

# L'importanza della diagnosi rapida: Stewardship Diagnostica

Antonio Curtoni

S.C. Microbiologia e Virologia U.

Direttore Prof.ssa Rossana

Cavallo

A.O.U.

Città della Salute e della Scienza  
di Torino



**TORINO**

GOLDEN PALACE

SALA DIAMANTE

Via Arcivescovado, 18

**12 NOVEMBRE 2019**

**FOCUS**  
**LOTTA ALLE INFETZIONI CORRELATE  
ALL'ASSISTENZA**

2019 MOTORE  
**SANITA'**  
Gestire il Cambiamento

# Diagnostic stewardship: are we using the right term?

Clin Microbiol Infect 2018

O.J. Dyer <sup>1,\*</sup>, J. Moran-Gilad <sup>2</sup>, G. Greub <sup>3</sup>, C. Pulcini <sup>4</sup>, on behalf of the ESGMD Executive Committee and the ESGAP Executive Committee

**"Clinical microbiologists... have a key role to play in influencing how antimicrobial agents are used..."**

**"A good prescription starts with a precise diagnosis..."**

## A.O.U. Città della Salute e della Scienza di Torino

Molinette – CTO - OIRM/S.Anna

S.C. Microbiologia e Virologia U.

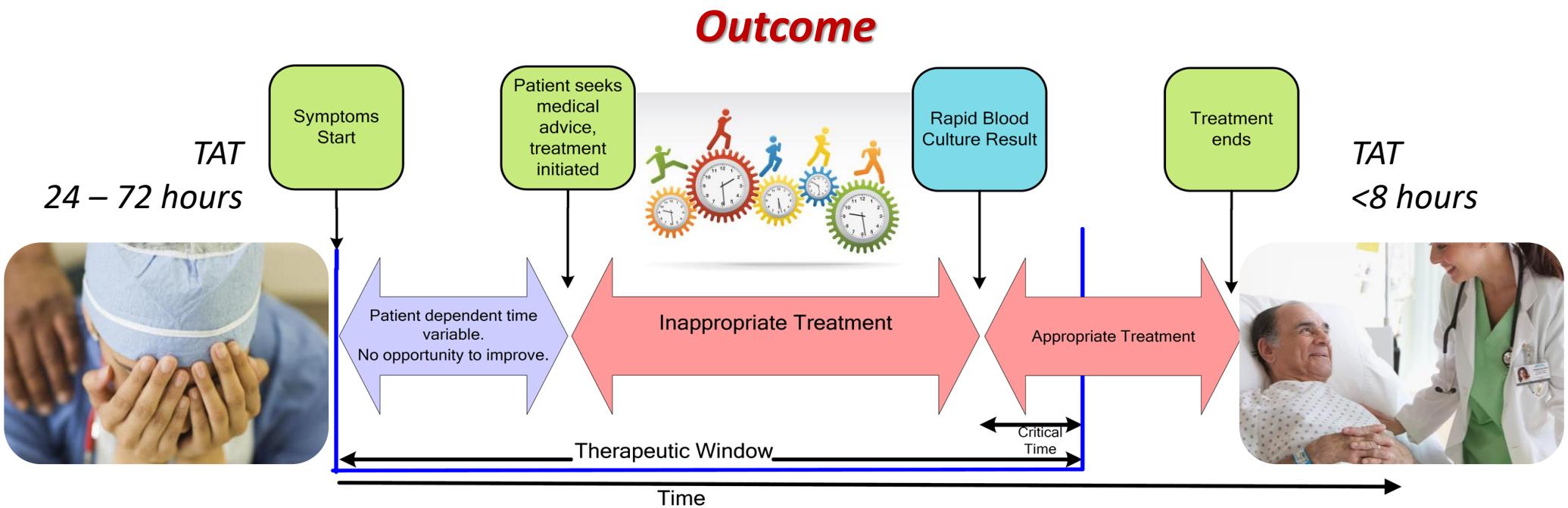
Campione	N./anno	N./giorno	Antibiogrammi/giorno
Urocolture	>35.000		
Respiratori*	>13.000		
Emocolture	>7.000		



**75 antibiogrammi / giorno**

\*BAL, broncoaspirati, aspirati tracheali, tamponi faringei

# *Turn-around Time*



1. **Interruzioni di terapie antimicrobiche non necessarie (infezioni virali vs. batteriche vs. fungine)**
2. **Tempestivo passaggio da terapie empiriche a terapie mirate**
3. **Precoce attuazione di interventi di *Infection Control***



