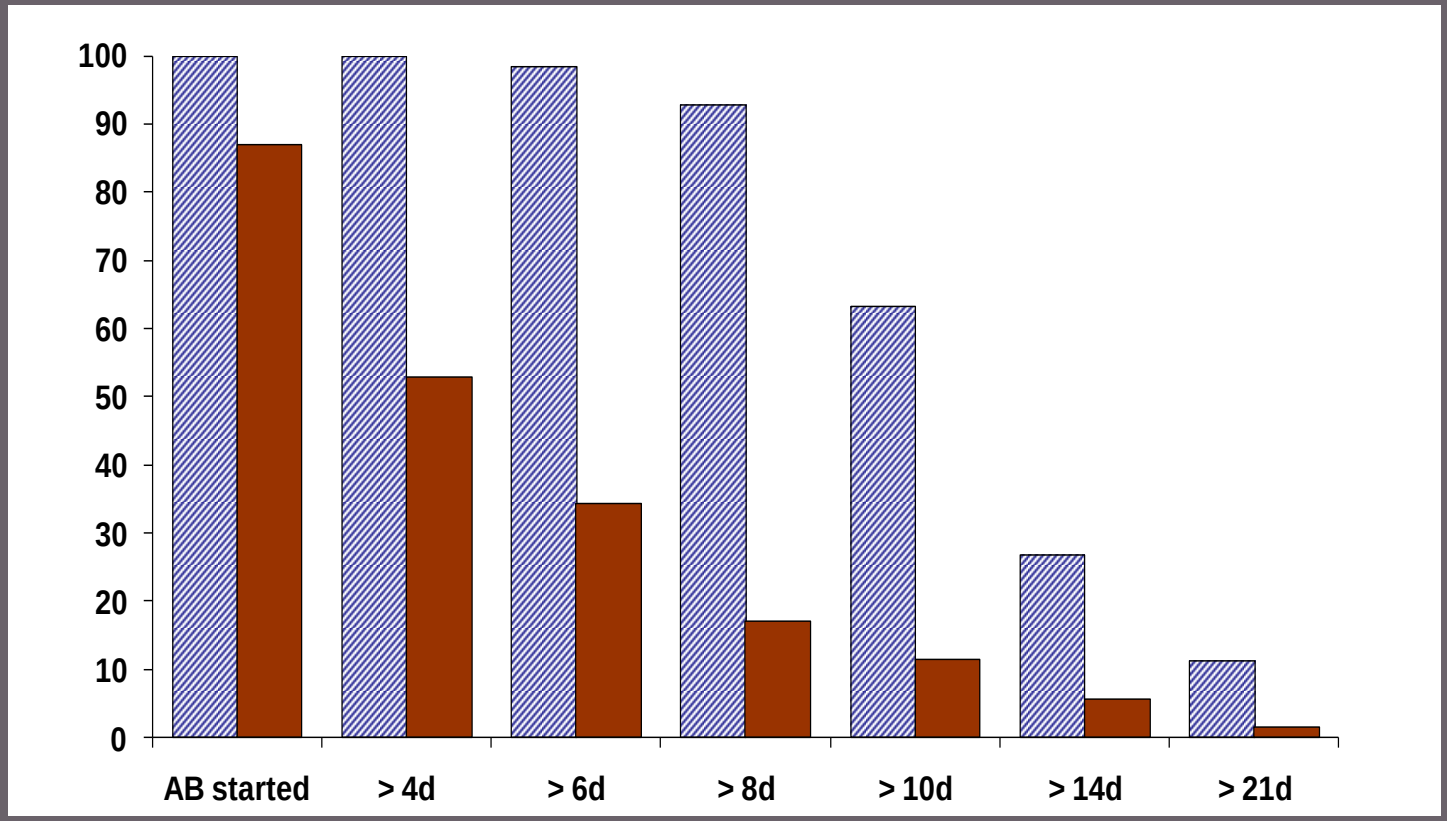
The ProResp-Study
Antibiotic Use in LRTI 83% → 44%



Christ-Crain M et al, Lancet 04

The ProCAP* Study – Antibiotic Duration





***Community Acqu Pneumonia**

Christ-Crain M et al, Am J Respir Crit Care Med 2006

Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD
Mirjam Christ-Crain, MD
Robert Thomann, MD
Claudine Falconnier, MD
Marcel Wolbers, PhD
Isabelle Widmer, MD
Stefanie Neidert, MD

Context In previous smaller trials, a procalcitonin (PCT) algorithm redu
otic use in patients with lower respiratory tract infections (LRTIs).

Objective To examine whether a PCT algorithm can reduce antibiotic exp
out increasing the risk for serious adverse outcomes.

Design, Setting, and Patients A multicenter, noninferiority, rando
trolled trial in emergency departments of 6 tertiary care hospitals in Switz
an open intervention of 1359 patients with mostly severe LRTIs randomiz
October 2006 and March 2008.

