Come ottimizzare l'uso dei nuovi BL/BLI

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Gruppo di Studio SIBIOC "Therapeutic Drug Monitoring (TDM) e Personalizzazione della Terapia"

Antonio D'Avolio
Disclosure/Conflict of Interest

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Shareholder Company: CoQua Lab

from last 5 years to date

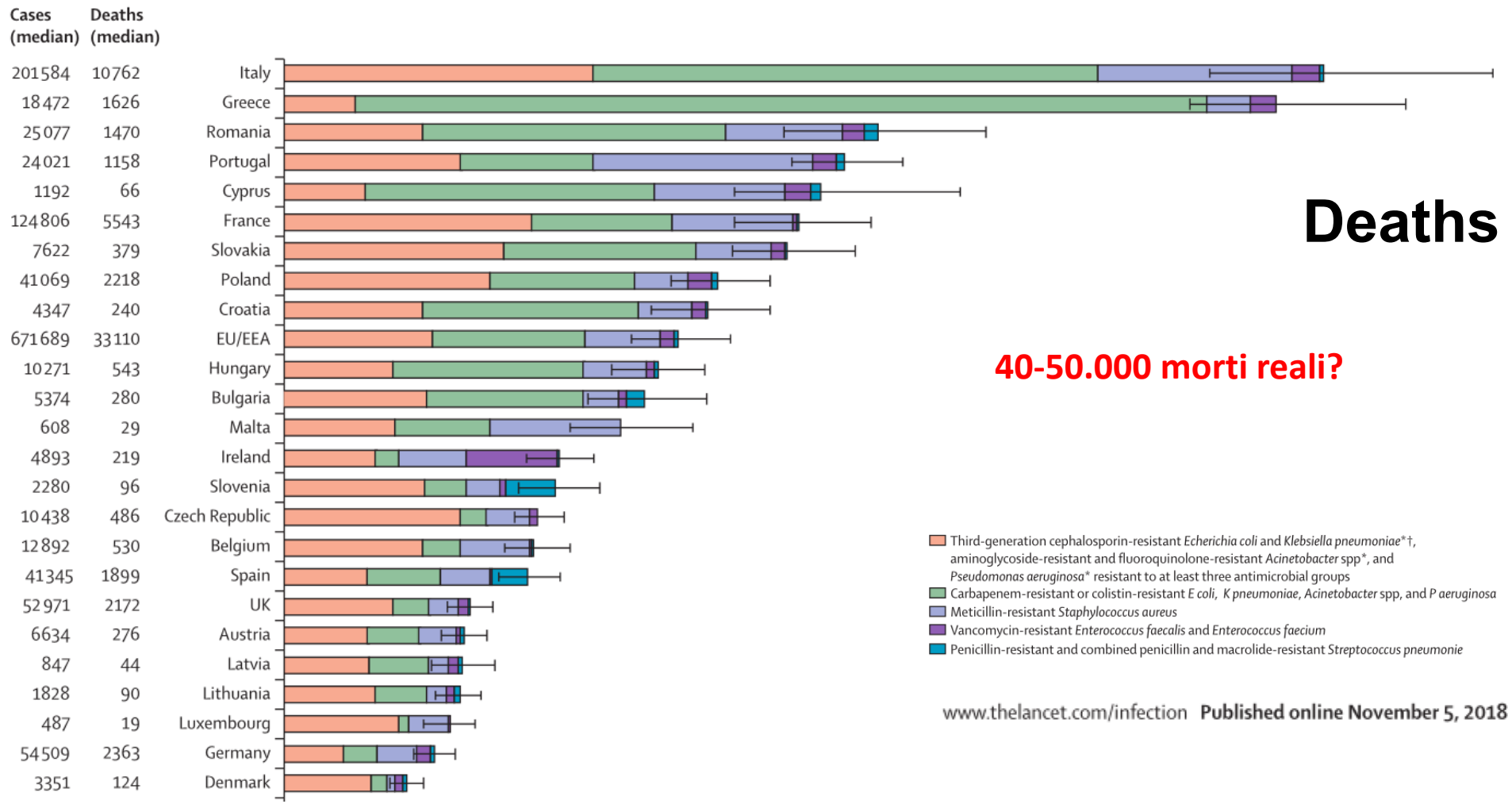
Antibiotico-resistenza: alcuni dati…

- Secondo una stima OCSE, **fra il 2015 e il 2050**, se le attuali tendenze non cambieranno, il trattamento delle infezioni resistenti, nei Paesi del G7, comporterà in media una spesa straordinaria, ogni anno, di circa 7 milioni di giorni di degenza ospedaliera in più e **l'Italia contribuirà a questo calcolo con circa 1,3 milioni di giorni di degenza ospedaliera in più ogni anno.**
- Nel 2019 l'Organizzazione mondiale della sanità (OMS) ha dichiarato la **resistenza antimicrobica una delle 10 principali minacce per la salute pubblica a livello mondiale.**
- Nel luglio 2022 la Commissione europea, insieme agli Stati membri, ha definito la **resistenza antimicrobica una delle tre principali minacce prioritarie per la salute nell'UE.**
- Secondo le stime più recenti il costante **aumento della resistenza provocherebbe 10 milioni di decessi l'anno a livello mondiale e oltre 35 000 morti l'anno nell'Unione europea** (compreso lo Spazio Economico Europeo). Circa un terzo dei decessi a livello europeo si verificano in Italia.

Antibioticoresistenza: ogni anno in Europa 33mila morti, più di quelli causati da influenza, tubercolosi e Aids messi insieme. Studio Ecdc

Antibiotici: maneggiare con cura

06 NOV - Lo studio spiega che il 75% del carico di malattia è dovuto a infezioni associate all 'assistenza sanitaria (HAI) e che la riduzione di questo attraverso adeguate misure di prevenzione e controllo delle infezioni, nonché la gestione antibiotica, potrebbe essere un obiettivo raggiungibile in ambito sanitario e mostra che il 39% del carico è causato da infezioni batteriche resistenti a antibiotici di ultima generazione. Leggi >



Upsala Journal of Medical Sciences. 2014; 119: 103–107

informa
healthcare

REVIEW ARTICLE

Selection of antibiotic resistance at very low antibiotic concentrations

LINUS SANDEGREN

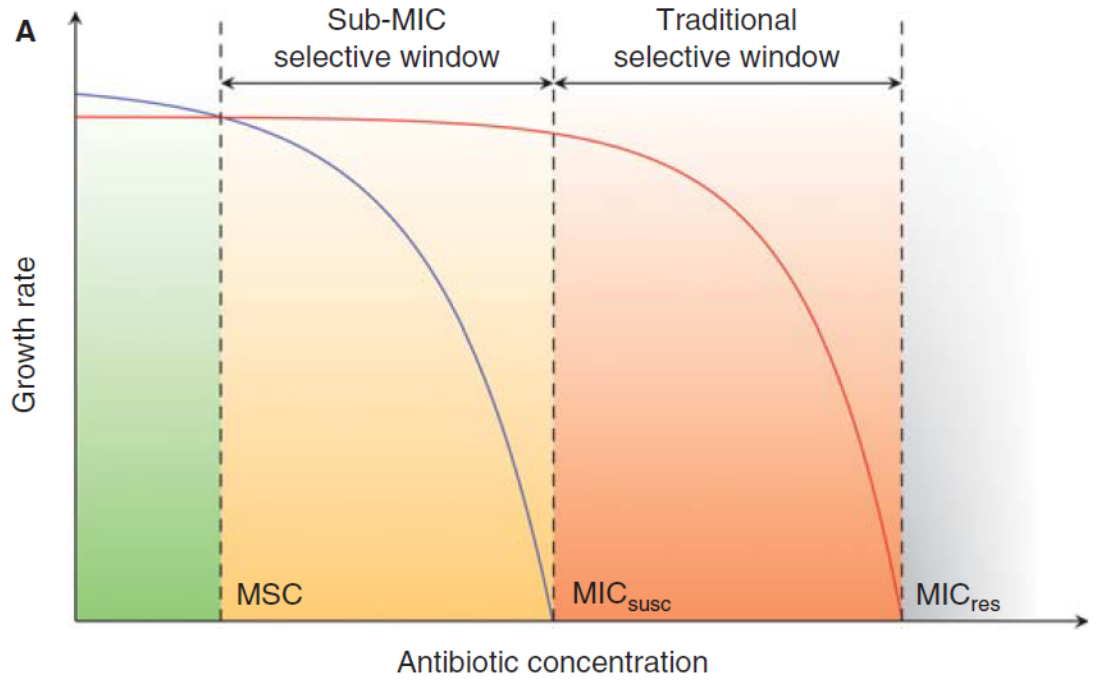


Figure 1. Schematic representation of growth rates as a function of antibiotic concentration. (MIC_{susc} = minimal inhibitory concentration of the susceptible strain; MIC_{res} = minimal inhibitory concentration of the resistant strain; MSC = minimal selective concentration.) In green is the concentration range below the MSC in which the susceptible strain (blue line) will outcompete the resistant strain (red line) due to fitness cost of resistance. Orange (sub-MIC selective window) and red (traditional mutant selective window) indicate concentration intervals where the resistant strain will outcompete the susceptible strain due to the selective effect of antibiotic. Reproduced from (5).

Aspetti Laboratoristici come «armi per la terapia delle infezioni batteriche MDR» a supporto del clinico

- Il laboratorio di Microbiologia ed il Microbiologo

- Il laboratorio di Farmacologia ed il Farmacologo

Aspetti Laboratoristici come «armi per la terapia delle infezioni batteriche MDR» a supporto del clinico

- **Il laboratorio di Microbiologia ed il Microbiologo**

- Il laboratorio di Farmacologia ed il Farmacologo

L'importanza di individuare correttamente il tipo di carbapenemasi presente

Attività dei nuovi antibiotici anti-Gram-negativi nei confronti di ceppi produttori di diversi tipi di carbapenemasi

Enzima	CAZ/AVI	MER/VAB	IMI/REL	CFDC	*ATM/AVI*
KPC	+	+	+	+	+
OXA-48	+	-	-	+	+
VIM	-	-	-	+	+
NDM	-	-	-	+	+
IMP	-	-	-	+	+

CAZ/AVI = ceftazidime/avibactam; MER/VAB = meropenem/vaborbactam
IMI/REL = imipenem/relebactam; CFDC = cefiderocol
ATM/AVI = aztreonam/avibactam

<u>Nel tempo più breve possibile</u>, per iniziare nel più breve tempo possibile la terapia mirata con i BL/BLI (corretti).