## Diagnostic stewardship

A guide to implementation in antimicrobial resistance surveillance sites



2016

# (Microbiological) Diagnostic Stewardship

## Global Antimicrobial Resistance Surveillance System Manual

*“coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection, and pathogen identification and accurate, timely reporting of results to guide patient treatment.”*

The main objectives of microbiological diagnostic stewardship:

- *Patient management guided by timely microbiological data to deliver safer and more effective and efficient patient care*
- *Accurate and representative AMR surveillance data to inform treatment guidelines, and AMR control strategies.*

# Infezioni Correlate all'Assistenza



In Italia...

1. Infezioni respiratorie → 24%
2. Infezioni delle vie urinarie → 21%
3. Infezioni del torrente circolatorio → 16%

Diagnostic Stewardship for Healthcare-Associated Infections:  
Opportunities and Challenges to Safely Reduce Test Use

*Infect. Control Hosp. Epidemiol. 2018*

Gregory R. Madden, MD;<sup>1</sup> Robert A. Weinstein, MD;<sup>2</sup> Costi D. Sifri, MD<sup>1,3</sup>

A major objective for diagnostic stewardship for HAIs is to identify the “sweet spot” of test utilization that **minimizes overdiagnosis and false positive** results while **maximizing** appropriately indicated testing and **true positive results**. This spot likely will be infection and population (eg, disease prevalence) specific

# Advances and Challenges in the Diagnosis and Treatment of Urinary Tract Infections: the Need for Diagnostic Stewardship

Kimberly C. Claeys<sup>1</sup> • Natalia Blanco<sup>2</sup> • Daniel J. Morgan<sup>2</sup> • Surbhi Leekha<sup>2</sup> • Kaede V. Sullivan<sup>3</sup>

Curr. Infect. Dis. Rep. 2019

## 1. Education

- Institution-specific guidelines
- Nurse training on appropriate UC collection
- Patients education on clean-catch technique

## 2. Ordering & Reflex urine culturing

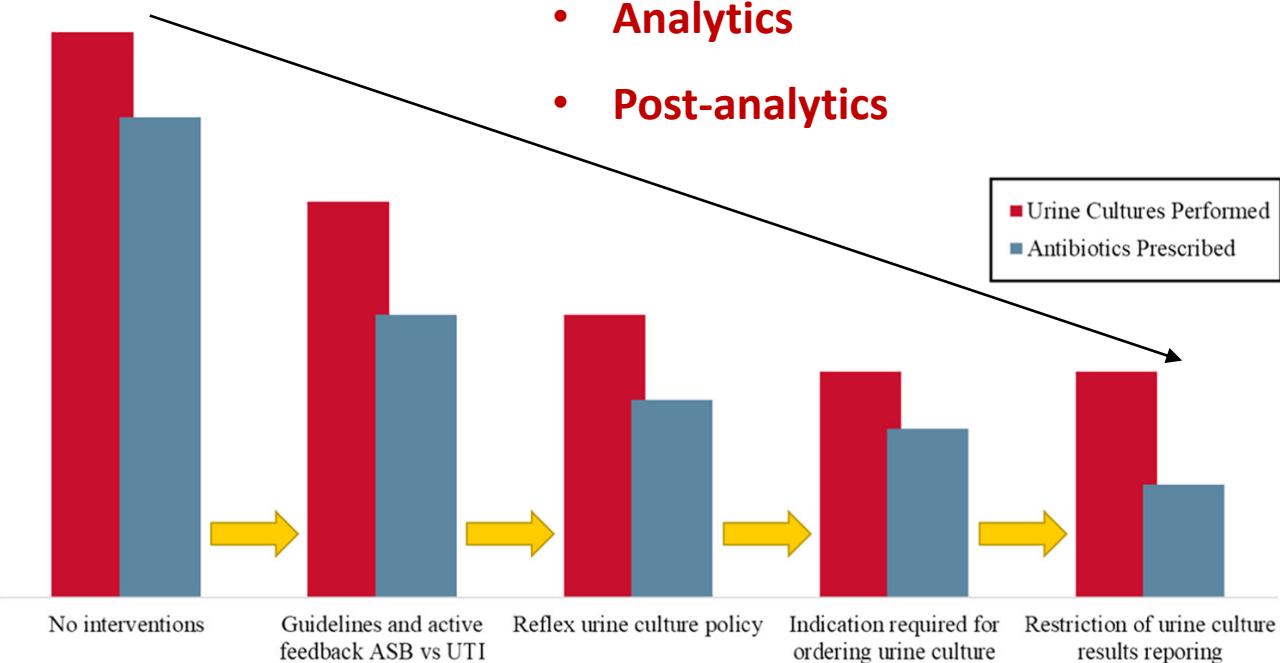
- Only when clinical indications are met (EBM)
- UC cancelled if specific criteria are not met