JAMA 2009; 302: 1059-66

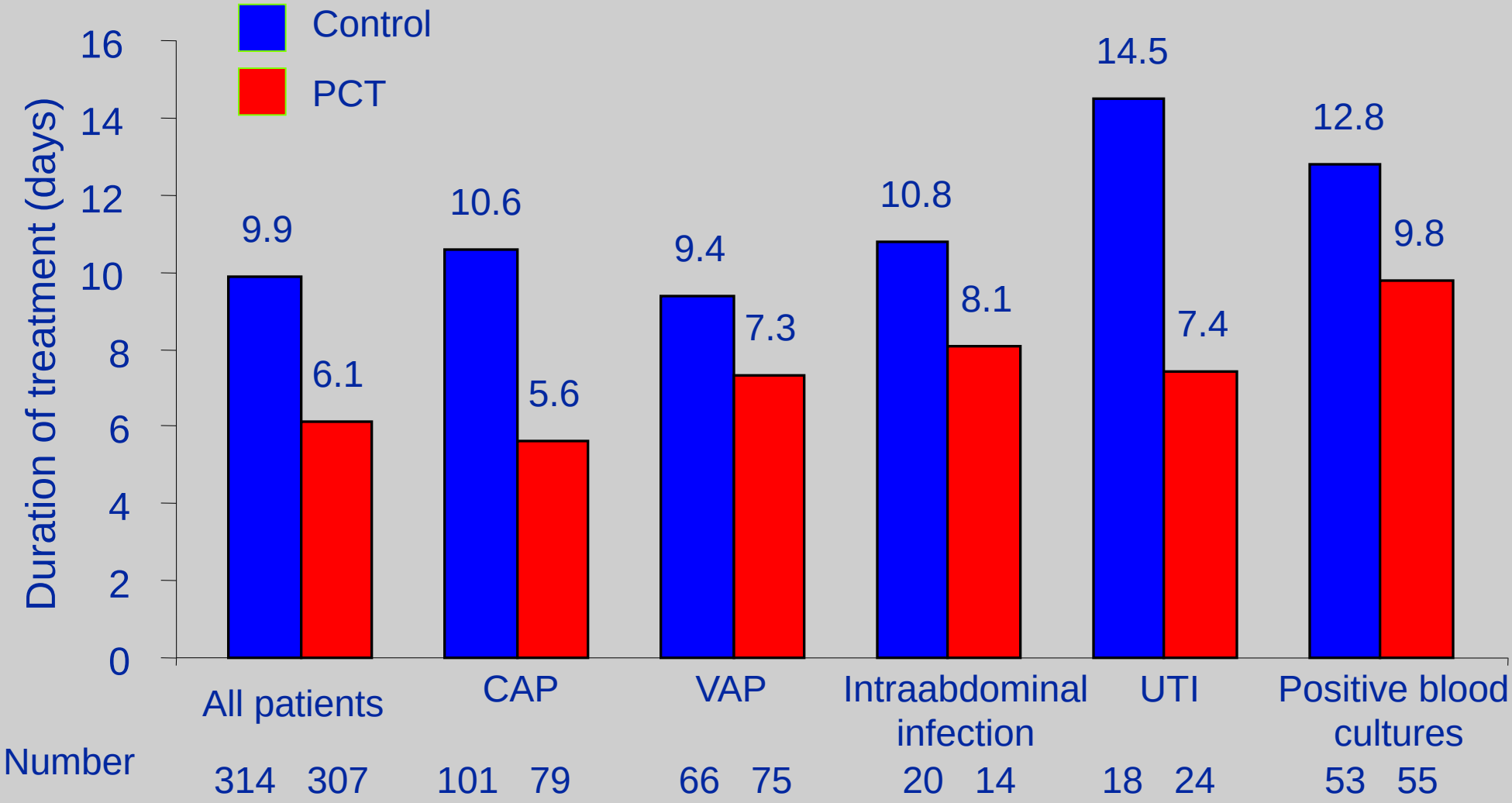
-- 09.09.09 --

ProHOSP: Main Results

- In the PCT group, antibiotic exposure significantly lower than controls (35% reduction, $p<0.001$)
- Antibiotic-associated side effects less frequent in the PCT group (19.8% vs. 28.1%; $p<0.001$)
- BUT rate of adverse outcomes similar in PCT and control group (15.4% vs. 18.9%)

