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Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

La «Fast Microbiology» applicata alla sepsi: prospettive ed opportunità

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AMCLI associazione microbiologi clinici italiani

Associazione Culturale Giuseppe Dossetti – Tutela e sviluppo dei diritti

SIM Società Italiana di Microbiologia

GIORNATA MONDIALE DELLA SEPSI

Diagnosi e gestione clinica della sepsi

Giovedì, 13 settembre 2018

ore 9.00 – 17.00

Sala Capitolare
Chiostro del Convento di Santa Maria sopra Minerva
Presso il Senato della Repubblica
Piazza della Minerva, 38 - Roma

Con il patrocinio di

SIAPIOS

SEPSI CHIRURGIA

Rapid diagnostic tests: the John Bartlett's game changers in infectious diseases

- We concur with Dr. John Bartlett, retired infectious diseases physician, who stated in 2010 that rapid diagnostic tests are 'game changing' in the management of infectious diseases.
- However, in 2018, we concur with a modification of his statement as suggested by Bauer and Goff, that is: "Rapid diagnostic tests and antimicrobial stewardship economics will 'change the game' of managing patients with infectious diseases."

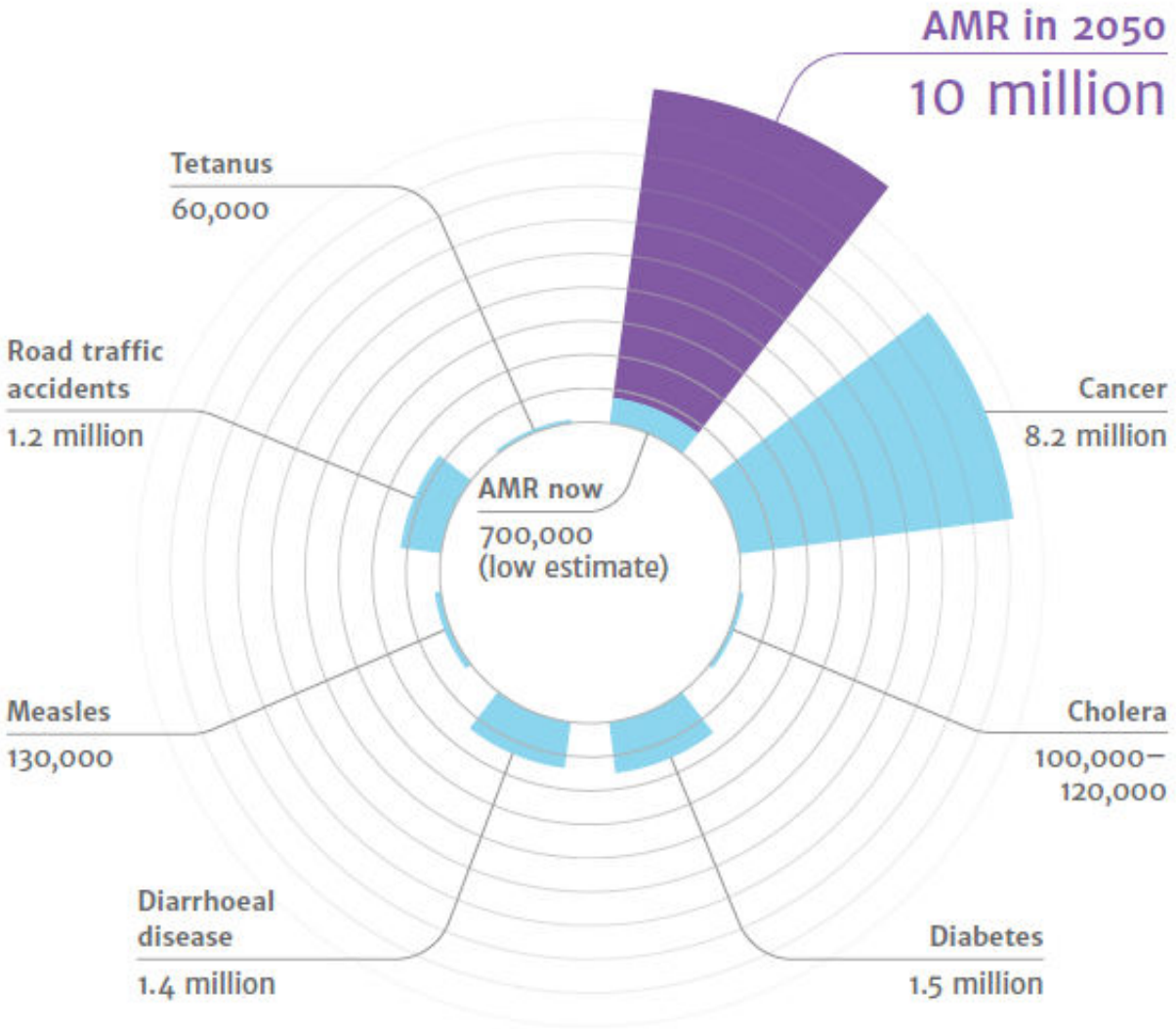
Bartlett, Medscape, 2011
Bauer and Goff, CID, 2015

Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL

MAY 2016



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stop sepsis save lives

Every few seconds someone dies of sepsis.

Sepsis arises when the body's response to an infection injures its own tissues and organs. It may lead to shock, multiple organ failure, and death, especially if not recognized early and treated promptly.

A global burden: Sepsis is one of the most common but least recognized diseases.



~ 27,000,000
people per year develop sepsis

~ 19,000,000
people per year survive

Survivors
may face lifelong complications

~ 8,000,000
people per year die

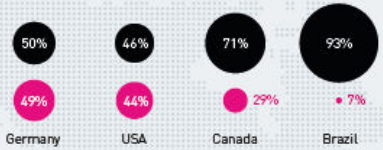
~ 6,000,000
neonates and children under five die of sepsis[1]

Maternal Death
Sepsis is one of the most common causes

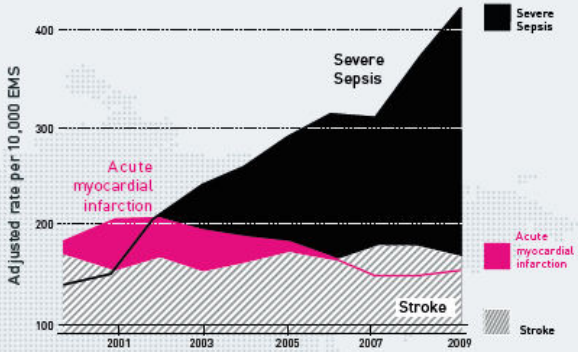
Everybody
can develop sepsis following an infection

Have you ever heard the term "Sepsis"?

NO / YES



Changes in the rates of hospitalizations with severe sepsis among emergency medical services[2]



Sepsis is one of the most common diseases[3]
Cases per 100,000 population (US/ *Europe)

US$ in millions spent for state-funded research in 2011

Sepsis research receives the lowest funding[4]



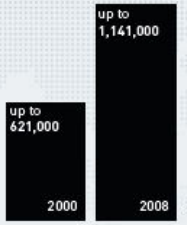
Sepsis is one of the most expensive conditions treated in the US and Germany[5]



US$ 20,298,000,000
have been spent in US hospitals in 2011

€ 5,000,000,000
estimated economic burden due to direct costs of sepsis in Germany per year

People hospitalized with sepsis in US[6]



Children hospitalized with sepsis in US[7]
per year

~20,000 to 40,000

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European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3292-9

ORIGINAL ARTICLE

Incidence and antimicrobial resistance trends in bloodstream infections caused by ESKAPE and *Escherichia coli* at a large teaching hospital in Rome, a 9-year analysis (2007–2015)

Giulia De Angelis[1] · Barbara Fiori[1] · Giulia Menchinelli[1] · Tiziana D'Inzeo[1] · Flora Marzia Liotti[1] · Grazia Angela Morandotti[1] · Maurizio Sanguinetti[1] · Brunella Posteraro[2] · Teresa Spanu[1]