## 3. Optimizing urine collection and processing

- Clean-catch technique
- Minimize contaminations
- Transportation and preservation
- Process only when UC results are significant

## 4. Reporting

- Comments
- Selective reporting of antimicrobials



*Estimates of effect based on peer reviewed literature*

Fig. 2 Potential cumulative benefits of diagnostic stewardship interventions

# Pneumonia Panel

## Biofire Pneumonia Panel

Sample

**BAL** (including mini-BAL)

**Sputum** (including **endotracheal aspirate**)

## Performance

BAL: 96.2% Sensitivity and 98.3% Specificity

Sputum: 96.3% Sensitivity and 97.2% Specificity

## ATYPICAL BACTERIA

Qualitative Bacteria

*Chlamydia pneumoniae*

*Legionella pneumophila*

*Mycoplasma pneumoniae*

## VIRUSES

*Adenovirus*

*Coronavirus*

*Human Metapneumovirus*

*Human Rhinovirus/Enterovirus*

*Influenza A*

*Influenza B*

*Parainfluenza Virus*

*Respiratory Syncytial Virus*

## BACTERIA

### Semi-Quantitative Bacteria

*A. calcoaceticus-baumannii complex*

*Enterobacter cloacae complex*

*Escherichia coli*

*Haemophilus influenzae*

*Klebsiella aerogenes*

*Klebsiella oxytoca*

*Klebsiella pneumoniae group*

*Moraxella catarrhalis*

*Proteus spp.*

*Pseudomonas aeruginosa*

*Serratia marcescens*

*Staphylococcus aureus*

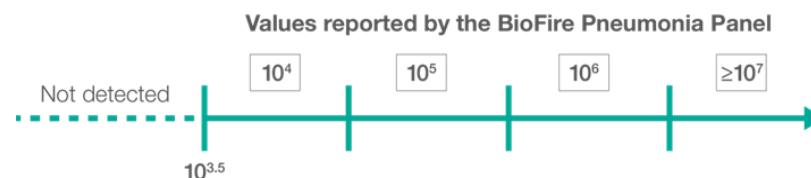
*Streptococcus agalactiae*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