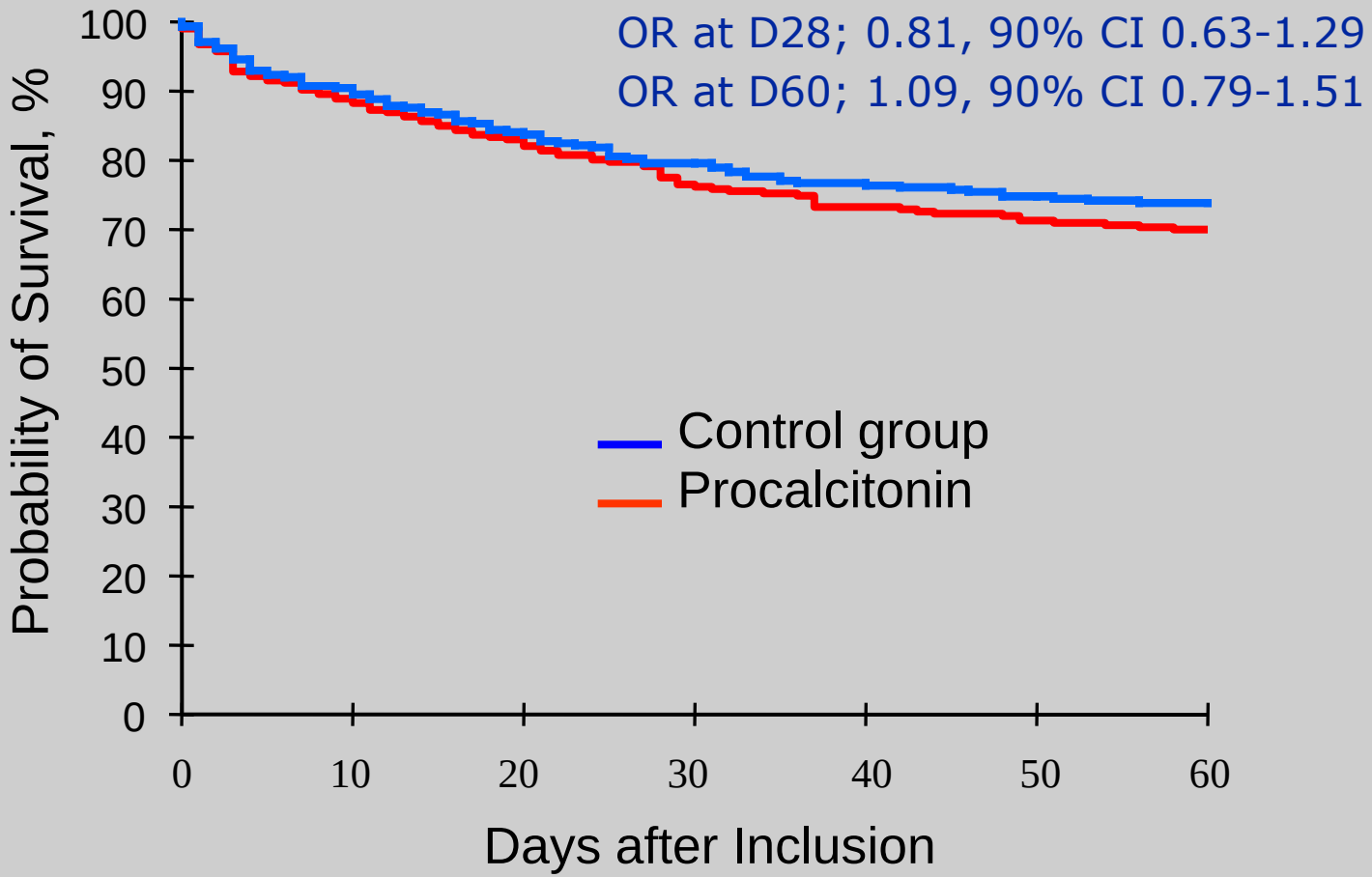
Schuetz P et al. JAMA 2009; 302: 1059-66

Procalcitonin Use to Shorten ICU Antibiotic Exposure: The ProRata Trial *Bouadma et al. Lancet 2010*



The ProRata Trial: No difference in survival despite lower AB use

Bouadma et al. Lancet 2010



Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review

Clinical Infectious Diseases 2011;53(4):379–387

Rajender Agarwal[1] and David N. Schwartz[2,3]

- Appears to decrease AB ICU use
- MAY decrease length of stay
- Limited role for the starting of Antibiotic treatment
  - 28% of proven infections had PCT < 0.25 (False negatives)
  - 29% of non-infected patients with PCT >1 (False positives)

BC Comment: Ignore Gram positive issues!

Conclusions PCT

- PCT is not a perfect biomarker,
  but currently the most effective tool to:
  - Individualize antibiotic use
  - Reduce AB treatment duration in the hospital setting

- Obviously, any infection is far too complex to be reduced to a single cutoff of any biomarker.

Measurement of Interleukin 8 in Combination With C-Reactive Protein Reduced Unnecessary Antibiotic Therapy in Newborn Infants: A Multicenter, Randomized, Controlled Trial

Pediatrics 2004;114:1– 8

Axel R. Franz, MD*; Karl Bauer, MD‡; Andreas Schalk, MD§; Suzanne M. Garland, MD‖; Ellen D. Bowman, MD¶; Kerstin Rex, MD#*; Calle Nyholm, MD**; Mikael Norman, MD‡‡; Adel Bougatef, MD§§; Martina Kron, PhD‖‖; Walter Andreas Mihatsch, MD*; and Frank Pohlandt, MD*, for the International IL-8 Study Group

Use both markers

- Together they significantly ($p<0.001$) reduced unnecessary antibiotic use

Intervention Group	Control Group
237/656 (36%)	315/635 (50%)

- Interleukin 8 better in early infections
- CRP in later infections

Agenda

- Procalcitonin:
  - Findings from recently published RCTs

- **Update on rapid (molecular) diagnostic tools for diagnosis of severe infections and guiding antimicrobial stewardship (few studies of the latter)**

Potential Benefits of Rapid Diagnostics

- Better patient outcomes (less morbidity/mortality)
- More effective infection prevention and control
- Reduction in empirical antimicrobial prescriptions
  - Preservation of broad spectrum antimicrobials
  - Reduction in duration and costs of treatment
  - Overall reduction antimicrobial usage and
  - Levels of resistance ?????
    Most antibiotics are used in agriculture and aquaculture so we should be as focused there as we are in humans!