Published online: 09 June 2018

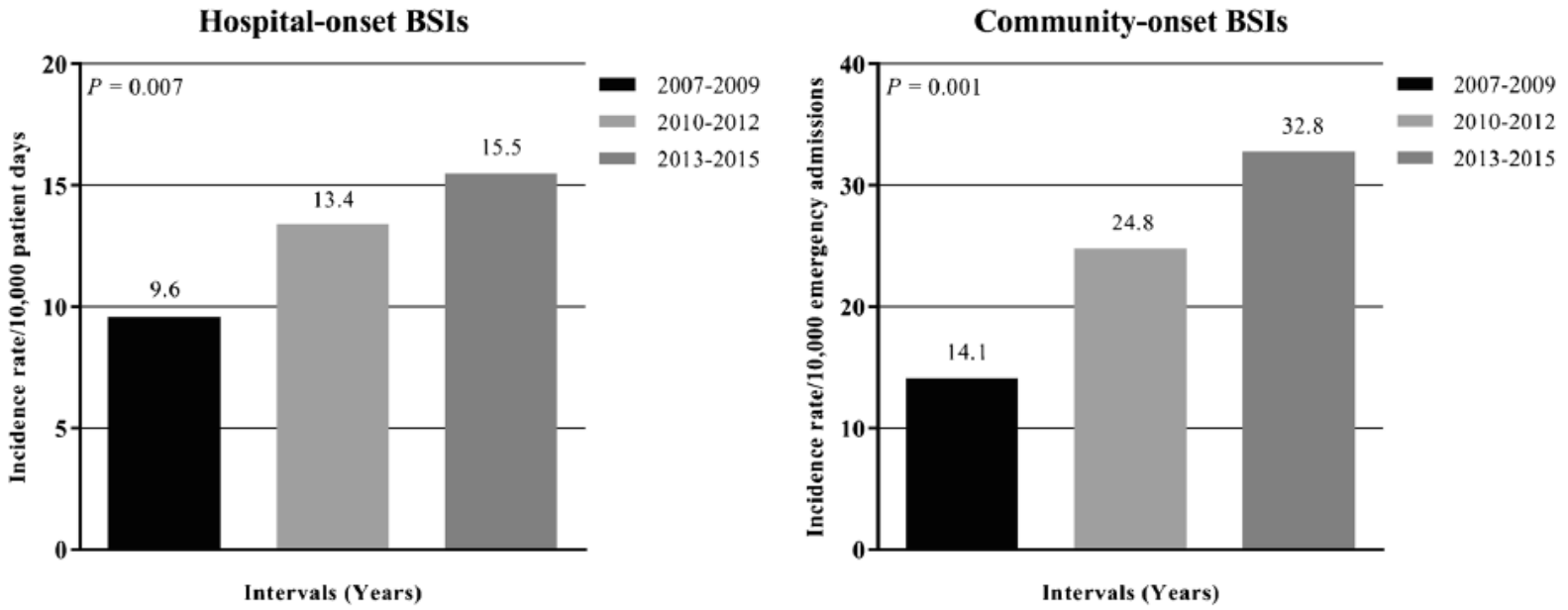


Fig. 1 Incidence rates of bloodstream infections (BSIs) in three 3-year intervals (2007 to 2015), according to the onset (hospital or community) of BSI

When the Laboratory is the POC: How do we

- Determining how such POC tests would best incorporated into clinical diagnostic algorithms
- Determining the clinical and economic benefits of a syndrome-based testing approach
- On this basis we selected the following tests:
  - T2 magnetic resonance
  - Automated microscopy (Accelerate Diagnostics)
  - β-D-glucan detection
  - Multiplex PCR (FilmArray, Unyvero, etc.)
  - LFIA tests (*Legionella*, *S. pneumoniae*, RSV)
- And these clinical syndromes
  - Sepsis (Target 1, implemented)
  - Gastroenteritis (Target 2, implemented)
  - Pneumonitis (Target 3, in progress)
  - Meningitis (Target 4, in progress)