## ANTIMICROBIAL RESISTANCE GENES

- *mecA/C* and *MREJ*
- *KPC*
- *NDM*
- *OXA-48-like*
- *VIM*
- *IMP*
- *CTX-M*

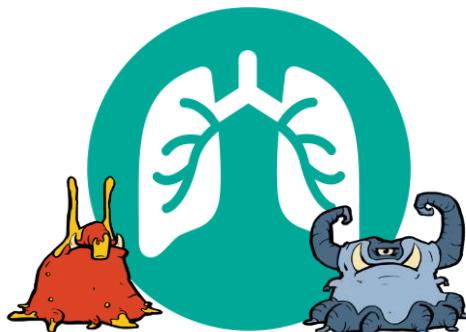


### **Semi-quantitative results** (copies/mL)

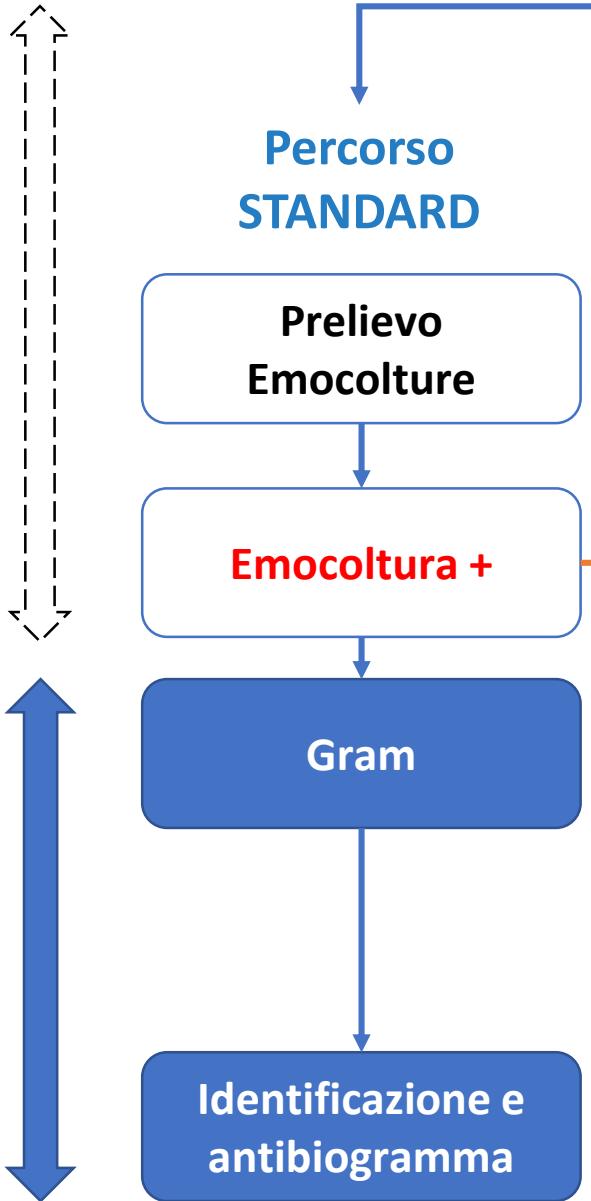
for 15 common colonizers

Concentration based on an internal Quantified Standard Material

Values calculated **below  $10^{3.5}$  copies/mL** are reported as “not detected”



TAT 24-72 ore



Paziente con BSI

Amplificazione genica  
MALDI-TOF MS

IC

...

2

Da emocolture positive

S.C. MICROBIOLOGIA E VIROLOGIA U. - Direttore Prof.ssa Rossana Cavallo

Materiale: Sangue

Esame/Ricerca Risultato

Esame batterioscopico (GRAM)  
Coccoi Gram pos.  
Identificazione preliminare con tecnologia MALDI TOF: Enterococcus faecalis

ID Campione: 3517447401

Esame/Ricerca

Emocoltura prelievo periferico

Ceppi isolati/identificati

Ceppo 1 Enterococcus faecalis

Gli Enterococchi sono intrinsecamente resistenti all'aminoacido monofosfato di manganato che è inefficace. Si ottiene un effetto sinergico associando aminoacidosidi e penicilline. L'enterococco è sensibile agli aminoacidosidi ad alto dosaggio e alle penicilline.

Antibiogramma

MIC = Concentrazione minima inibitrice (ug/ml)

S/I/R/I = Categorie di interpretazione: S = Sensibile I = Intermedio R = Resistente IE = Evidence insufficienti per definire l'attività della molecola su questo microrganismo.

	Antibiotico	S	I	R	IE	Note
Ampicillina		2	4	8		
Imipenem		<500	S			
Gentamicina HL		<1000	S	2	2	
Streptomicina HL		<2	S	4	4	
Tekoplanina		2	S	4	4	
Vancosicina		2	IE	4	4	
Daptomicina		<2	S	4	4	
Lincosid						

Referito

Direttamente da sangue/plasma

Amplificazione genica  
T2MR  
NGS  
...

FAST  
TRACK

Identificazione e/o  
«antibiogramma»

TAT ≤8 ore

# The Cost-Effectiveness of Rapid Diagnostic Testing for the Diagnosis of Bloodstream Infections with or without Antimicrobial Stewardship

Clin. Microbiol. Rev. 2018

Elina Eleftheria Pliakos,<sup>a</sup> Nikolaos Andreatos,<sup>a</sup> Fadi Shehadeh,<sup>a</sup> Panayiotis D. Ziakas,<sup>a</sup> Eleftherios Mylonakis<sup>a</sup>