Rapid diagnosis to inform IPC and ASt

- Technical challenges
  - Rapidly improving landscape e.g. new generation MALDI-TOF, cassette systems with IT to laboratory
  - Molecular assays do not thus far replace blood cultures
- Costly: potential savings due to rapid identification of organisms without a laboratory
- IPC & ASt: studies underway: experts are the best advocates to implement and help justify

Molecular diagnosis of bloodstream infections: planning to (physically) reach the bedside

N. Leggieri[a], A. Rida[b], P. François[c] and Jacques Schrenzel[a,c]

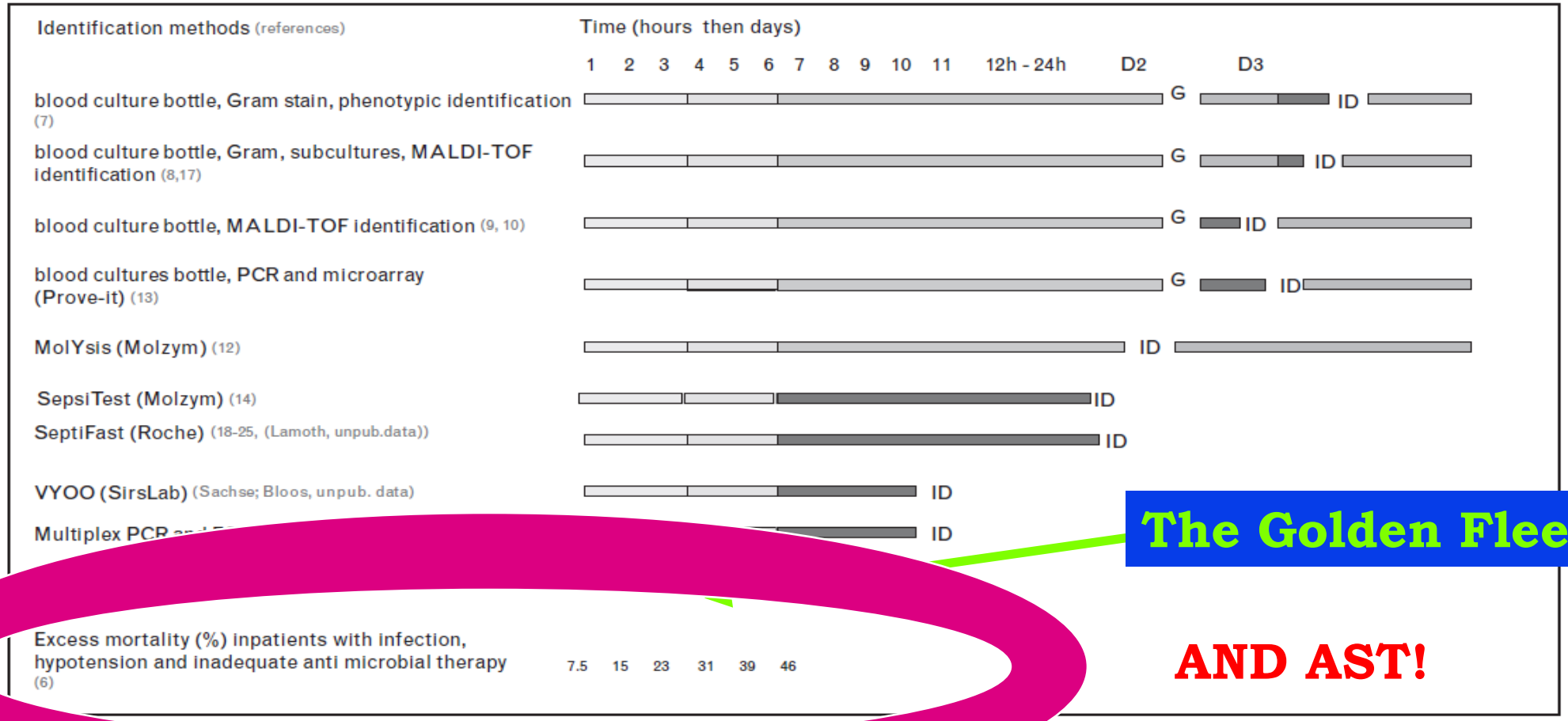
Current Opinion in Infectious Diseases 2010, 23:311–319

- Commercial PCR-based techniques have improved with the use of bacterial DNA enrichment methods, challenging bacterial culture

- Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS): standard diagnostic procedure on cultures in many European tertiary care centres

• Change in clinical practice?
Need real-life applicability & robust clinical-impact oriented studies.

Figure 1 Identification methods and time for reporting results



The Golden Fleece

AND AST!

, between working hours; , culture;

ionization time-of-flight (MALDI-TOF) or point-of-care technologies (POCT).