Sanguinetti, unpublished

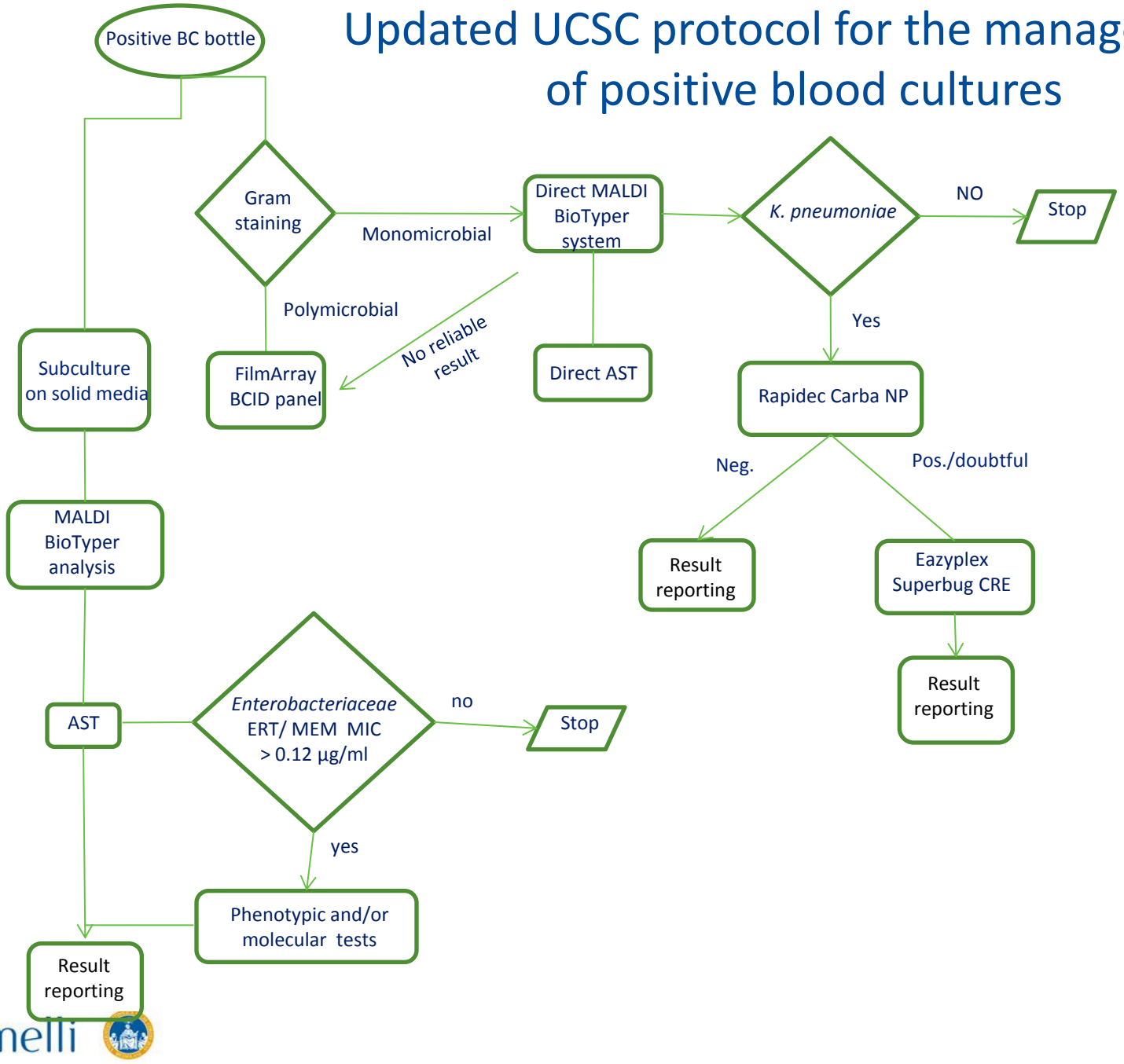
When the Laboratory is the POC: possible outcomes

- Better management of severe infections (e.g., sepsis) and reduction of the associated mortality
- Increased money reducing the length of stay and the use of antibiotics/antifungals
- Better real-time assessment of the local microbial epidemiology of the Hospital and to establish efficacious guidelines for the antimicrobial (empirical) therapy