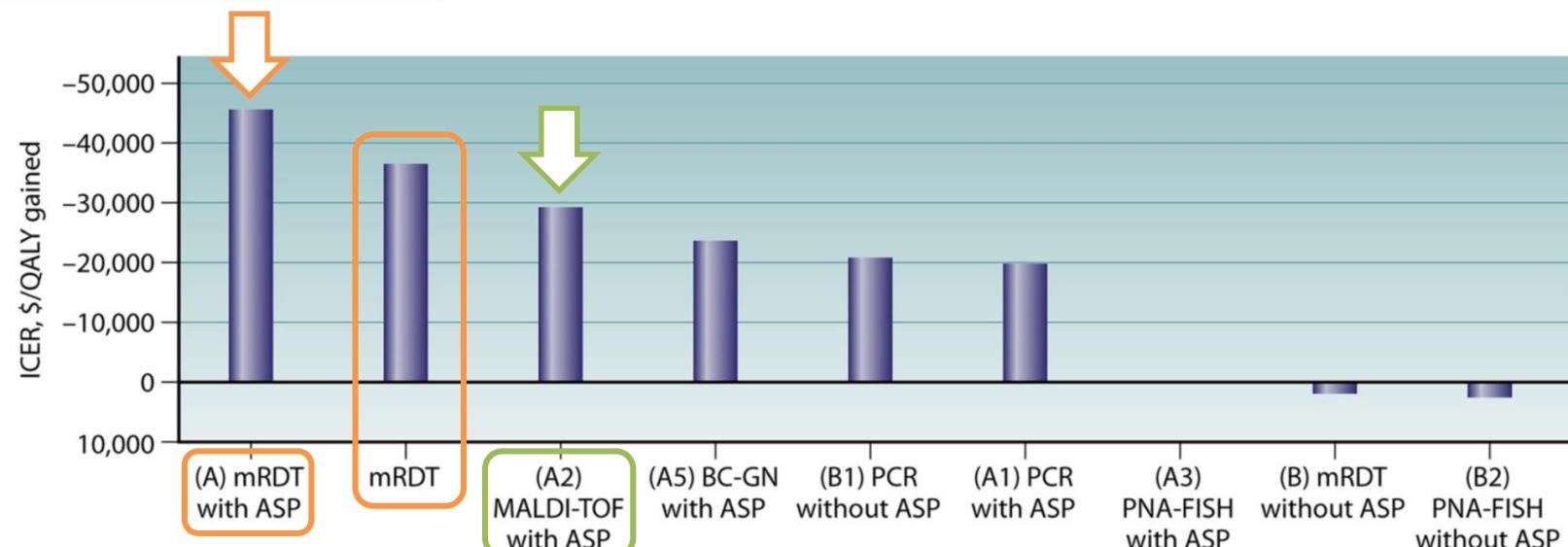
TABLE 3 Base-case analysis results for competing strategies

Strategy	Cost (\$)	Effect		ICER	
		Probability of survival	QALY value	\$/death averted	\$/QALY gained
mRDT (with and without ASP)	36,301.50	0.89	11.9883	-490,763	-36,434
mRDT with ASP (A)	31,274.24	0.89	11.9883	-616,445	-45,764
mRDT without ASP (B)	57,220.14	0.90	12.1230	25,762	1,913
PCR with ASP (A1)	47,917.58	0.88	11.8536	-267,148	-19,833
MALDI-TOF analysis with ASP (A2)	28,394.21	0.92	12.3924	-393,397	-29,205
PNA-FISH with ASP (A3)	53,226.09	0.85	11.4495	0	0
BC-GP with ASP (A4)	24,904.91	0.84	11.3148	Dominated	Dominated
BC-GN with ASP (A5)	33,691.47	0.92	12.3924	-317,722	-23,587
PCR without ASP (B1)	47,430.21	0.88	11.8536	-283,394	-21,039
PNA-FISH without ASP (B2)	58,284.16	0.92	12.3924	33,602	2,495
Conventional laboratory methods with ASP (C)	41,723.98	0.84	11.3148	Dominated	Dominated
Conventional laboratory methods without ASP (D)	55,932.02	0.85	11.4495	Baseline	Baseline

The probabilities of cost-effectiveness:

- 80.0% with an ASP
- 41.1% without an ASP

Superiority of using mRDT with ASP



Total cost = (3 X cost of blood culture)+ cost of mRDT + (cost of hospitalization per day X length of stay for mRDT)

ICER = (total cost of mRDT - total cost of baseline strategy)/(QALY value with mRDT - QALY value for baseline strategy)