N. Leggieri[a], A. Rida[b], P. François[c] and Jacques Schrenzel

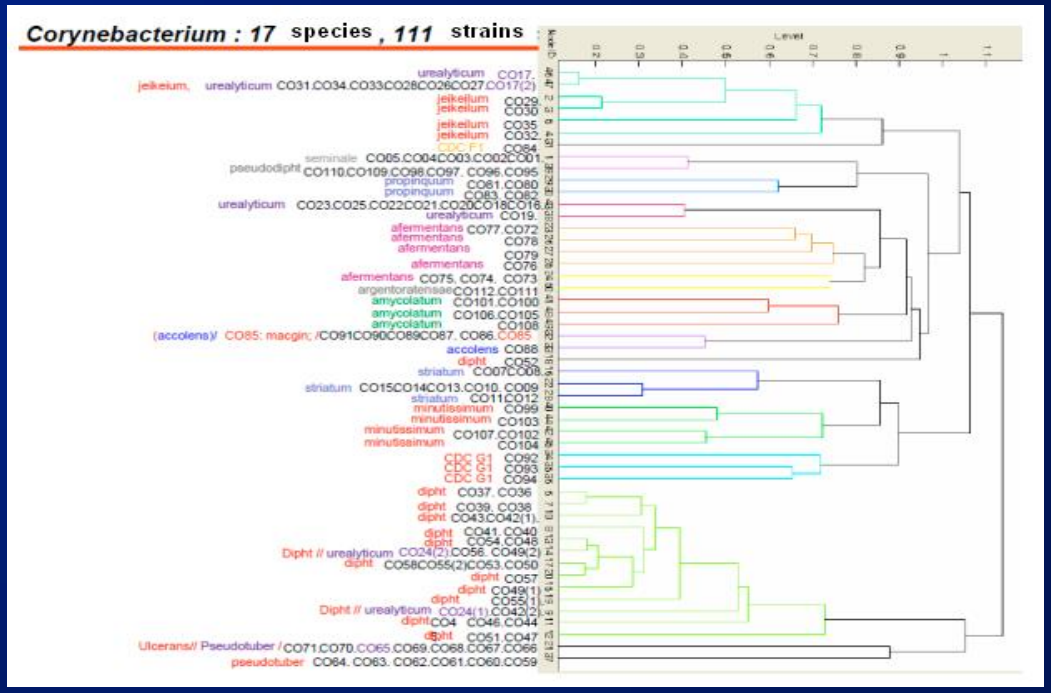
Current Opinion in Infectious Diseases 2010, 23:311–319

Clinical experience with Maldi-TOF

	Samples	n	Correct identification	
La Scola B. 2009	BC- Bactec 9240	562	76	G +/- 67%/94%
Stevenson LG. 2010	BC- Bactec 9240	212	80	**Poor *S mitis***
Prod'hom G. 2010	BC- Bactec Plus	126	78.7	**Poor S pn**
Ferroni A. JCM 10	BC- Bact/Alert	312	91	S.a. vs CNS 100%
Christner M JCM 10	BC- Bactec Plus	304	95	S.a better AN bottles
Risch M. 2010	BC, urine, genital, wounds, etc	204	87	**Poor S pn**
Moussaoui W. 2010	BC- Bactec 9240	503	90	G +/- 89%/91%
Ferreira L. 2011	BC- Bactec 9240	330	NR	G +/- 31.8%/83% Poor Candida detection

Maldi-TOF potential

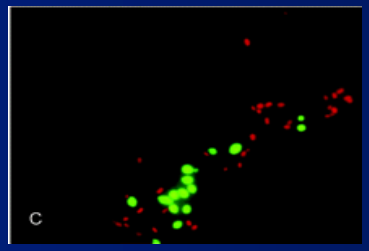
- Genotyping
- Different samples
- Resistance
  - R marker protein
  - Degradation of Ab
  - Induced R marker
- Fungus, virus, parasites
- Virulence
- Quantification?



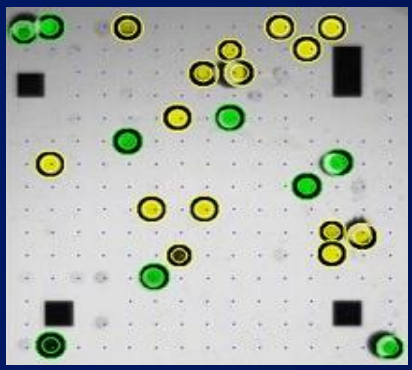
RESEARCH IS ONGOING

Need larger databases

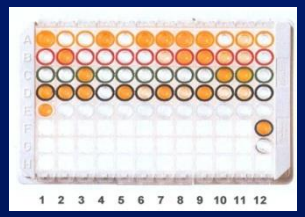
New Diagnostic Methods in sepsis

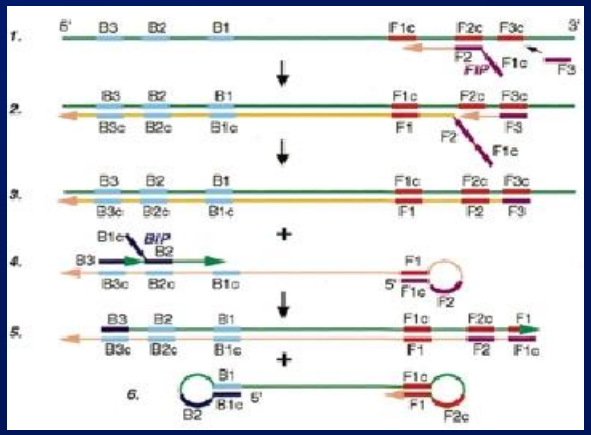


- Hybridisation:
  - → oligonucleotide – FISH
  - → Peptide Nuc. Acid -FISH (PNA FISH)