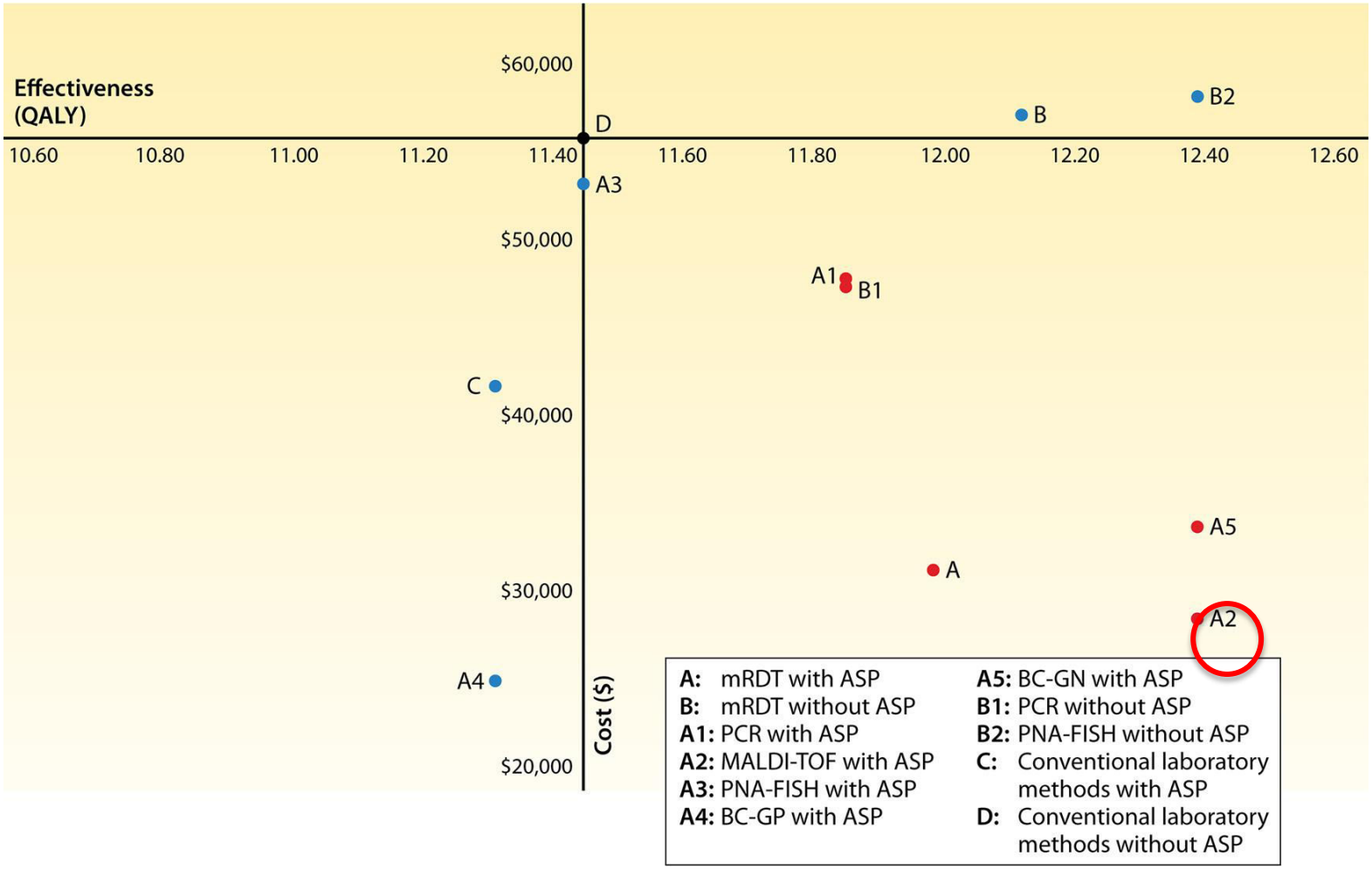
Target 1: Sepsis

- Objectives of the project
  1. To speed up the “classical” blood culture workflow including POC or POC-like tests (MALDI-TOF mass spectrometry, FilmArray, Accelerate Pheno, molecular methods to detect genes involved in drug resistance)
  2. To implement rapid tests for the detection of microbial and fungal pathogens directly from blood
  3. To include the β-D-glucan detection in an integrated diagnostic algorithm for the rapid de-escalation of antifungal therapy

Updated UCSC protocol for the management of positive blood cultures



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- **Cost-effectiveness plane for rapid identification of blood cultures using molecular methods and MALDI**.
- The y axis represents the average cost of a strategy, while the x axis represents the average effectiveness of a strategy.
- Cost-effective strategies are depicted with red markers, the baseline strategy is depicted with a black marker, and the remaining strategies that are suboptimal or not cost-effective are indicated with blue markers.