## Cost-effectiveness study

### Molecular Rapid Diagnostic Tests (mRDT)

- Cost-effective alternative to conventional laboratory methods
- Whether used in combination with an ASP or not

**Effect of Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) Alone versus MALDI-TOF MS Combined with Real-Time Antimicrobial Stewardship Interventions on Time to Optimal Antimicrobial Therapy in Patients with Positive Blood Cultures**

Maya Beganovic,<sup>a\*</sup> Michael Costello,<sup>b</sup> Sarah M. Wieczorkiewicz<sup>a</sup>

*J. Clin. Microbiol.* 2017

**TABLE 2** AMS interventions

Intervention type	No. (%) of interventions <sup>a</sup>
Narrowed coverage	25 (33.3)
Discontinued therapy	24 (32)
Initiated/broadened coverage	15 (20)
Other	11 (14.7)
Total	75 (100)

<sup>a</sup>Interventions were accepted 88% of the time ( $n = 66$ ).

239 pazienti con BSI

116 MALDI-TOF vs 123 MALDI-TOF + AS

**Impatto su «Time To Optimal Treatment (TTOT)»**

TTOT 75,17 vs 43,06 h (p<0,001)

Contaminazioni 48,21 vs 11,75 h (p<0,001)

Gram - 71,83 vs 35,98 h (p<0,001)

Gram + 64,04 vs 41,61 h (p=0,082)

**Impatto su Hospital «Length Of Stay (LOS)»**

LOS 15,03 vs 9,02 (p=0,021)

**Costi diretti**

\$/pz. 28,677 vs 15,784 (p=0,010)

# Potenziale impatto della refertazione rapida delle emocolture positive nella gestione della terapia antibiotica

Percorsi diagnostici applicati

Flowchart 1

- Studio monocentrico prospettico osservazione
- Metodica fenotipica rapida (<8h)