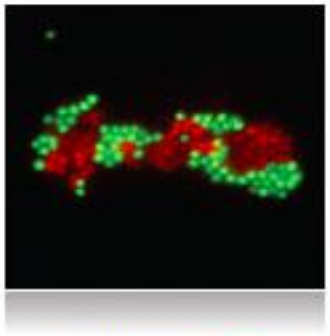
- Amplification & arrays
  - → Prove-it™ Sepsis
  - → Hyplex Bloodscreen
  - → LAMP
  - → SeptiFast



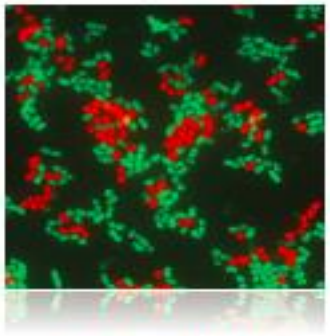


Specific organism identification using molecular methods

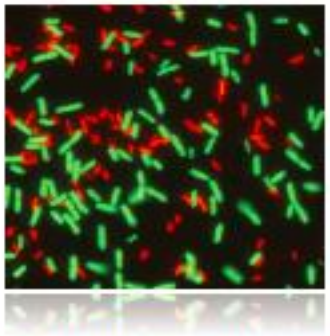
PNA-FISH



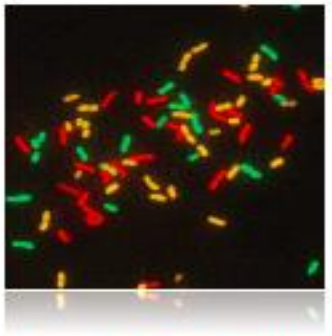
S. aureus/CNS



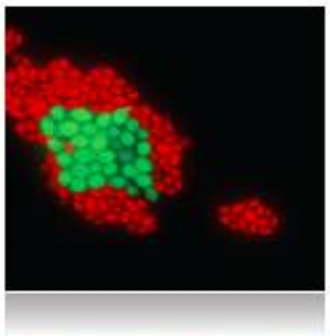
E. faecalis/OE



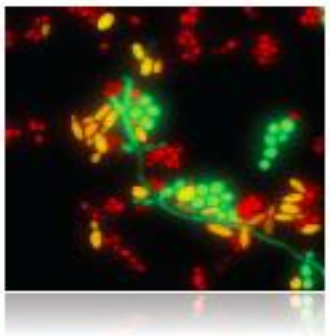
E. coli/*P. aeruginosa*



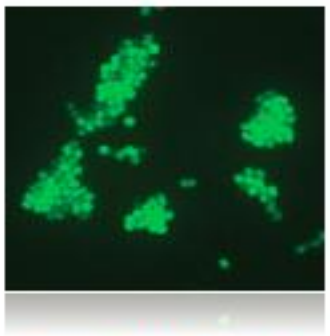
GNR Traffic Light®



C. albicans/*C. glabrata*



Yeast Traffic Light®



GBS PNA FISH®

http://www.advandx.com

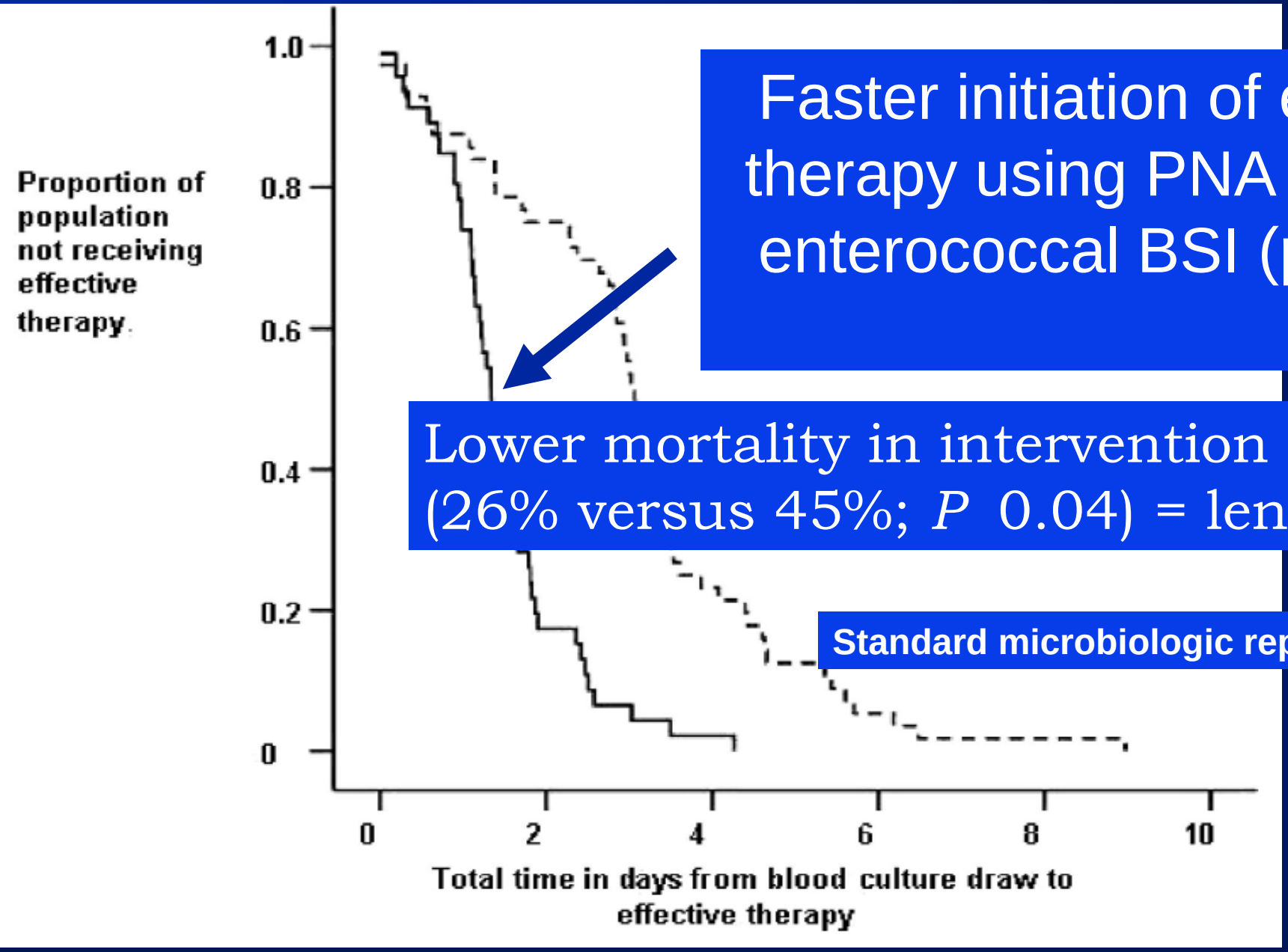
Impact of PNA FISH for rapid identification of presumed coagulase-negative staphylococci (CNS) pseudobacteraemia with no ASt

Study design: A retrospective, pre-post FISH study in patients with CoNS in the absence of active ASt intervention.

Results:

- **NSD mean days Vancomycin Rx (4.15/3.5d <>)**
- **NSD overall hospital LOS**
- ***S. aureus PNA FISH™ assay* when implemented without active reporting of results or additional support from an antimicrobial stewardship team did not reduce LOS or vancomycin use**

Holtzman C, Whitney D, Barlam T, Miller NS.
J Clin Microbiol. 2011;49:1581-2.



Forrest GN et al. AAC 2008; 52: 3558-3563

Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study

Päivi Tissari, Alimuddin Zumla, Eveliina Tarkka, Sointu Mero, Laura Savolainen, Martti Vaara, Anne Aittakorpi, Sanna Laakso, Merja Lindfors, Heli Piiparinen, Minna Mäki, Caroline Carder, Jim Huggett, Vanya Gant

Amplification with Prove-itTM

Interpretation Definitive identification of bacterial species with this microarray platform was highly sensitive, specific, and faster than was the gold-standard culture-based method. This assay could enable fast and earlier evidence-based management for clinical sepsis.