Tecnologie diagnostiche molecolari per emocoltura (pannello sindromico)

Sepsi, post-chirurgia addominale

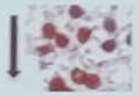
Meropenem
Vancomicina

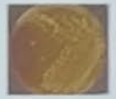
TERAPIA EMPIRICA

Sangue

14 h

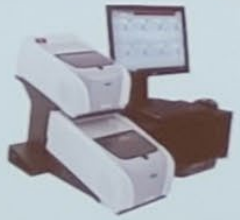
Gram





ID MALDI

Incubazione | Subcoltura | AST + 2 giorni



TTR: 70 min

Fenotipo atteso:

Nuove diagnostiche molecolari rapide

Definitivo (≥3 giorni)

K. pneumoniae

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Cla	16 R
Pip/Tazo	28 R
Ceftriaxone	>4 R

TERAPIA MIRATA

Ceftazidime-avibactam o Meropenem-vaborbactam

Meropenem	32 R
Amikacina	>16 R
Gentamicina	1 S
Ciprofloxacina	>4 R
Colistina	1 S
CAZ/AVI	1 S
Tigeciclina	0.5
MEM/VAB	<=0.25 S

ID molecolare:

***Klebsiella pneumoniae* group**

Antibiogramma genotipico:

CTX-M	Non rilevato
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

PROBABILE RESISTENZA A:
- VECCHI BLIC
- CEFALOSPORINE III-IV GENERAZ.
- CARBAPENEMI
- CEFTOLOZANO-TAZOBACTAM

PROBABILE SENSIBILITA A:
- CEFTAZIDIME-AVIBACTAM
- MEROPENEM-VABORBACTAM
- IMIPENEM-RELEBACTAM
- CEFIDEROCOL

NON POSSIBILI PREVISIONI SU:
- AMINOGLICOSIDI
- FLUOROCHINOLONI
- FOSFOMICINA
- COLISTINA
- COTRIMOSSAZOLO

REVISIONE PRECOCE

Ceftazidime-avibactam o Meropenem-vaborbactam

Antibiogr. molecolare	
CTX-M	Non rilevato
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

Antibiotico	MIC mg/L (S/I/R)
Meropenem	64 R
CAZ-Avib	1 S
MER-Vabor	0.25 S
IMI-Releb	0.5 S
Cefiderocol	1 S

Antibiogr. molecolare	
CTX-M	Non rilevato
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

Antibiotico	MIC mg/L (S/I/R)
Meropenem	1 S
CAZ-Avib	>32 R
MER-Vabor	0.25 S
IMI-Releb	0.5 S
Cefiderocol	4 R

Antibiogr. molecolare	
CTX-M	Non rilevato
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

Antibiotico	MIC mg/L (S/I/R)
Meropenem	32 R
CAZ-Avib	>32 R
MER-Vabor	8 S
IMI-Releb	0.5 S
Cefiderocol	4 R

Antibiogr. molecolare	
CTX-M	Non rilevato
KPC	RILEVATO
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	Non rilevato

Antibiotico	MIC mg/L (S/I/R)
Meropenem	32 R
CAZ-Avib	>32 R
MER-Vabor	>32 R
IMI-Releb	>16 R
Cefiderocol	4 R

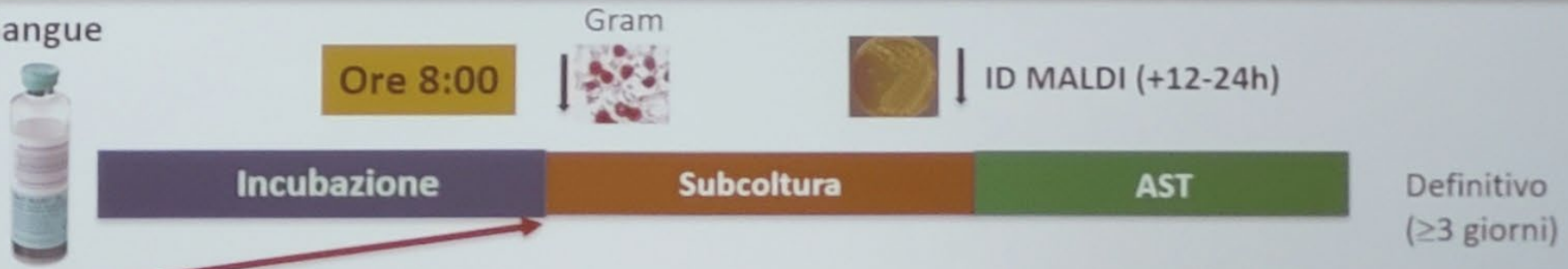
Antibiotico	MIC mg/L (S/I/R)
Meropenem	(R)
CAZ/AVI	(S)
MER/VBR	(S)
IMI/REL	(S)
Cefiderocol	(S)

4 isolati di *K. pneumoniae*

Fenotipo atteso

4 isolati con profilo molecolare uguale, avevano il profilo fenotipico diverso!

Tecnologie per antibiogramma fenotipico rapido da emocoltura positiva



Nuove diagnostiche fenotipiche rapide

Vantaggi:	Limiti:
Rapidità: risposta 2-6 ore da emocoltura positiva	*Solo colture monomicrobiche*
Informazione convenzionale (MIC, S/I/R)	*Necessità di ID rapida*
Stessa informazione ATB classico	*Numero di specie limitato*
Può sostituire percorso tradizionale	*Composizione pannelli/accuratezza*

Aspetti Laboratoristici come «armi per la terapia delle infezioni batteriche MDR» a supporto del clinico

- Il laboratorio di Microbiologia ed il Microbiologo

- **Il laboratorio di Farmacologia ed il Farmacologo**

Il TDM come arma per la gestione dei ottimale degli antibiotici ed evitare l'insorgenza di mutanti resistenti.

Therapeutic Drug Monitoring Ratio

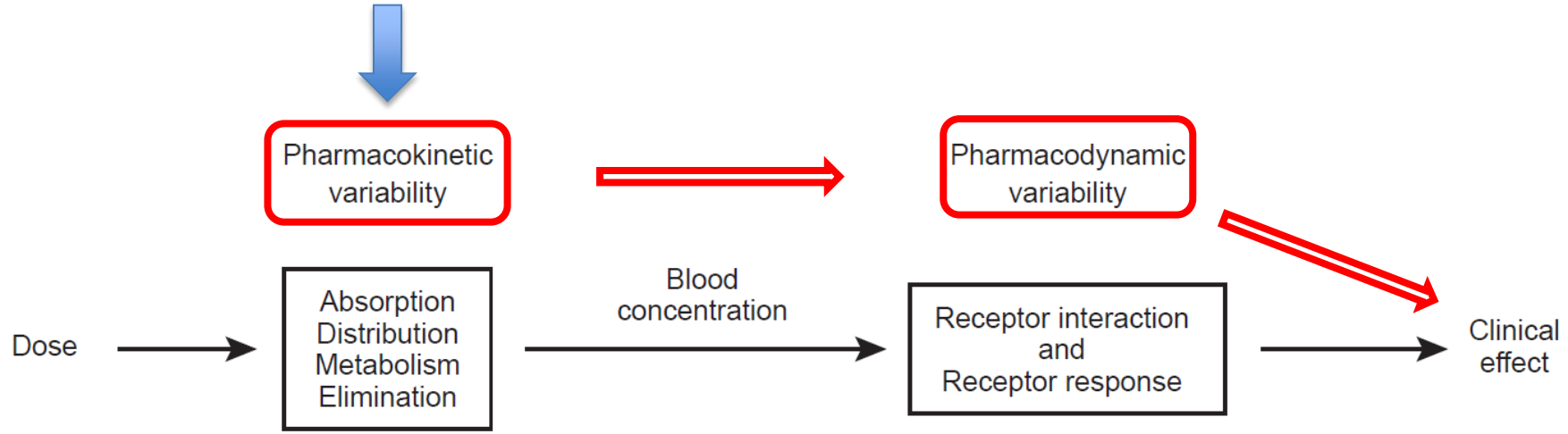


Figure 1 Pharmacokinetics and pharmacodynamics contribute to variability in the relationship between drug dose and response.

Best practice in therapeutic drug monitoring

Annette S. Gross
Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards NSW 2065, Australia

 Br J Clin Pharmacol, **52**, 5S–10S

Measuring the drug, we can guide the clinical effect.

J Antimicrob Chemother 2022; **77**: 1532–1541
https://doi.org/10.1093/jac/dkac101 Advance Access publication 31 March 2022

Journal of Antimicrobial Chemotherapy

A systematic review of the effect of therapeutic drug monitoring on patient health outcomes during treatment with penicillins

Timothy Luxton [1]*, Natalie King[2], Christoph Wälti[3], Lars Jeuken[2,4] and Jonathan Sandoe [5]

…penicillin treatment guided by **TDM has the potential to reduce AMR.** A recent systematic review, investigating the antibiotic concentrations required to suppress AMR in Gram-negative bacteria, showed a β-lactam Cmin/MIC ratio of ≤4 can result in the emergence of AMR. Results from Al-Shaer et al. could be a promising sign that **AMR emergence could be tackled through TDM**...

Sumi CD, Heffernan AJ, Lipman J et al. What antibiotic exposures are required to suppress the emergence of resistance for gram-negative bacteria? A systematic review. Clin Pharmacokinet 2019; 58: 1407–43.

Al-Shaer MH, Rubido E, Cherabuddi K et al. Early therapeutic monitoring of β-lactams and associated therapy outcomes in critically ill patients. J Antimicrob Chemother 2020; 75: 3644–51.

