

**Ceftazidime-avibactam to treat
severe deep-seated infections
due to KPcp in the critically ill**

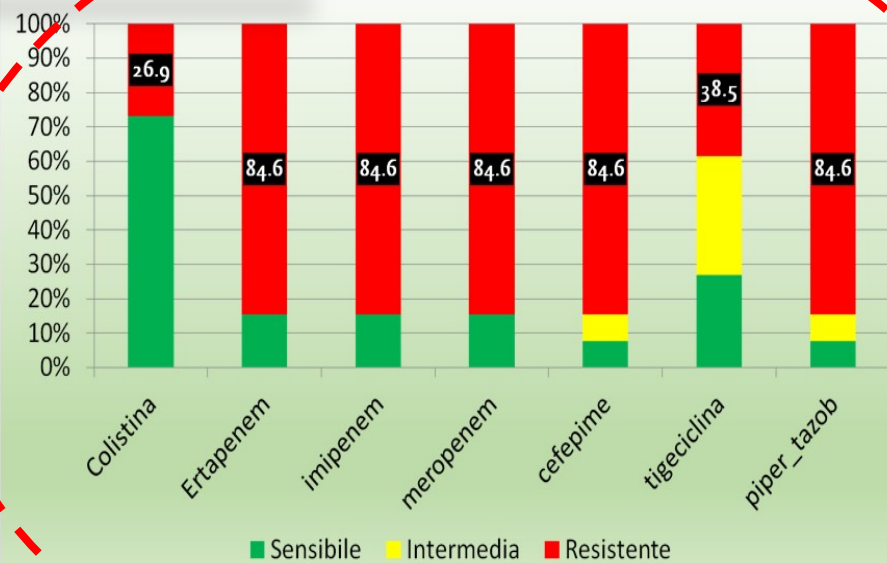
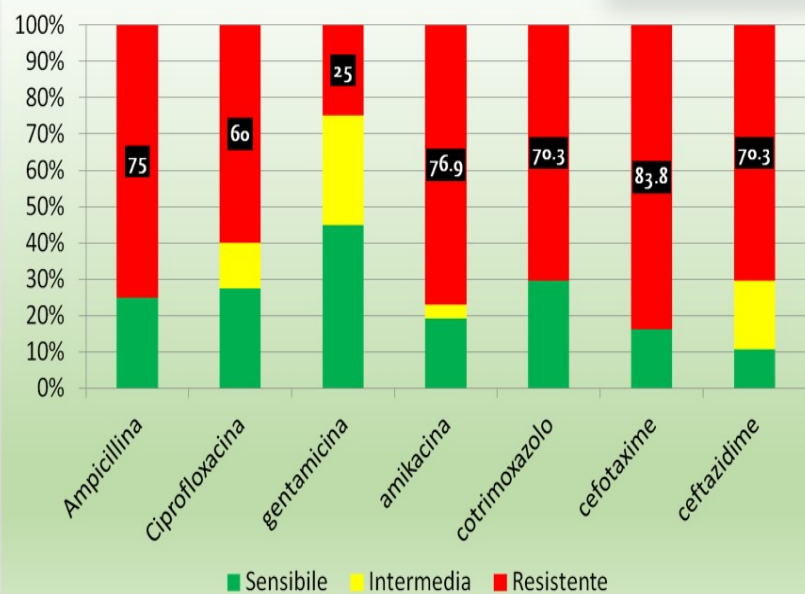
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**Nuove Prospettive nellaterapia delle infezioni da
batteri Gram negativi MDR
Milano, Hotel Michelangelo 17/04/2018**

Background

Klebsiella pneumoniae



Methods

Uso Compassionevole ceftazidime-avibactam



- Autorizzazione «fast track» via Gruppo Ristretto Comitato Etico, Area 1, Milano: Presidente Prof. Anna Maria Di Giulio
- Tempo medio di Risposta: < 24 ore

Results-1: Demographics

Results-1: Demographics

Variable	Values
M:F (ratio)	3:1
Età yrs - mean (SD) / median (IQR)	58,1 (15,7) / 59,5 (42,5-4,5)
ICU LoS days - mean (SD) / median (IQR)	35,7 (31,3) / 29 (9-46)
H LoS days - mean (SD) / median (IQR)	74,8 (56,1) / 50 (32-121)
ED / Ward (ratio)	1:0,85

Results-2a: Risk factors

• Pregresse IVU • Pregresse infezioni MDR • Pregresse infezioni XDR	• 2/18 (E. coli / KP-cp) • 6/18 • 7/18 (6 class A, 1 class B, β-lactam.)
• MRSA-carrier • ESBL-carrier • VRE-carrier	• 2/18 • 0/18 • 0/18
• Pregressa Chirurgia	• 15/18 • 7 addominale • 4 CCH • 2 urologica • 1 ortopedica
• CVC • CV • SNG	18/18 18/18 15/18