Tissari P et al. Lancet 2010

Prove-it™ Sepsis in clinical setting: Benefits

- Covers +/- 90% of all bacterial sepsis cases
- Reliable bacterial identification 16-20 hours earlier than with conventional techniques
- Examples of clinical benefits:
  - Direct identification of MRSA or MSSA or CNS
  - Distinguishing *E. faecium*, *E. faecalis* or streptococci
  - Detection of autolyzed *S. pneumoniae*
  - *Enterobacteriaceae* or *Pseudomonas* or *Acinetobacter* or *Stenotrophomonas*
  - *E. coli* or *Klebsiella* or *ampC* producers
- Easy to implement into laboratory routine
- No IPC or ASt exploration

LightCycler® SeptiFast (Roche Molecular Systems)

Diagnostic Performance of a Multiple Real-Time Polymerase Chain Reaction Assay in Patients with Suspected Sepsis Hospitalized in an Internal Medicine Ward

- NSD from blood cultures in 391 prospective cases (242 SIRS compliant) even though some pathogens not included in database
- **Useful in addition to BC especially where antibiotic Rx patients**
- **ASt and IPC NOT formally evaluated e.g. what to do with sole PCR positive patients, some negative patients (technical failures?)**

Pasqualini L et al. J Clin Microbiol. 2012;50:1285-8

DNA Technologies
Towards Point of Care (POC)

- Cepheid GeneXpert
  - Cassettes: include TB; MRSA;
    Carb resistance rectal swabs soon (KPC, VIM, NDM)
- Curetis UnyVero
  - Cassettes <4h
  - Developing implant; bloodstream & TB
    Diverse list of resistance genes – *mecA*, macrolides,
    ESBLs, KPC, OXA-51, integron markers, FQ^R mutations
  - No validation yet

DNA POC Technologies

Nanosphere Verigene

- Bloodstream in ~2.5h, respiratory tract and gastrointestinal tract
- Gram pos; *mecA*, *vanA*, *vanB*
  FDA cleared but streptococcal identification problems
- Gram-negative: KPC, NDM, IMP, VIM, CTX-M, OXA. No evaluation available yet