TDM is part of Antibiotic Stewardship

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY JUNE 2013, VOL. 34, NO. 6

ORIGINAL ARTICLE

Sustained Savings from a Longitudinal Cost Analysis of an Internet-Based Preapproval Antimicrobial Stewardship Program

Anna C. Sick, MPH;[1] Christoph U. Lehmann, MD;[2] Pranita D. Tamma, MD, MHS;[3] Carlton K. K. Lee, PharmD, MPH;[3,4] Allison L. Agwu, MD, ScM[3,5]

MAJOR ARTICLE

Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship

With documented direct and indirect economic savings!

ANTIMICROBIAL STEWARDSHIP MISSION

TREAT patients correctly and PREVENT MDR selection

1. Start and choice antimicrobials using a risk assessment based approach
2. Not be impulsive in starting antimicrobial therapy

3. Properly use microbiology lab resources (for diagnosis, epidemiology, infection control)

4. Avoid redundant prescriptions and useless combinations
5. Be aware about PK/PD issues
6. Early rethink how antibiotics are prescribed, trying to target treatment asap
7. Shorten therapy duration and Shorten Length of Hospital stay

8. Share the right place in therapy of any new (and old) drugs in a multidisclinary way

The added value of the PK/PD driven approach

The double role of Pharmacology

The "real time" Pharmacology

TDM driven daily dose adjustment

The "Pharmacological culture"

PK/PD driven drug choice

PK/PD driven modality of administration

Allora questa strategia è applicata ovunque per ottimizzare i BL (e gli altri farmaci)!?!?!?

J Antimicrob Chemother 2023; **78**: 2810–2815
https://doi.org/10.1093/jac/dkad296 Advance Access publication 12 October 2023

Journal of Antimicrobial Chemotherapy

Real-world experience of therapeutic drug monitoring and PK/PD achievement of ceftaroline administered by different infusion regimens in patients with confirmed infections caused by Gram-positive bacteria

Daniel Fresán[1]†‡, Sonia Luque[2,3,4]†, Adela Benítez-Cano[5], Luisa Sorlí[3,4,6,7]*, María Milagro Montero[3,4,6,7], Marta De-Antonio[2], Victoria Vega[8], Jason A. Roberts[9,10,11,12], Juan P. Horcajada[3,4,6,7]† and Santiago Grau[2,3,4,7]†

European Journal of Drug Metabolism and Pharmacokinetics (2022) 47:561–566
https://doi.org/10.1007/s13318-022-00772-x

Conclusions: The administration of ceftaroline by **prolonged infusion together with TDM may be a useful** strategy for achieving the desired PK/PD target in these patients.

ORIGINAL RESEARCH ARTICLE

Therapeutic Drug Monitoring and Prolonged Infusions of Ceftolozane/Tazobactam for MDR/XDR *Pseudomonas aeruginosa* Infections: An Observational Study

María Eugenia Navarrete-Rouco[1] · Sònia Luque[1,2,3,4] · Luisa Sorlí[2,3,4,5,6] · Adela Benítez-Cano[2,7] · Jason A. Roberts[8,9,10] · Santiago Grau[1,2,3,4,6]

Conclusions The administration of C/T by **prolonged infusion with TDM-guided dosing allowed the achievement of a pharmacokinetic/pharmacodynamic target** even at lower doses. C/T showed a high efficacy for treating MDR/XDR P. aeruginosa infections.

J Antimicrob Chemother 2023; **78**: 678–683
https://doi.org/10.1093/jac/dkac439 Advance Access publication 10 January 2023

Journal of Antimicrobial Chemotherapy

Pharmacokinetics/pharmacodynamics and therapeutic drug monitoring of ceftazidime/avibactam administered by continuous infusion in patients with MDR Gram-negative bacterial infections

D. Fresan[1]†, S. Luque[2,3,4]†, A. Benítez-Cano[5], L. Sorlí[3,4,6,7]*, M. Milagro Montero[3,4,6,7], M. De-Antonio[2], N. Prim[8], V. Vega[9], J. P. Horcajada[3,4,6,7]† and S. Grau[2,3,4,7]†

Conclusions: Administering ceftazidime/avibactam by CI enabled the desired PK/PD target to be achieved in a large proportion of patients, even at lower doses than those recommended for a 2 h extended infusion. We suggest that the use of **CI with TDM may be a useful tool** for reducing initial doses, which could help to reduce antimicrobial-related adverse effects and treatment costs.

J Antimicrob Chemother 2024; **79**: 2801–2808
https://doi.org/10.1093/jac/dkae290 Advance Access publication 19 August 2024

Journal of Antimicrobial Chemotherapy

An innovative population pharmacokinetic/pharmacodynamic strategy for attaining aggressive joint PK/PD target of continuous infusion ceftazidime/avibactam against KPC- and OXA-48- producing *Enterobacterales* and preventing resistance development in critically ill patients

Pier Giorgio Cojutti[1,2], Manjunath P. Pai [3]*, Milo Gatti [1,2], Matteo Rinaldi[1,4], Simone Ambretti[1,5], Pierluigi Viale[1,4]

Methods: A retrospective analysis of adult patients receiving CI ceftazidime/avibactam and therapeutic drug monitoring (TDM) of both compounds was performed. Population PK/PD modelling identified the most accurate method for estimating ceftazidime/avibactam clearance based on kidney function and Monte Carlo simulations investigated the relationship between various CI dosing regimens and aggressive joint PK/PD target attainment of ceftazidime/avibactam.

Conclusions: This study suggests that adjusting ceftazidime/avibactam dosing regimen based solely on eCLcr might be suboptimal for critically ill patients. **Higher daily doses delivered by CI and adjusted based on TDM have the potential to improve aggressive joint PK/PD target attainment and potentially clinical/microbiological outcomes**. Further investigations are warranted to confirm these findings and establish optimal TDM-guided dosing strategies for ceftazidime/avibactam in clinical practice.

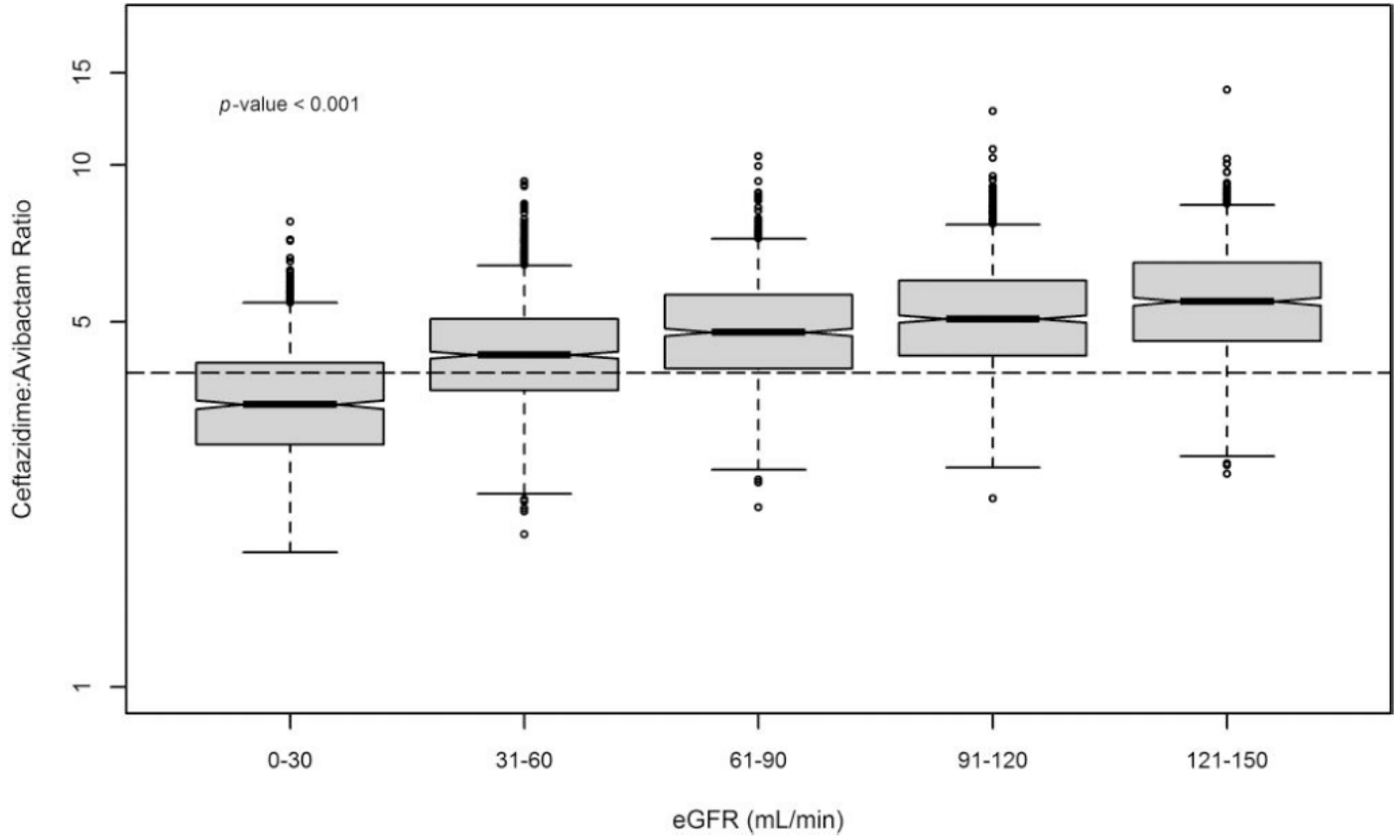


Figure 1. Box and whisker plot (5th–95th percentiles) of simulated ceftazidime:avibactam concentration ratio across different classes of renal function. The dashed line represents the expected value of the concentration ratio based on the 4:1 proportion between ceftazidime and avibactam.

The probability of target attainment (PTA) of aggressive joint PK/PD target of **ceftazidime/avibactam** were assessed by testing the highest permissible dosing regimens for each class of renal function against the MIC distribution ranging between 0.0625 and 64 mg/L.

The PTAs were considered as optimal when both the likelihood of attaining fCssCAZ/MIC ratio ≥4 and fCssAVI/CT ratio ≥1 were both ≥90%, quasi-optimal if only one of the two thresholds was ≥90% and suboptimal if none of the two thresholds was ≥90%.