Pliakos et al., CMR, 2018

The GRES (Gestione Rapida Emocolture Sepsi) study

	Total N=743	Study period 1 N=197	Study period 2 N=233	Study period 3 N=313	*P*-value
Mean time to start antibiotic therapy (SD), days	0.70 (1.4)	0.92 (1.7)	0.71 (1.4)	0.55 (1.1)	0.01
Percentage of effective therapy at the start of antibiotic therapy (SD)	92.6 (18.2)	93.9 (19.0)	91.4 (21.1)	92.6 (15.2)	0.37
Percentage of optimal therapy at the start of antibiotic therapy (SD)	62.2 (38.9)	59.0 (42.0)	51.9 (43.0)	71.9 (30.6)	<0.001
Mean duration of antibiotic therapy (SD), days	19.3 (13.3)	21.9 (15.4)	19.3 (13.3)	17.7 (11.5)	0.002
Mean length of hospital stay (SD), days	26.5 (24.5)	29.7 (29.3)	26.8 (24.7)	24.2 (20.7)	0.04
Died at 30 days, n (%)	118 (15.9)	31 (15.7)	39 (16.7)	48 (15.3)	0.90

Study Period 1: the ID physician was called by a ward physician when patients had positive blood cultures.
Study Period 2: the ID physician were called directly by the microbiologist immediately after a pathogen was isolated from blood culture.
Study Period 3: the ID physician was called by the microbiologist immediately after a pathogen was identified from the blood culture, and all cases were re-evaluated at bedside 72 h after starting antibiotic therapy in order to optimize therapy

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Murri et al., Diag. Microbiol. Infect. Dis., 2018

Molecular detection of resistance

- Identification of microbial genes related to drug resistance directly from clinical specimens or from positive blood cultures (to reduce the time-to-result)
- Reduction of the time to appropriate antibiotic treatment (escalation or de-escalation therapy)
- Easy to use
- Relatively few genes included in the proposed panels
- Expensive (?)

New Drugs anti-CRE

Ceftazidime Avibactam	**KPC**	**OXA-48**		
Imipenem Relebactam	**KPC**			
Meropenem Vaborbactam	**KPC**			
Aztreonam Avibactam	**KPC**	**OXA-48**	**VIM**	**NDM**
Plazomicin	**KPC**	**OXA-48**	**VIM**	

Importance of identification of the resistance mechanism for antimicrobial stewardship purposes

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Courtesy: Prof. G.M. Rossolini

Rapid Identification of *Escherichia coli* and *Klebsiella pneumoniae* Producing CTX-M and Carbapenemases in Positive Blood Cultures Combined with Bedside Infectious Disease Consultation is Associated with Very Early Initiation of Adequate Antimicrobial Therapy

- We evaluated the performance and the advantages of a PCR-based rapid detection of bla_{CTX-M}, bla_{KPC}, bla_{VIM}, bla_{OXA-48} and bla_{NDM} genes (Eazyplex® SuperBug CRE) after direct detection of *E. coli* and/or *K. pneumoniae* using MALDI BioTyper and/or FilmArray BCID panel.
- We analyzed 425 cases of bloodstream infections with positive blood cultures (BCs).
- Resistance genes were detected in 43.5% (191/439) of the isolates with an overall agreement with the culture results of 100%.
- Total time to identification (median) of the direct method was 18 h (IQR, 8-23 h) versus 46 h (IQR, 36-68.8 h) ($P<0.001$) with the culture-based method.
- The therapeutic impact of the rapid strategy was evaluated in 327 cases.
- All these patients received an empirical treatment after BC collection, but it was inadequate in 58.1% of the cases.
- After real-time communications and bedside infectious disease interventions, 82.1% of the patients with inadequate therapy were switched to an effective coverage at a median time of 20 h (IQR, 10.3 to 25 h) from the starting of diagnostic procedure.