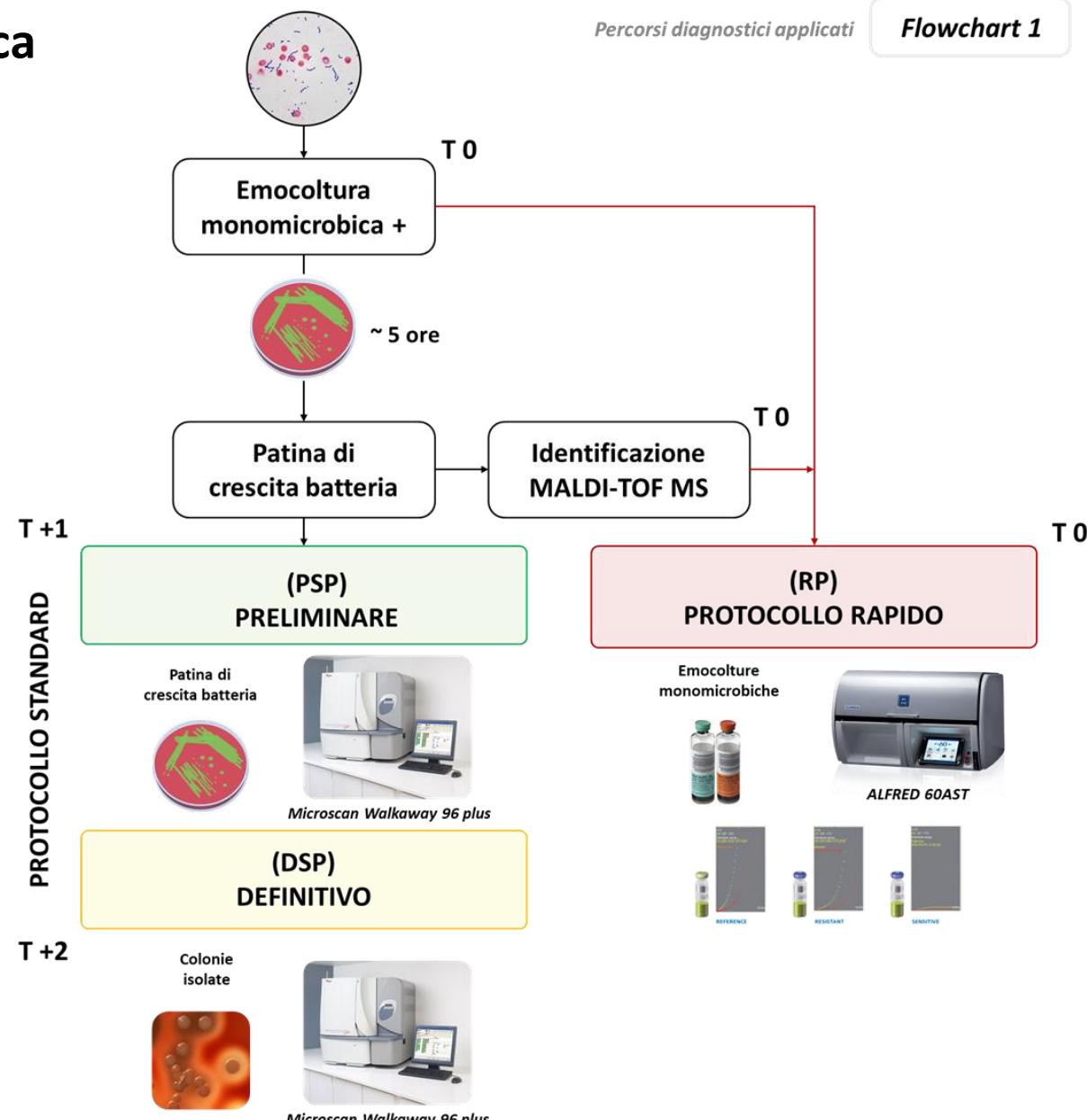
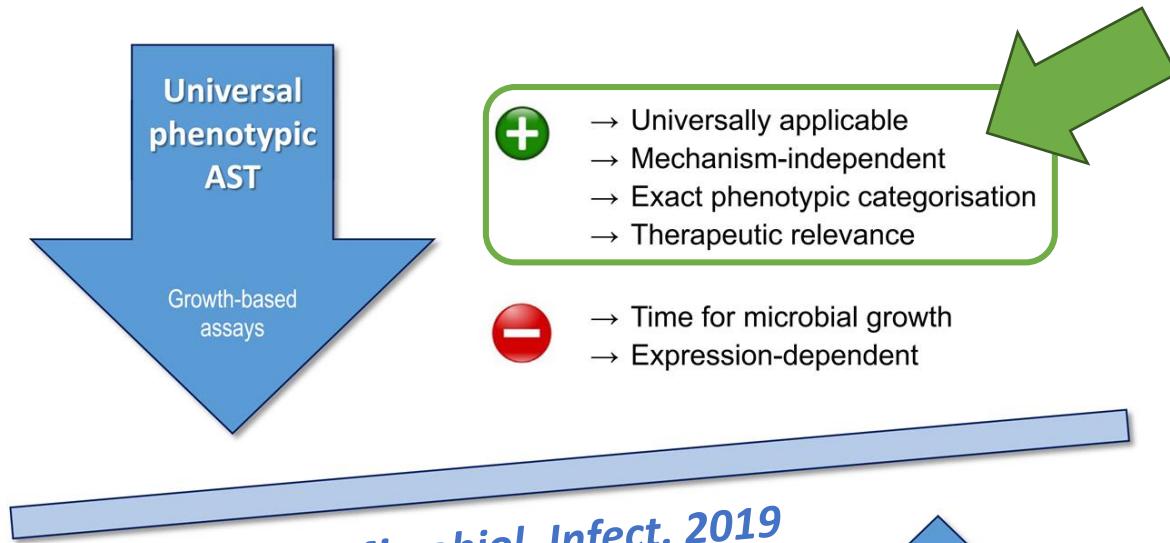


Fig. 1. Detection of particular resistance mechanisms vs. universal phenotypic susceptibility testing. AST, antimicrobial susceptibility testing.

# POTENZIALE IMPATTO DELLA REFERTAZIONE RAPIDA DELLE EMOCOLTURE NELLA GESTIONE DELLA TERAPIA ANTIBIOTICA: RISULTATI PRELIMINARI

- Risultati preliminari 50 pz
- TAT 6h 31' vs. 19h 12' ( $p<0,001$ )
- Concordanza globale 93,4% ( $k$  Cohen 0,82)

## Tempo 0

(giorno di positivizzazione delle emocolture)