Table 4. PTA (%) of optimal, quasi-optimal and suboptimal PK/PD target at day 3 with the tested permissible CI ceftazidime/avibactam dosages across the different eGFR classes in critically ill patients

		PTAs of CAZ and AVI at CAZ/AVI MIC (mg/L)															
		0.0625		0.125		0.25		0.5		1		2		4		8	
Classes of eGFR (mL/min)	Daily Dose (g)	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI
0–30	1.25	*100*	*72.7*	*100*	*72.7*	*100*	*72.7*	*100*	*72.7*	*94.8*	*72.7*	87.8	72.7	61.4	72.7	27.4	72.7
0–30	1.875	*100*	*85.5*	*100*	*85.5*	*100*	*85.5*	*100*	*85.5*	*100*	*85.5*	*94*	*85.5*	80.2	85.5	46.9	85.5
31–60	3.75	*100*	*84.1*	*100*	*84.1*	*100*	*84.1*	*100*	*84.1*	*99.8*	*84.1*	*95.4*	*84.1*	83.8	84.1	47.3	84.1
31–60	5	**100**	**92.5**	**100**	**92.5**	**100**	**92.5**	**100**	**92.5**	**100**	**92.5**	**96.1**	**92.5**	**92.6**	**92.5**	*64.9*	*92.5*
61–90	5	*100*	*76.3*	*100*	*76.3*	*100*	*76.3*	*100*	*76.3*	*100*	*76.3*	*95.5*	*76.3*	*78*	76.3	37.7	76.3
61–90	7.5	**100**	**90.1**	**100**	**90.1**	**100**	**90.1**	**100**	**90.1**	**100**	**90.1**	**99.6**	**90.1**	**91.2**	**90.1**	*62.5*	*90.1*
91–120	7.5	*100*	*82*	*100*	*82*	*100*	*82*	*100*	*82*	*100*	*82*	*98.4*	*82*	86.3	82	51.3	82
91–120	10	**100**	**90**	**100**	**90**	**100**	**90**	**100**	**90**	**100**	**90**	**100**	**90**	**94.2**	**90**	*68.9*	*90*
121–150	10	*100*	*83.9*	*100*	*83.9*	*100*	*83.9*	*100*	*83.9*	*100*	*83.9*	*100*	*83.9*	*91.9*	*83.9*	57.7	83.9

Optimal PTAs are identified in bold; quasi-optimal PTAs are italicized; suboptimal PTAs are underlined.

J Antimicrob Chemother 2024; **79**: 2801–2808

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Full-Length Text

Balancing the scales: achieving the optimal beta-lactam to beta-lactamase inhibitor ratio with continuous infusion piperacillin/tazobactam against extended spectrum beta-lactamase producing *Enterobacterales*

Pier Giorgio Cojutti,[1,2] Manjunath P. Pai,[3] Tommaso Tonetti,[1,4] Antonio Siniscalchi,[5] Pierluigi Viale,[1,6] Federico Pea[1,2]

Inadequate **piperacillin and tazobactam** exposure is likely in patients with eGFR ≥ 100 mL/min. Dose regimen adjustments informed by TDM should be evaluated in this specific population.

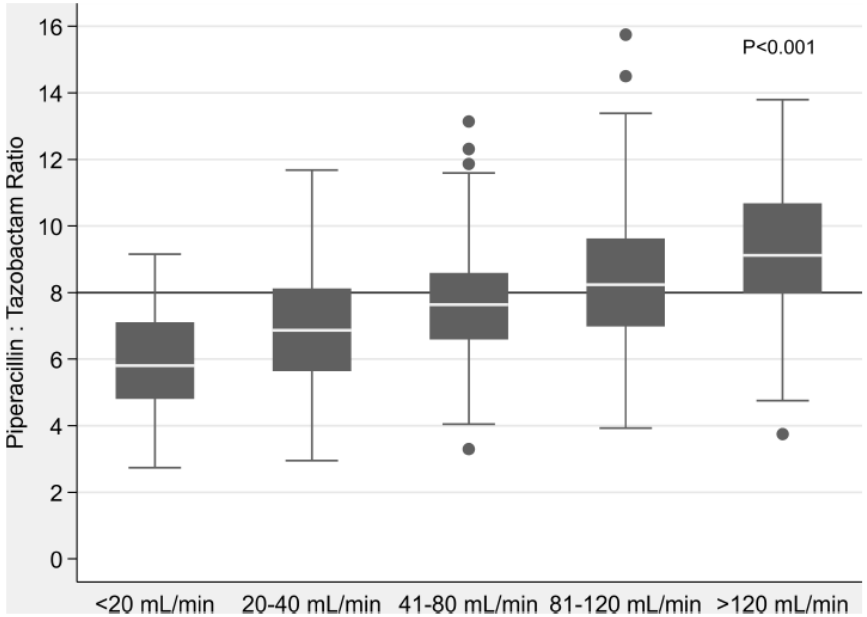


FIG 1 Box and whisker plot (5th and 95th percentiles) of observed piperacillin/tazobactam concentration ratio across different classes of kidney function. The solid line represents the expected value of the concentration ratio based on the 8:1 proportion between piperacillin and tazobactam.

TABLE 4 Probability of optimal, quasi-optimal, and sub-optimal joint PK/PD target attainment at day 3 with different dosages of continuous infusion piperacillin/tazobactam by eGFR in relation to the EUCAST clinical breakpoints of *Enterobacterales* of 8 mg/L[a]

eGFR (mL/min)	Piperacillin/tazobactam dosages (g/day by CI)													
	2.25		4.5		6.75		9		13.5		18		22.5[b]	
	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ
20	17.6	35.9	76.2	91.1	95.4	98.7	99.1	99.6	–[c]	–	–	–	–	–
40	0.7	2.5	25.0	38.1	63.4	75.5	84.5	90.3	–	–	–	–	–	–
60	–	–	–	–	36.6	42.4	62.9	69.9	92.2	93.6	–	–	–	–
80	–	–	–	–	17.3	20.2	38.4	43.0	74.7	80.0	94.2	94.9	–	–
100	–	–	–	–	–	–	–	–	–	–	84.1	84.3	94.6	95.2
120	–	–	–	–	–	–	–	–	–	–	78.5	73.4	87.8	87.0
140	–	–	–	–	–	–	–	–	–	–	66.1	60.6	84.5	80.8
160	–	–	–	–	–	–	–	–	–	–	55.3	50.8	76.0	70.5
180	–	–	–	–	–	–	–	–	–	–	50.4	40.3	67.4	61.8

[a]The shaded areas identify optimal (dark gray) and quasi-optimal (light gray) joint PK/PD target attainment.
[b]Intensified CI tested an increased dose of 22.5 g when eGFR ≥ 100 mL/min. A loading dose of 9 g infused over 1 h was used prior to initiation of the CI regimens.
[c]'–' means "Not assessed".

La clearance come parametro fondamentale assieme al TDM per la modulazione del rapporto tra BL/BLI

J Antimicrob Chemother 2024; **79**: 195–199
https://doi.org/10.1093/jac/dkad367 Advance Access publication 29 November 2023

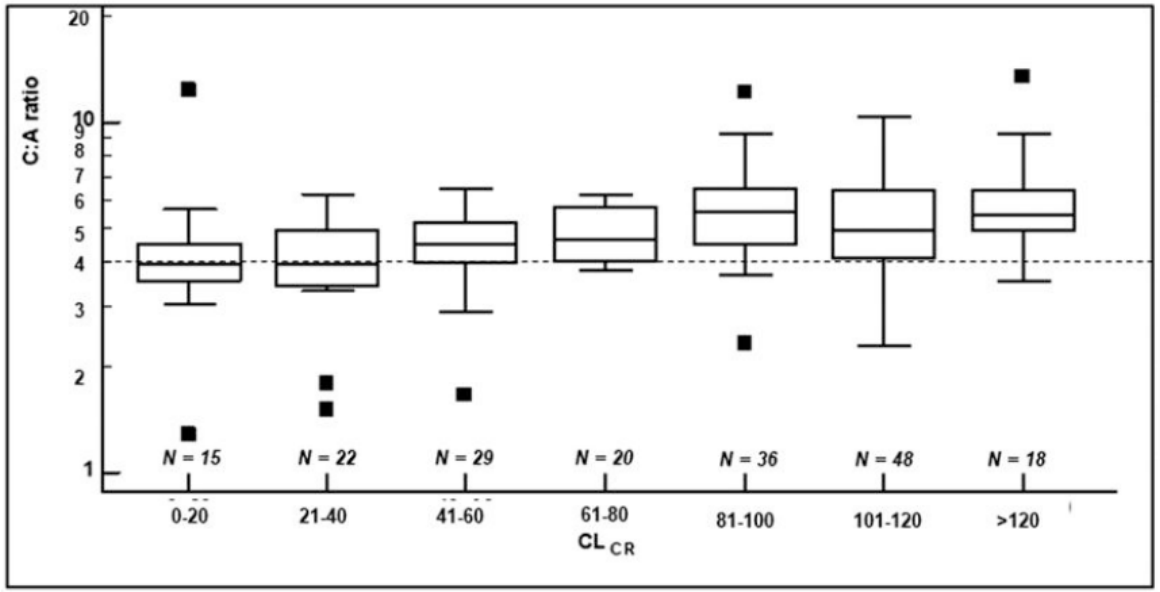
Journal of Antimicrobial Chemotherapy

Cit. «Two is megli che uan»

Therapeutic drug monitoring of ceftazidime/avibactam: why one leg is not enough to run

Milo Gatti [1,2], Pierluigi Viale[1,3] and Federico Pea [1,2]*

Conclusions: The findings may strengthen the contention that for properly assessing the PK/PD target attainment of **ceftazidime/avibactam**, **both ceftazidime and avibactam concentrations should be measured**, given the unpredictability of the ceftazidime-to-avibactam ratio occurring among patients.