DNA POC Technologies
UCL FP7 funded "RiD-RTI" project

- Integrated sample prep, cartridge based
- PCR & microarray detection
- Answer in < 2 hours & ability to scale up
- Community & Hospital acquired pneumonia
  - *S. aureus* & Gram negatives
  - Comprehensive ESBL and carbapenamase detection (CTX-M, TEM, SHV, IMP, VIM, KPC, NDM, OXA), *mecA*
  - Opportunistic fungal, bacteria and viral infections

RCT: Faster TAT for Vitek ID (13h) and AST (22h)

Journal of Antimicrobial Chemotherapy (2008) **61**, 428–435
doi:10.1093/jac/dkm497
Advance Access publication 21 December 2007

JAC

Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use

J. J. Kerremans[1]*, P. Verboom[2], T. Stijnen[3], L. Hakkaart-van Roijen[2], W. Goessens[1], H. A. Verbrugh[1] and M. C. Vos[1]

[1]Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Centre, Rotterdam, The Netherlands; [2]Institute for Medical Technology Assessment, Erasmus University Medical Centre, Rotterdam, The Netherlands; [3]Department of Epidemiology and Biostatistics, Erasmus University Medical Centre, Rotterdam, The Netherlands

6 less DDDs… no impact on overall mortality!

M. Bruins · H. Oord · P. Bloembergen ·
M. Wolfhagen · A. Casparie · J. Degener · G. Ruijs

Lack of effect of shorter turnaround time of microbiological procedures on clinical outcomes: a randomised controlled trial among hospitalised patients in the Netherlands

Eur J Clin Microbiol Infect Dis (2005) 24: 305–313
DOI 10.1007/s10096-005-1309-7

No clinical benefits from shorter Vitec 2 ID & AST TAT!

(i) mortality, (ii) length of hospital stay, (iii) length of ICU stay, (iv) number and costs of diagnostic procedures, (v) costs of antimicrobial agents, and (vi) special care (e.g. artificial respiration, lines)

Momentum BioScience

01 Mar 2013

Momentum BioScience completes feasibility study on antimicrobial susceptibility product

Enzymatic Template Generation & Amplification (ETGA) technology to detect DNA polymrase extension- polymerase chain reaction in a rapid antimicrobial susceptibility test (AST): Zweitzig et al, Nuc Acids Res, 2012, 1–12

doi:10.1093/nar/gks316

- Feasibility in spiked blood cultures including Gram +/- bacteria and fungi
- Measures AST via the difference in microbial enzyme activity in the presence of various antimicrobial compounds (~4hr)

Conclusions: New assays for rapid bacterial diagnosis/sepsis

- Can provide data more rapidly
- Could increase detection sensitivity
- At a given cost (tech time, reagents): look outside lab too!

BUT

- Critical examination needed: e.g. added value?
- Clinical significance remains to be determined
- Shorter TAT ?
- Antimicrobial Stewardship:
  estimate potential for different test strategies on adequacy of antibiotic therapy and patient outcomes (balancing measures)

Conclusions: New assays for rapid bacterial diagnosis/sepsis

Could be useful in particular settings:

- Bugs: difficult to grow?
- Infections: Antibiotic-pretreated patients?
- Increased sensitivity:
  Neonatal sepsis? Endocarditis?

Jeyaratnam et al, 2008	London, UK	General Wards; Cross Over	Commercial PCR admission & discharge	NSD in acquisitions
Hardie et al, 2010	Birmingham UK	Surgical Wards; Cross Over	Commercial PCR admission & discharge	Less MRSA acquired
Harbarth et al, 2008	Geneva, Switzerland	Surgical Wards; Cross Over	In-House PCR admission	NSD in MRSA infections. Acquisition ? Showed huge delays in action on the ward
Robicsek et al, 2008	Chicago, USA	ICU & Whole Hospital: Sequential ITS	Commercial PCR admission	Reduced MRSA infections. Acquisition ?

Extra comments for previous slide

- Check the Equator www site for evidence base
- In the studies check wheter the unded staff were involved in ensuring the specimens came to the lab quickly and reports were sent to the wards asap and even whether they also checked the ICT staff responded!

Cost-effectiveness of universal MRSA screening on admission to surgery

Murthy et al, CMI, 2011:16; 1747-1753

- Modelled their previous study data (Harbarth et al, 2008) and found:
  - PCR is cost effective at their MRSA endemic admission rate
  - If rate falls less effective than risk based isolation and culture screening
  - Ineffectiveness perhaps due to on-going transmissions whilst awaiting results?

- Bedside testing may be a way forward

- Local analysis and decision making is required

"It makes no sense to use twenty-first century technology to develop drugs targeted at specific infections whose diagnosis is delayed by nineteenth-century methods."

Nathan C. Antibiotics at the crossroads.
Nature 2004;431:899-902

Acknowledgements

Some of the slides were prepared for ESCMID ESGAP workshops. I am a member of the group that delivers the lectures.

Input into those slides came from: S Harbarth (CH), J Ramón Paño (E) , B. Müller (CH), P. Eggimann (CH), G. Ieven (B), P. Munoz (E) and J. Chastre (F)