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Spanu et al, unpublished

T2Dx: Rapid Identification of Sepsis-Causing Pathogens

T2Dx®



- As low as 1 CFU/mL LoD
- Easy to operate
- Minimal hands-on time
- Results in hours

T2Bacteria®

Sensitivity: 95.8%[1]
Specificity: 98.1%[1]

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Escherichia coli*

T2Candida®

Sensitivity: 91.1%[2]
Specificity: 99.4%[2]

- *Candida albicans*
- *Candida tropicalis*
- *Candida krusei*
- *Candida glabrata*
- *Candida parapsilosis*

1. T2Bacteria Pivotal Clinical Study.
2. Mylonakis, E., Clancy, C.J., Ostrosky-Zeichner, L., et al. (2015). T2 Magnetic Resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clinical Infectious Diseases, 2015

The T2 Magnetic Resonance (T2MR) system





- The T2Dx, an automated instrument platform, uses T2 magnetic resonance (T2MR) technology, to provide a “sample-to-result” clinical diagnostic test. The test was designed to enable multiplex detection, of ESKAPE pathogens, which comprise *Escherichia coli* instead of *Enterobacter* species, and are hereafter designated as ESKAPE* pathogens, with a single whole blood sample
- In addition, T2MR is able to accurately identify *Candida* pathogens in whole blood faster and easier than blood culture-based diagnostics.
- T2Candida and T2Bacteria are cleared by the US FDA and EMA for the diagnosis of bloodstream infections.

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Pfaller et al., Future Microbiol, 2016

T2Dx *Candida* panel

- T2MR demonstrated an overall specificity per assay of 99.4% with a mean time to negative result of 4.2 ± 0.9 hours. The overall sensitivity was found to be 91.1% (96.6% considering also other studies) with a mean time of 4.4 ± 1.0 hours for detection and species identification[1]

- Significant reduction of the time to appropriate therapy (from 20 to 28 hours)[2,3]
- Significant reduction of the time to detection of *Candida*[2]
- Significant reduction of the ICU length of stay[2]
- Significant reduction in antifungal consumption[3]
- Strong indicator of complications and poor outcomes[4]

1. Mylonakis E, et al. CID. 2015
2. Wilson et al, ID Week 2016
3. Patch et al., CMI, 2018
4. Munoz et al., CMI, 2018

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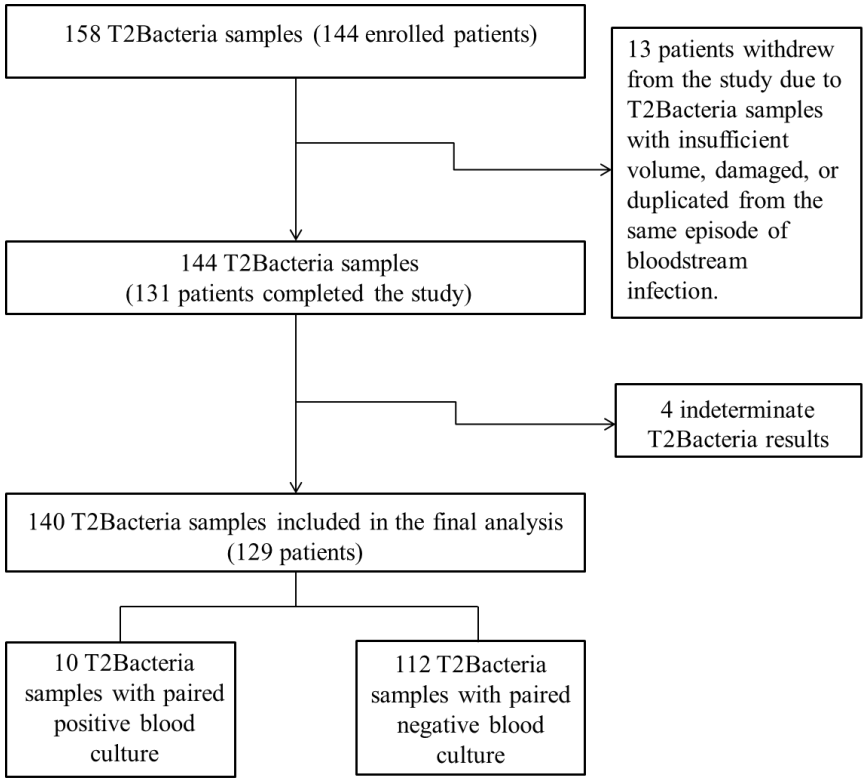
Performance of T2Bacteria Panel for rapid identification of bacteria responsible of bloodstream infections

Positive results more than 4.5 times faster: Positive results for a bacterial infection with T2Bacteria were available in 5.5 hours, compared to a mean time of 25 hours for blood culture. Every hour of providing targeted therapy to patients faster can reduce patient mortality rates by 7.6%.