CL_{CR}	0-20	21-40	41-60	61-80	81-100	101-120	>120
0-20		0.86	0.13	*0.03*	*0.002*	*0.007*	*0.002*
21-40	0.86		0.41	0.09	*0.002*	*0.016*	*0.002*
41-60	0.13	0.41		0.42	*0.009*	0.12	*0.009*
61-80	*0.03*	0.09	0.42		0.07	0.44	0.06
81-100	*0.002*	*0.002*	*0.009*	0.07		0.26	0.94
101-120	*0.007*	*0.016*	0.12	0.44	0.26		0.23
>120	*0.002*	*0.002*	*0.009*	0.06	0.94	0.23	

Figure 1. Box-and-whisker plots of the ceftazidime-to-avibactam ratios in the incremental classes of CL_{CR}. The dotted line indicates the ceftazidime-to-avibactam ratio value of 4:1 present in the vial of ceftazidime/avibactam. The table summarizes the *P* values obtained by comparing the ceftazidime-to-avibactam ratios in the different classes of CL_{CR} by means of the Mann–Whitney test.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae375

Journal of Antimicrobial Chemotherapy

Nelle infezioni severe, sostenute da germi multiresistenti… l'approccio PK/PD deve essere più aggressivo sia per BL che per BLI.

Therapeutic drug monitoring (TDM) of β-lactam/β-lactamase inhibitor (BL/BLI) drug combinations: insights from a pharmacometric simulation study

Amaury O'Jeanson[1], Elisabet I. Nielsen [1] and Lena E. Friberg [1]*

Table 2. Summary of PK/PD targets for each BL/BLI combination (extracted from EUCAST's rationale documents) and MIC increments used for computation of PTA

BL/BLI drugs	PK/PD target	EUCAST	Severe	Aggressive	$MIC_{BL/BLI}$ (mg/L)
Ceftazidime	$\%fT > MIC$	50%	75%	100%	1–2–4–**8**
Avibactam	$\%fT > C_T$[a]	50%	75%	100%	
Ceftolozane	$\%fT > MIC$	30%	45%	60%	0.5–1–2–**4**
Tazobactam	$\%fT > C_T$[a]	20%	30%	45%	
Imipenem	$\%fT > MIC$	6.5%	15%	35%	0.25–0.5–1–**2**
Relebactam	$fAUC_{0\text{-}24h}/MIC$	≥5.2	≥8	≥12	
Meropenem	$\%fT > MIC$	45%	70%	100%	1–2–4–**8**
Vaborbactam	$fAUC_{0\text{-}24h}/MIC$	≥35	≥50	≥65	
Piperacillin	$\%fT > MIC$	40%	70%	100%	1–2–4–**8**
Tazobactam	$\%fT > C_T$[a]	40%[b]	70%	100%	

In bold: non-species related breakpoints. EUCAST: PK/PD targets sourced from EUCAST rationale documents for BL/BLI combinations; Severe: PK/PD targets for patients with a severe infection; Aggressive: aggressive PK/PD targets.
[a]Threshold concentration (C_T) of 1 mg/L.
[b]The defined portion of the dosing interval for the TAZ target was extrapolated since unspecified in the rationale document.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae375

Therapeutic drug
inhibitor (BL/
pha

Amaury O'Je

La PTA è strettamente legata alla concentrazione del BLI (oltre che del BL) nel sito di infezione.

BL e BLI hanno una differente capacità di penetrare nei vari tessuti/distretti

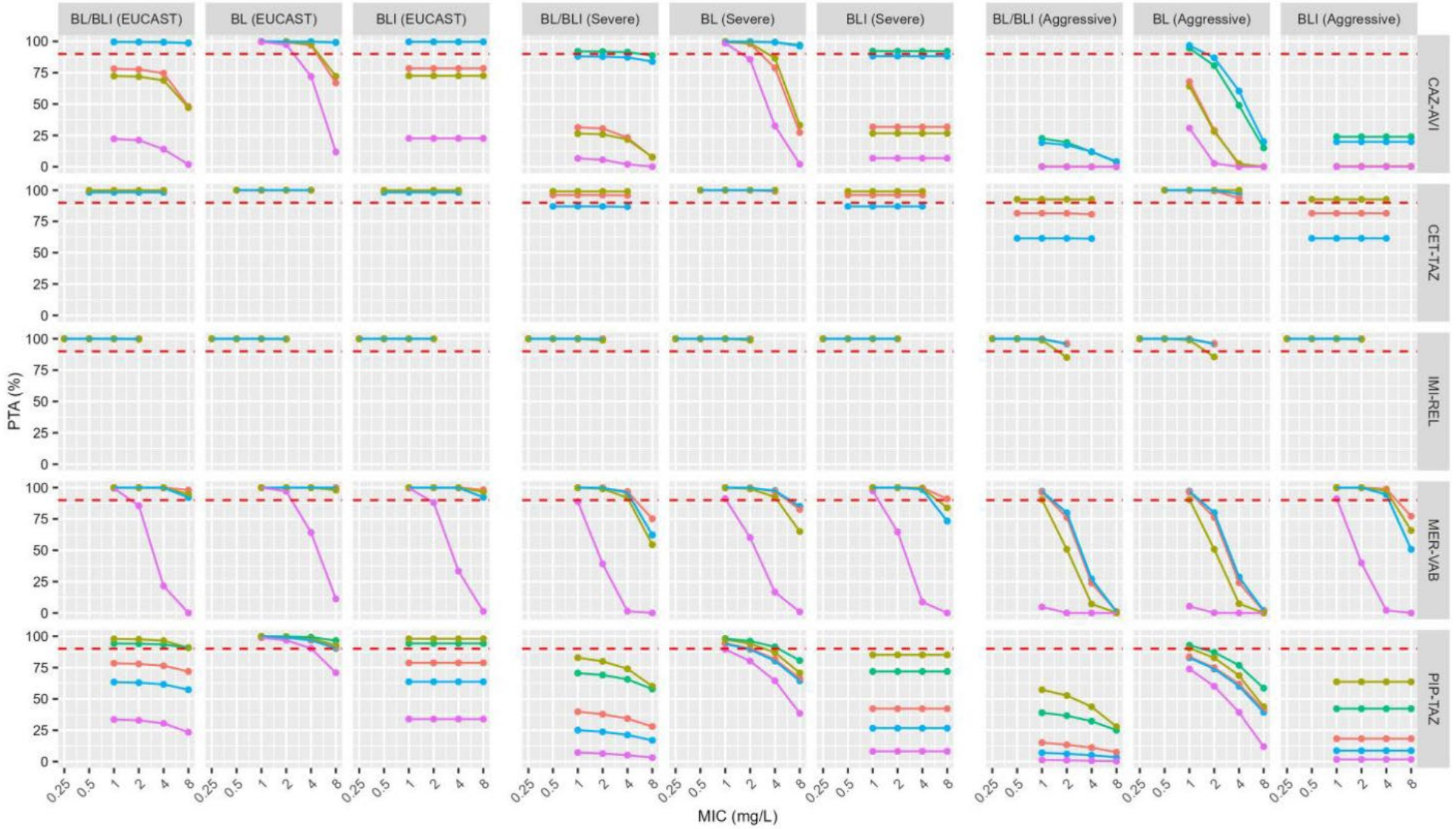


Figure 1. PTA results for CAZ-AVI, CET-TAZ, IMI-REL, MER-VAB and PIP-TAZ in the TRC population. PTA results are stratified by PK/PD targets (EUCAST Severe and Aggressive) and outputted for the BL/BLI combination as a whole, the BL drug alone and the BLI drug alone. Therapeutic indications are cIAI (orange), hospital-acquired pneumonia and ventilator associated pneumonia (mustard), cUTI (including pyelonephritis; cyan), associated bacteraemia (green), and prostatitis (purple). Red dashed line represents 90% PTA threshold. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae375

Journal of Antimicrobial Chemotherapy

Criticità teorica:

- Modelli matematici e simulazioni… guidati però dal TDM.

Criticità pratica:

- Non tutti sono in grado di dosare i BL (e soprattutto i BLI)

Therapeutic drug monitoring (TDM) of β-lactam/β-lactamase inhibitor (BL/BLI) drug combinations: insights from a pharmacometric simulation study

Amaury O'Jeanson[1], Elisabet I. Nielsen [1] and Lena E. Friberg [1]*

Results: Using EUCAST targets, satisfactory (≥90%) PTA was observed for BLs in patients with typical renal clearance (CrCL of 80 mL/min) across various sites of infection. However, results varied for BLIs. Avibactam achieved satisfactory PTA only in plasma, with reduced PTAs in abdomen (78%), lung (73%) and prostate (23%). Similarly, tazobactam resulted in unsatisfactory PTAs in intra-abdominal infections (79%), urinary tract infections (64%) and prostatitis (34%). Imipenem-relebactam and meropenem-vaborbactam achieved overall satisfactory PTAs, except in prostatitis and high-MIC infections for the latter combination.

Conclusions: This study highlights the risk of solely relying on TDM of BLs, as this can indicate acceptable exposures of the BL while the BLI concentration, and consequently the combination, can result in suboptimal performance in terms of bacterial killing. Thus, **dose adjustments also based on plasma concentration measurements of BLIs**, in particular for avibactam and tazobactam, can be valuable in clinical practice to obtain effective exposures at the target site.

antibiotics

MDPI

Article

Role of a Real-Time TDM-Based Expert Clinical Pharmacological Advice Program in Optimizing the Early Pharmacokinetic/Pharmacodynamic Target Attainment of Continuous Infusion Beta-Lactams among Orthotopic Liver Transplant Recipients with Documented or Suspected Gram-Negative Infections

Milo Gatti [1,2,*], Matteo Rinaldi [1,3], Cristiana Laici [4], Antonio Siniscalchi [4], Pierluigi Viale [1,3] and Federico Pea [1,2]

...nella Real Life...