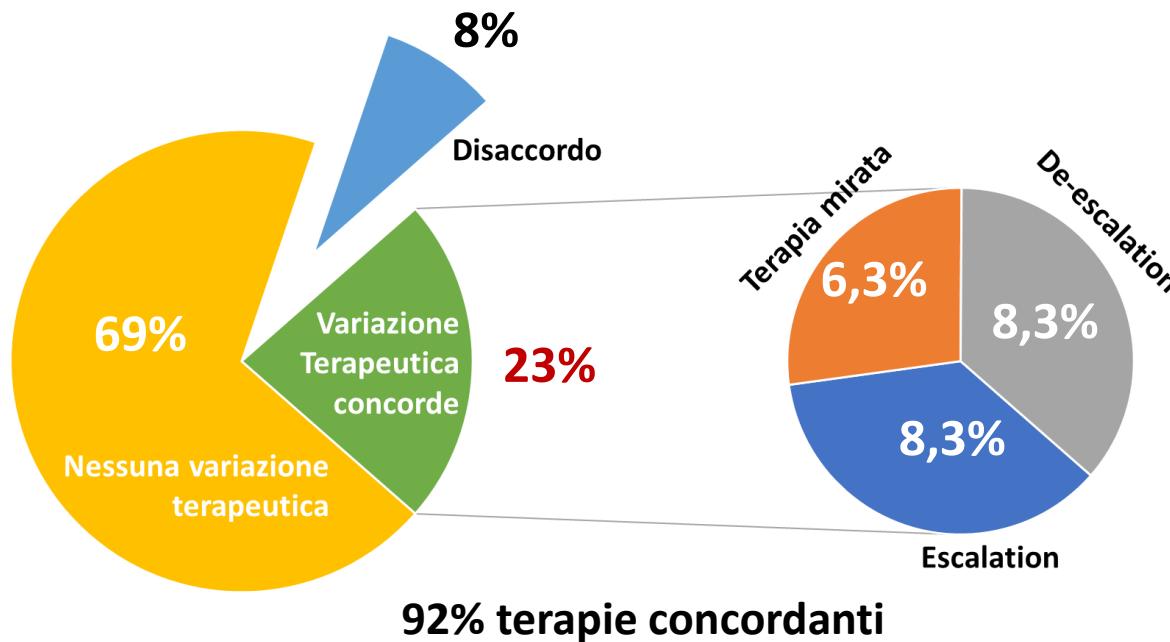
### Cambiamenti terapeutici

#### Clinica 6%

*Analisi concordanza gestione terapeutica RP e PSP*

PSP		Cambiamento terapeutico		
RP	Cambiamento terapeutico	Si		No
		Si (stessa terapia)	Si (terapia diversa)	No
Si	Si	11	2	1
No	No	1	-	33

\*La concordanza è stata calcolata considerando il cambiamento terapeutico con molecole diverse un disaccordo



23% variazioni anticipate di 1 giorno

# The GISA call to action for the appropriate use of antimicrobials and the control of antimicrobial resistance in Italy

*Int J Antimicrob Agents 2018*

Francesco Menichetti<sup>a,\*</sup>, Marco Falcone<sup>a</sup>, Pierluigi Lopalco<sup>b</sup>, Carlo Tascini<sup>c</sup>, Angelo Pan<sup>d</sup>, Luca Busani<sup>e</sup>, Bruno Viaggi<sup>f</sup>, Gian Maria Rossolini<sup>g</sup>, Fabio Arena<sup>h</sup>, Andrea Novelli<sup>i</sup>, Francesco De Rosa<sup>j</sup>, Stefania Iannazzo<sup>k</sup>, Jonathan Cohen<sup>l</sup>, for GISA (Italian Group for Antimicrobial Stewardship)<sup>†</sup>

- 1) Produce reports on a regular basis** (at least at semi-annual intervals) on stratified cumulative AST data at hospital level, to assist the development of local guidelines for empirical therapy.
- 2) Make every effort to reduce identification and AST turnaround times** (adopt matrix-assisted laser desorption time of flight and molecular diagnostic systems for microbial identification and detection of key resistance mechanisms).
- 3) Design personalized diagnostic workflows and rationalize the use of new technologies, adopting patient stratification criteria (severity of illness and/or risk of rapid clinical progression).**
- 4) Actively support ASP components and other clinicians in interpretation of the clinical microbiology laboratory results.**
- 5) Implement the use of rapid diagnostics in primary care settings**, in order to guide antibiotic prescription by general practitioners.