Negative results 20 times faster: A negative result took 120 hours (5 days) for blood culture, compared to 6.1 hours with the T2Bacteria Panel.

Excellent accuracy: The T2Bacteria Panel had 89.5% sensitivity and 98.4% specificity in comparison with clinical criterion of a true infection. The authors point out that blood culture-based diagnostics have a sensitivity as low as 65% for the first blood culture draw.

Potential impact on therapy: The authors found that 66.7% of the clinically infected patients missed by blood culture and correctly identified by T2Bacteria were being inappropriately treated at the time of the T2Bacteria result.



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De Angelis et al., JAC, 2018

Clinical Case Study: Rapid identification of polymicrobial infection by T2MR

M 68 year old patient, miastenia gravis, admitted to ICU for respiratory failure. High fever, chills, flush skin, tachycardia and rapid breathing. Suspect focus of infection was abdomen. Started therapy with meropenem and vancomycin.

~41 hours to Species Identification

- **DAY0**
  - 3:00pm: BCs collected
  - 3:50pm: start BCs incubation
  - 9:26pm: BCs positive (TTP - 5h30')
- **DAY1**
  - 8:10am: BCs bottle unload
  - 10:00am: *E.coli* by direct MALDI-TOF
- **DAY2**
  - 8:00am subculture show also *K.pneumoniae*

~4 hours to Species Identification

- **DAY0**
  - 3:00pm: T2 sample collected
  - 3:25pm: T2 start time
  - 7:07pm: *E.coli+K.pneumoniae*

SepsiScan workflow

✓ Preclinical study

Positive blood cultures



1:1000 dilution in NaCl

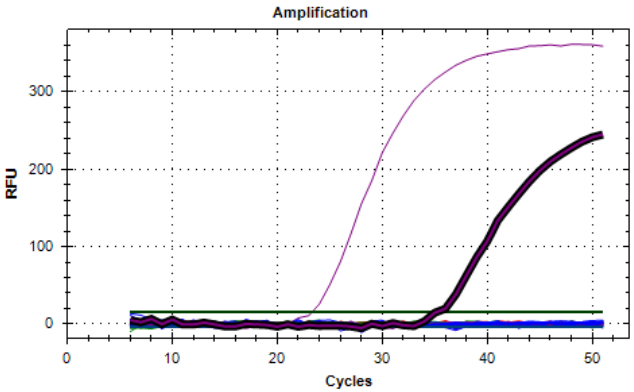


100 µL









1) 23° cycle: Rnasi internal control
2) 35° cycle: Positive result for *E. faecalis*

✓ Clinical study

Whole blood sample







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Microrganismi e geni di resistenza antimicrobica utilizzati come target			
Batteri Gram-negativi	**Batteri Gram-positivi**	**Lieviti**	**Geni di resistenza**
E. coli	*Staphylococcus* spp.	*C. albicans*	mecA
Klebsiella spp.	*S. aureus*	*C. glabrata*	bla_{KPC}
P. mirabilis	*E. faecalis*	*C. krusei*	vanA/B
S. marcescens	*E. faecium*	*Candida* spp.	
E. aerogenes	*Streptococcus* spp.		
E. cloacae	*S. pneumoniae*		
P. aeruginosa			
A. baumannii			

SepsiScan results in all patients by		
	sample, in comparison with:	sample, in comparison with:
	Blood culture	Clinical information
Matched positives, n	15	27
Matched negatives, n	72	72
SepsiScan overdetections, n	15	3
SepsiScan misses, n	6	6
Overall agreement, %	80.5	92.0
Sensitivity, %	71.4	82.0
Specificity, %	82.8	96.0
Positive predictive value, %	50.0	90.0
Negative predictive value, %	92.3	92.3

Conclusions

- More than ever, it is emphasized the primary role of a clinical microbiology laboratory, that is to assist clinicians in the diagnosis and treatment of infectious diseases, and to support infection control specialists in their tasks.
- In many instances, however, the delay between the collection of the specimen and the results of the microbial culture makes the latter unhelpful for the clinician.
- Therefore, advances in diagnostic methods (such as POC or POC-like tests) and/or procedures might satisfy the ‘need for speed’, particularly when clinicians, infection control specialists, and microbiologists confront with a septic patient or, in general, with a patient with a systemic infection, or deal with an emerging epidemic.

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