Results:
Overall, 77 critically ill OLT recipients (median age, 57 years; male, 63.6%; medianMELD score at transplantation, 17 points) receiving a total of 100 beta-lactam treatment courses, were included. Beta-lactam therapy was targeted in 43% of cases. Beta-lactam dosing adjustments were provided in 76 out of 100 first TDM assessments (76.0%; 69.0% decreases and 7.0% increases), and overall, in 134 out of 245 total ECPAs (54.7%). Optimal PK/PD target was attained early in 88% of treatment courses, and throughout beta-lactam therapy in 89% of cases. **Augmented renal clearance (ARC; OR 7.64; 95%CI 1.32–44.13) and MIC values above the EUCAST clinical breakpoint (OR 91.55; 95%CI 7.12–1177.12) emerged as independent predictors of failure in attaining early optimal beta-lactam PK/PD targets.**
Conclusion:
A real-time TDM-guided ECPA program allowed for the attainment of optimal beta-lactam PK/PD targets in approximately 90% of critically ill OLT recipients treated with CI beta-lactams during the early post-transplant period.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

AGGIORNAMENTI 2019

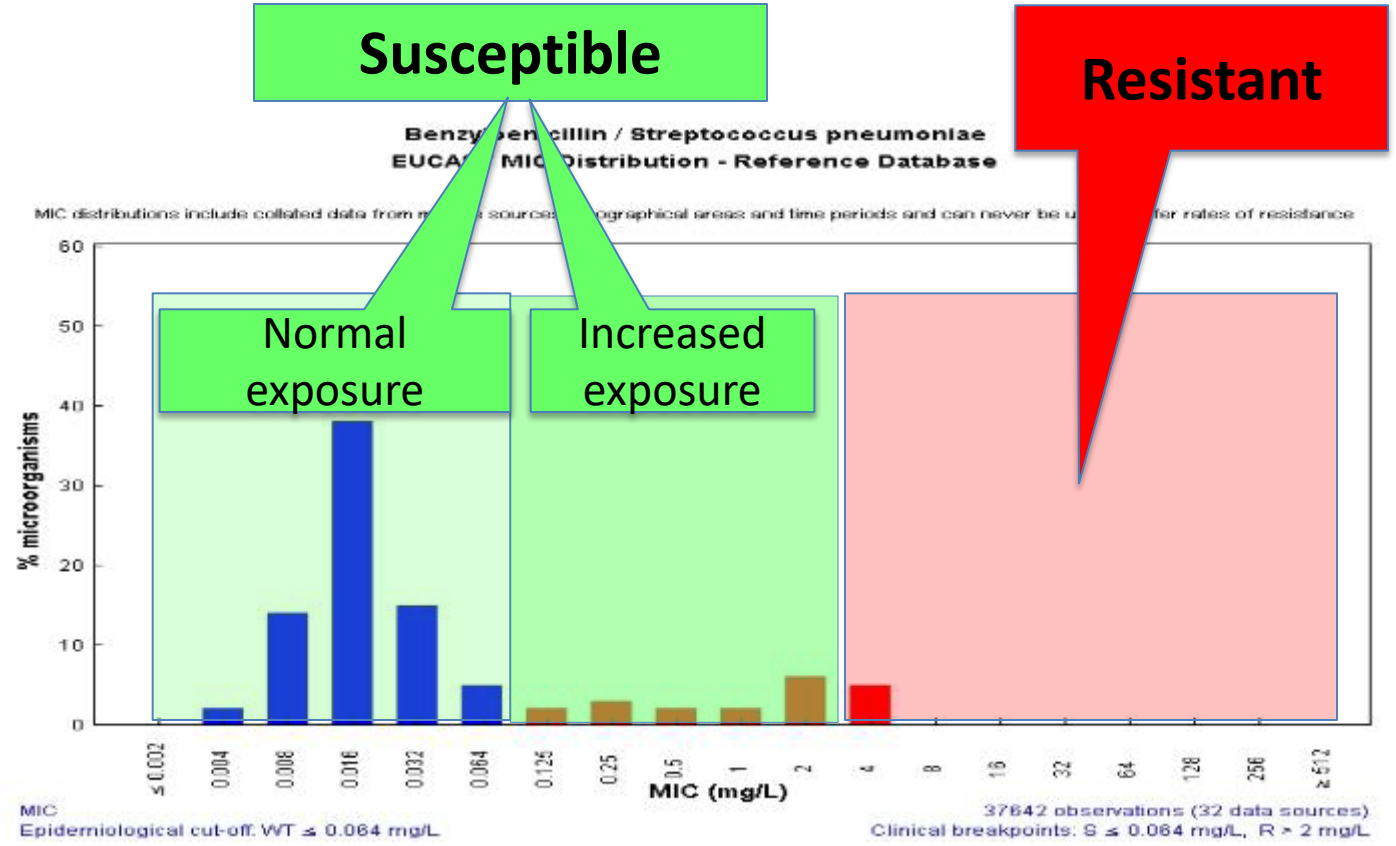
Il cambiamento più significativo

EUCAST ha deciso di cambiare la definizione di ceppo **SENSIBILE**, **INTERMEDIO** e **RESISTENTE** mantenendo le abbreviazioni S, I e R.

I Breakpoints nelle ”tabelle breakpoint” sono **clinici**, cioè sono indicativi per predire l’outcome

SIR - new definitions 2019

a role for therapeutic drug monitoring



Siamo tutti convinti?

Chiediamo tutti il TDM ai nostri laboratori per BL/BLI?

General limitations to TDM for anti-infective drugs

The two **most relevant limitations**:

- **Availability of TDM equipment set up (LC-MS/MS)** by **bioanalytical experts** with **analytical methods having short turnaround times (TAT)**

- **Appropriate interpretation of TDM results** by clinical pharmacological experts for prompt dosing adaptation

Gatti *et al. Critical Care* (2022) 26:178

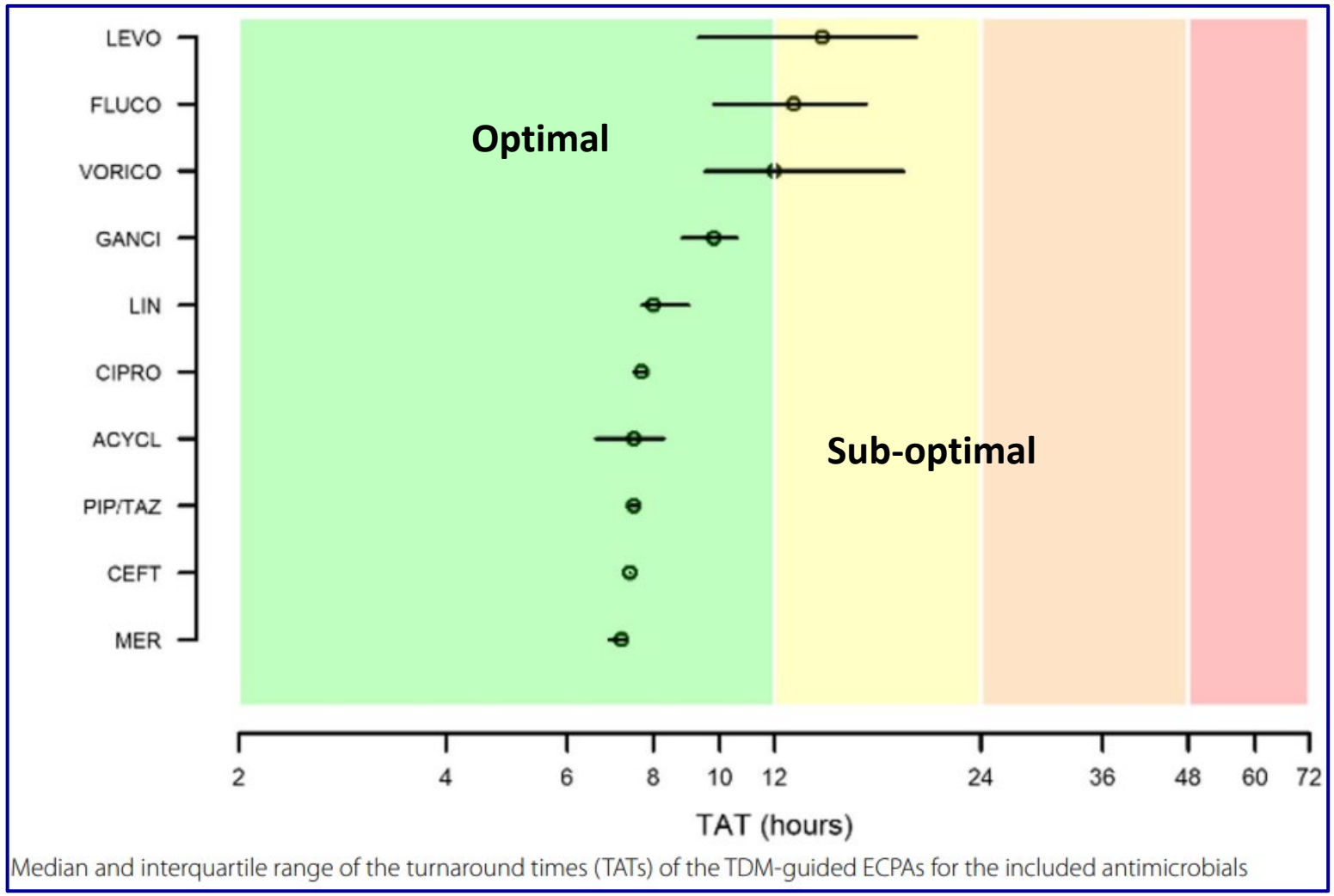
Mission Impossible?

RESEARCH Open Access

Expert clinical pharmacological advice may make an antimicrobial TDM program for emerging candidates more clinically useful in tailoring therapy of critically ill patients

Milo Gatti[1,2], Pier Giorgio Cojutti[2], Michele Bartoletti[1,3], Tommaso Tonetti[1,4], Amedeo Bianchini[5], Stefania Ramirez[6], Giacinto Pizzilli[4], Simone Ambretti[7], Maddalena Giannella[1,3], Rita Mancini[6], Antonio Siniscalchi[5], Pierluigi Viale[1,3] and Federico Pea[1,2*]

Gatti *et al. Critical Care* (2022) 26:178
https://doi.org/10.1186/s13054-022-04050-9



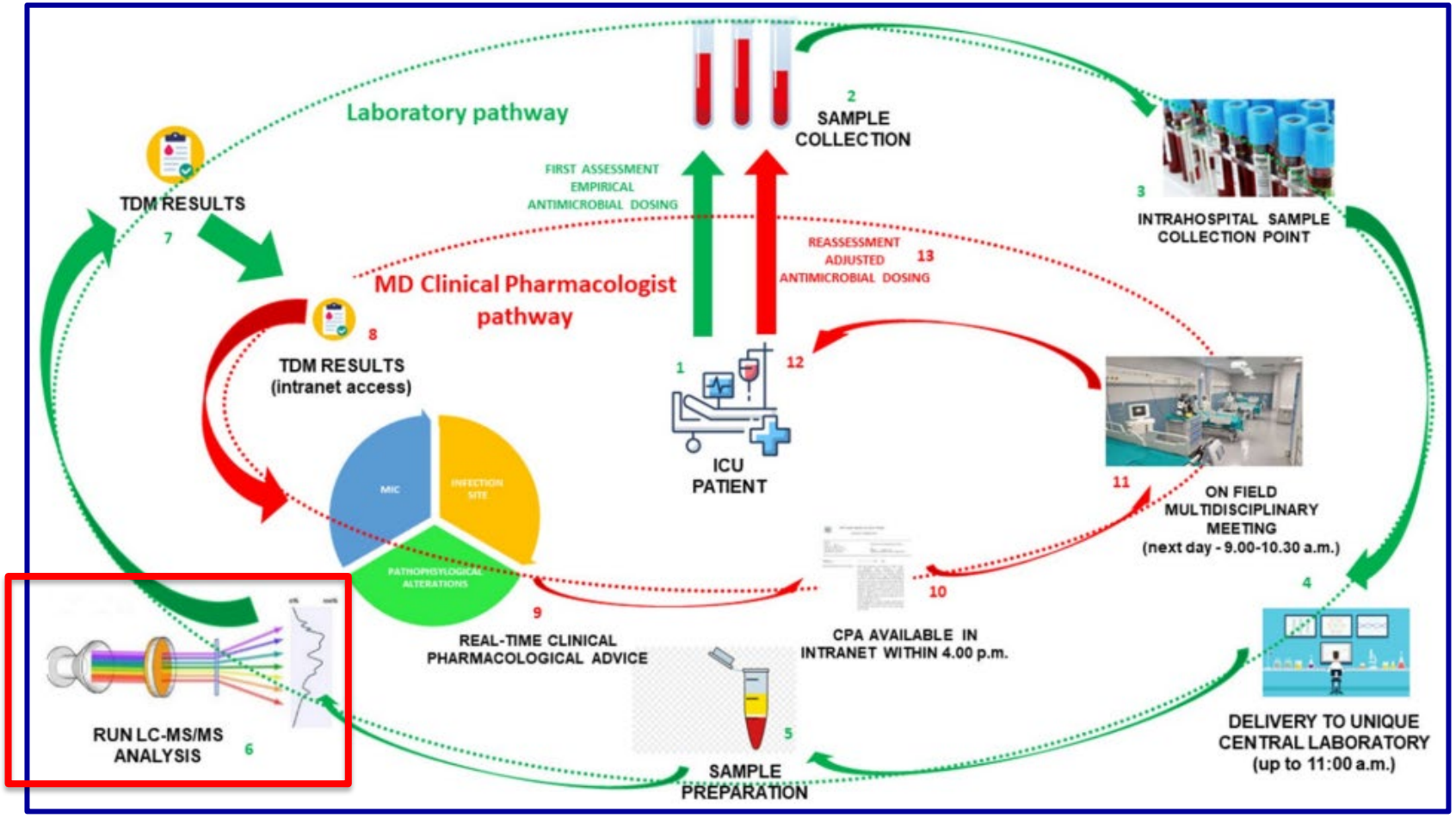
Median and interquartile range of the turnaround times (TATs) of the TDM-guided ECPAs for the included antimicrobials

RESEARCH Open Access

Expert clinical pharmacological advice may make an antimicrobial TDM program for emerging candidates more clinically useful in tailoring therapy of critically ill patients

Milo Gatti[1,2], Pier Giorgio Cojutti[2], Michele Bartoletti[1,3], Tommaso Tonetti[1,4], Amedeo Bianchini[5], Stefania Ramirez[6], Giacinto Pizzilli[4], Simone Ambretti[7], Maddalena Giannella[1,3], Rita Mancini[6], Antonio Siniscalchi[5], Pierluigi Viale[1,3] and Federico Pea[1,2*]

Experience from University of Bologna: Optimizing organizational phase, analytical phase and pharmacological counselling phase for ICU



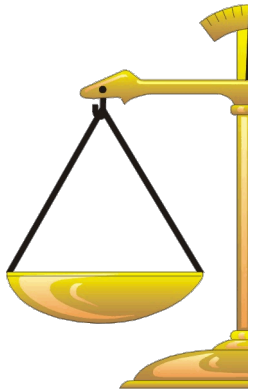
Gatti *et al. Critical Care* (2022) 26:178
https://doi.org/10.1186/s13054-022-04050-9

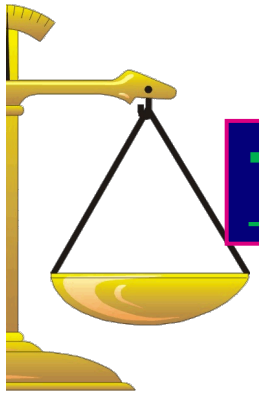
Pharmacology Laboratory

How can performance be improved?

AUTOMATION

NEED





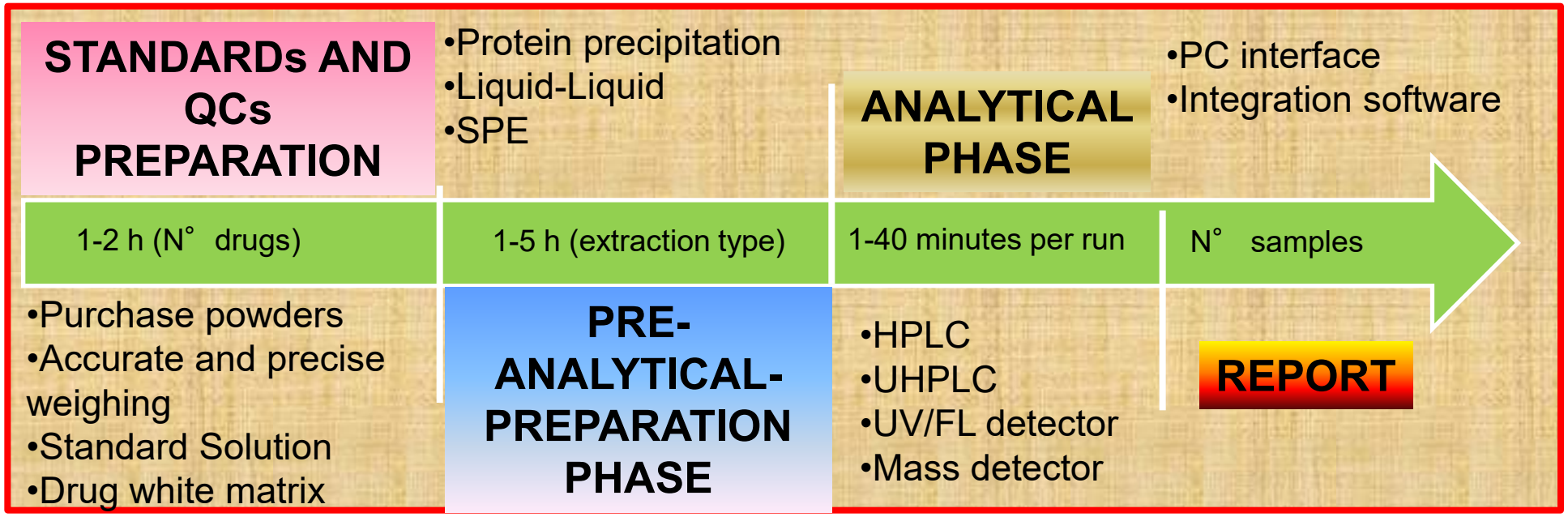
TECHNOLOGY

- Number of samples
- Time reduction
- Cost reduction (personnel)

…following the example of fast-microbiology…

- Transport of the test tube to the laboratory
- Reagents / Calibrators-Controls KIT
- Sample extraction
- Analytical Instrumentation
  - HPLC-UHPLC / UV-FL-MS / MS
  - Immunometric assays

QUANTIFICATION OF DRUGS IN CHROMATOGRAPHY (from a fast-pharmacology perspective)



These phases can be:

- **AUTOMATED**
- **FASTER**
- **MORE ACCURATE AND PRECISE**

Fast-microbiology

Virtuous example to follow!

RESULTS of Fast-Microbiology

- 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

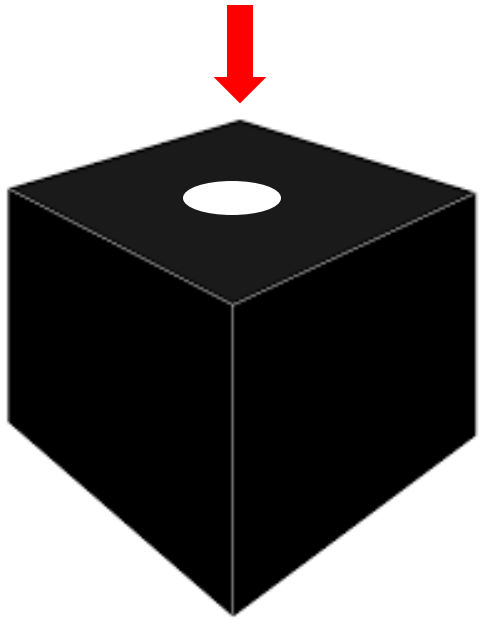
increase in direct costs
impact of the organization on the laboratory

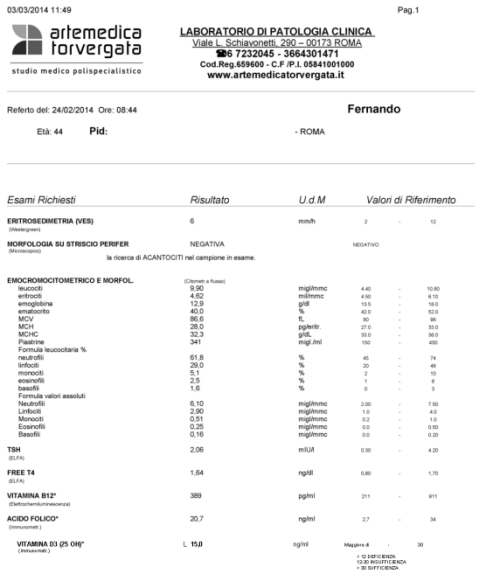
New diagnostic technologies make it possible to significantly shorten response times (they do not depend only on the choice of the test but also on the organization of the laboratory)

- **New biomarkers**
- **POCT**
- **Liquid handler**
- **Analyzers**
- **….other….**

The ideal solution (together with the KIT) is…

Withdrawal **Black-Box with a single button!** **Report!**





03/03/2014 11:49 Pag.1

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Referto del: 24/02/2014 Ore: 08:44 **Fernando**

Età: 44 **Pid:** - ROMA

Esami Richiesti	*Risultato*	*U.d.M*	*Valori di Riferimento*
ERITROSEDIMETRIA (VES)	6	mm/h	2 - 12
MORFOLOGIA SU STRISCIO PERIFER	NEGATIVA		NEGATIVO
la ricerca di ACANTOCITI nel campione in esame.			
EMOCROMOCITOMETRICO E MORFOL.			
leucociti	9,90	mig/mmc	4.40 - 10.60
eritrociti	4,62	mil/mmc	4.50 - 6.10
emoglobina	12,9	g/dl	13.5 - 18.0
ematocrito	40,0	%	40.0 - 53.0
MCV	86,6	fL	80 - 98
MCH	28,0	pg/eritr.	27.0 - 33.0
MCHC	32,3	g/dL	33.0 - 36.0
Piastrine	341	migl./ml	150 - 450
Formula leucocitaria %			
neutrofili	61,8	%	45 - 74
linfociti	29,0	%	20 - 46
monociti	5,1	%	2 - 10
eosinofili	2,5	%	1 - 6
basofili	1,6	%	0 - 3
Formula valori assoluti			
Neutrofili	6,10	migl/mmc	2.00 - 7.50
Linfociti	2,90	migl/mmc	1.0 - 4.0
Monociti	0,51	migl/mmc	0.2 - 1.0
Eosinofili	0,25	migl/mmc	0.0 - 0.50
Basofili	0,16	migl/mmc	0.0 - 0.20
TSH (ELFA)	2,06	mIU/l	0.30 - 4.20
FREE T4 (ELFA)	1,64	ng/dl	0.80 - 1.70
VITAMINA B12° (Elettrochemiluminescenza)	389	pg/ml	211 - 911
ACIDO FOLICO° (Immunometr.)	20,7	ng/ml	2.7 - 34
VITAMINA D3 (25 OH)° (Immunometr.)	L 15,0	ng/ml	Mag-giu-ott 4 - 30

< 10 DEFICIENZA
10-30 INSUFFICIENZA
> 30 SUFFICIENZA

Liquid handling + LC-MS/MS

Coming soon…

Others on the way?!?!

Implementation of Fast-Pharmacology should allow to…

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2020, VOL. 13, NO. 4, 355–366
https://doi.org/10.1080/17512433.2020.1759413

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

The management of anti-infective agents in intensive care units: the potential role of a 'fast' pharmacology

Dario Cattaneo [a,b], Alberto Corona [c], Francesco Giuseppe De Rosa [d], Cristina Gervasoni [b,e], Danijela Kocic [f] and Deborah Je Marriott [g]

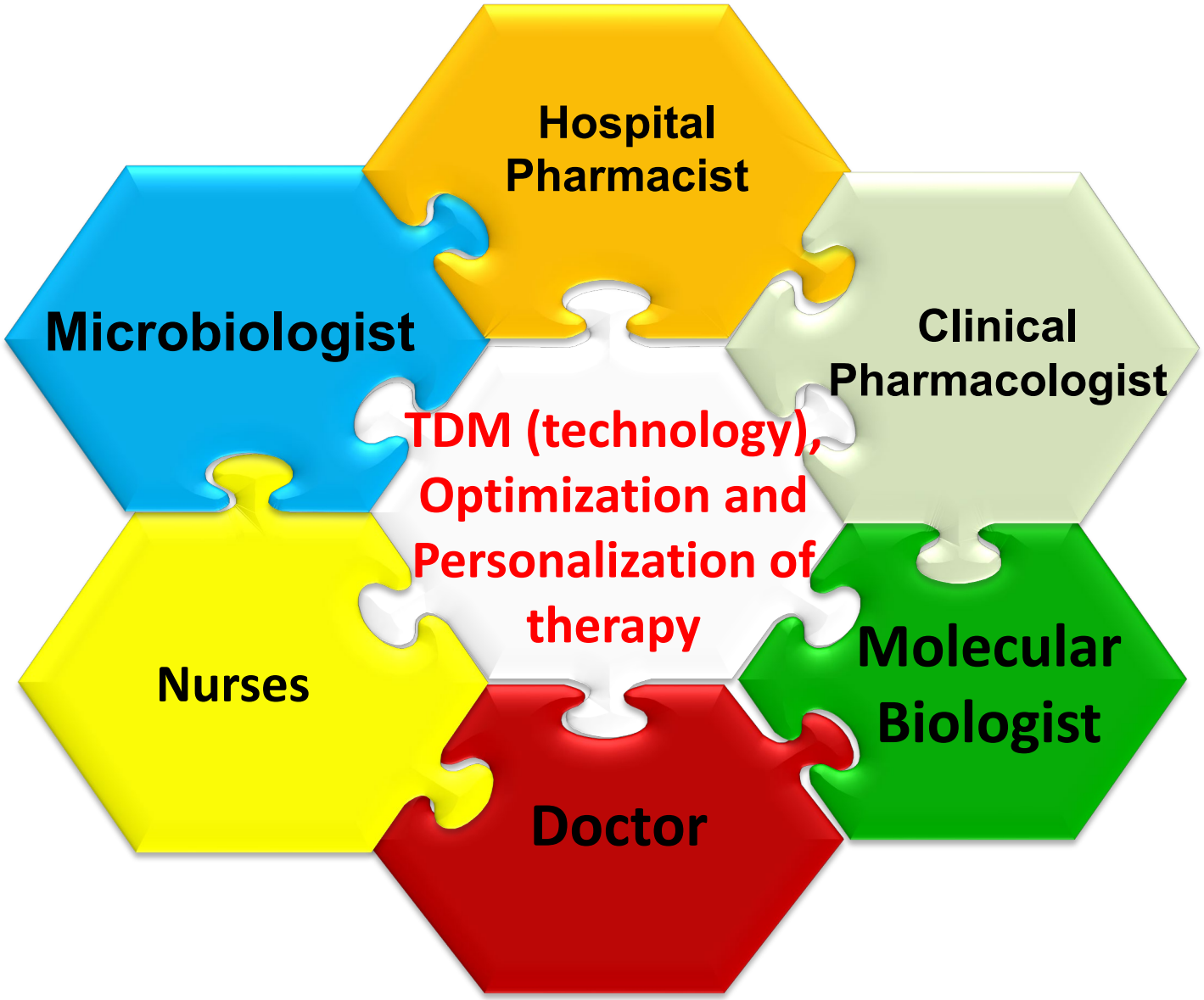
- ✓ Rapid diagnostic tests for therapeutic drug monitoring
- ✓ Matching pharmacology with clinics
- ✓ Prompt reactions to suboptimal drug exposure
- ✓ **PK/PD assessments at the bedside**

Moreover

- ✓ It is cost-effective!!!

- Cattaneo, Expert Rev Clin Pharmacol 2020 -

Anti-infective therapy… many professionals participate (or should participate) in the success of the «FAST» personalization of the therapy.



Conclusions

- **Therapeutic monitoring (TDM) of anti-infective drugs (BL/BLI) represents an important activity aimed at improving drug therapies** in terms of:
  - Percentage of clinical and microbiological cure
  - Duration of treatment
  - Containment of healthcare costs and indirect costs
  - Prediction of potential drug interactions
  - Avoid the onset of resistance (further new resistances)

- **TDM is useful both in the management of antibiotic and antifungal therapy ... but only with a very rapid TAT (less than 4-6 hours; maximum 12-24 hours depending by drug), associated with the MIC for the use of the most appropriate PK/PD parameters.**

- **BL/BLI must be both quantified with TDM**

- **Fast-pharmacology is possible, but there is a need for investment in new technologies (kits, automatic preparers, LC-MS/MS) and dedicated personnel…. As happened for fast-microbiology 15-20 years ago!**

- **Beginning: clinicians (in ITALY) must start requiring for the TDM to get it !!!**
  (need to reach a critical number of requests to justify the technological implementation) …to make it come REALITY.

Presidente della Regione Liguria
Marco Bucci

Ministro della Sanità
Orazio Schillaci

…Rasi… e molti altri…

TDM costs from a fast-pharmacology perspective...criticality? ...sustainable?

Rate schedule Piedmont Region (2013) for TDM

CODBRANCA	CODPRESTAZIONE	DESCRPRESTAZIONELARGE	TARIFFA
98	90.20.8	FARMACI con test di 2° livello (HPLC o gasmassa)	25.00

98		90.08.3	ANTIBIOTICI - Aminoglicosidi, Vancomicina.		8,90

New “LEA” 2024/25???

ALLEGATO 2

PRESTAZIONI di ASSISTENZA SPECIALISTICA AMBULATORIALE
(ALLEGATO 4 DPCM LEA 12.01.2017)

90.17.B	**FARMACI CON METODI CROMATOGRAFICI**	**€ 10,25**
90.17.C	**FARMACI CON TECNICHE NON CROMATOGRAFICHE**	**€ 6,80**

- Economic differences in reimbursability ... numbers make a difference to compensate for new technology!!!
- We need investment in diagnostics!!!

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Prof. Andrea Calcagno
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Laura Trentini
Letizia Marinaro
Giuseppe Cariti
Lucio Boglione
Silvia Corcione

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Gianluca Bianco
. Maria Alessandra Pavan .
Marco Simiele
Domenico Maiese
Fabio Favata
Elena Cat Genova

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