Results-2b: Risk factors

- Drenaggio chirurgico
- VAM
- CVVH
- CVC
- NPT
- NE
- COPD
- IRC
- Immunosoppressione
- CCI: mean (SD) - median (IQR)
- Antibiotici (0-90 gg)
- (durata media 18 giorni)

• 12/18

• 11/18

• 7/18

• 18/18

• 15/18

• 4/18

• 4/18

• 6/18

• 3/18

• 3.7 (2.3) - 3 (2-7)

• 13/18

- Carbapenemici

- Chinolonici

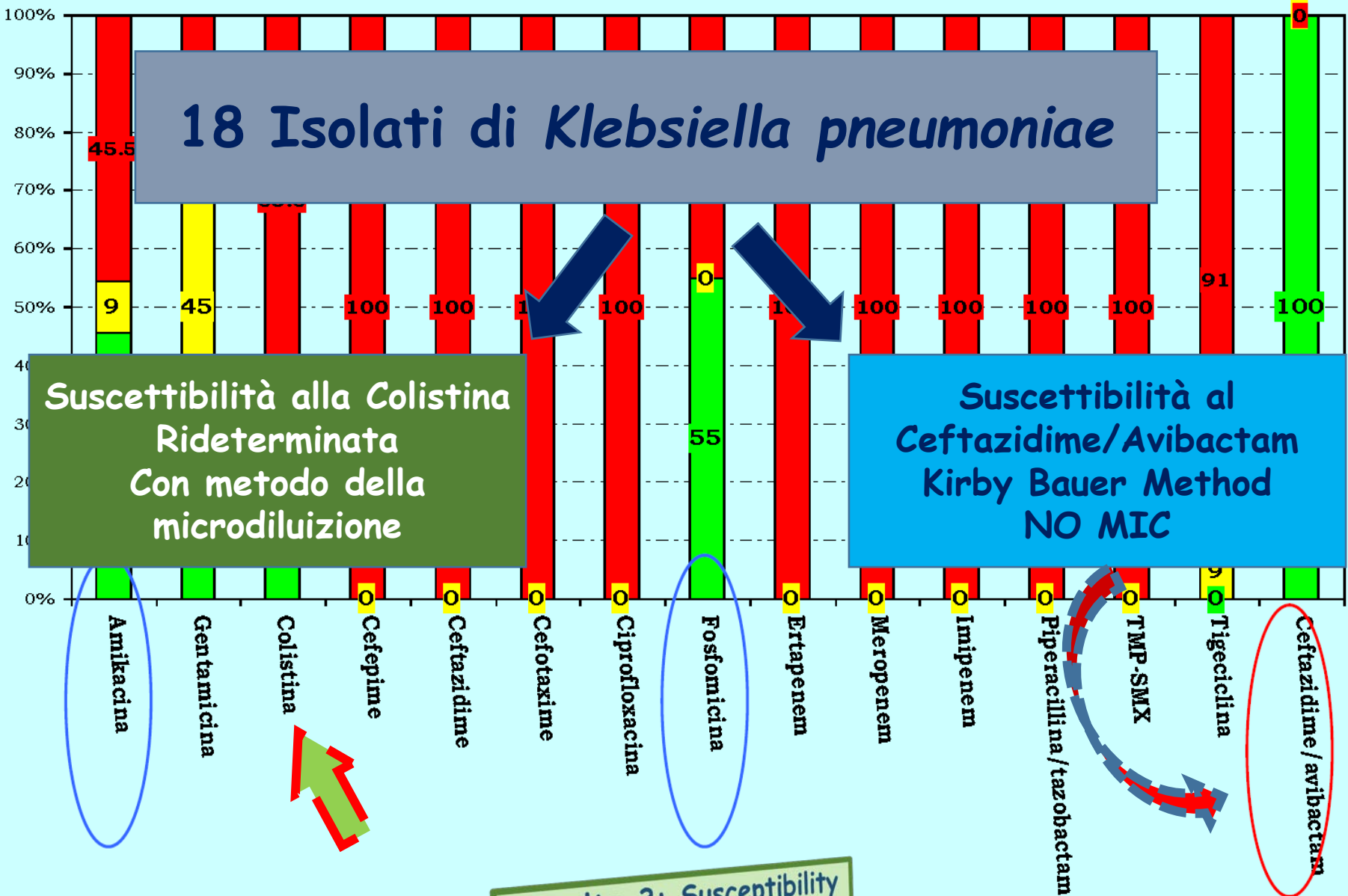
- Piperacillina/tazobactam



18 Isolati di *Klebsiella pneumoniae*

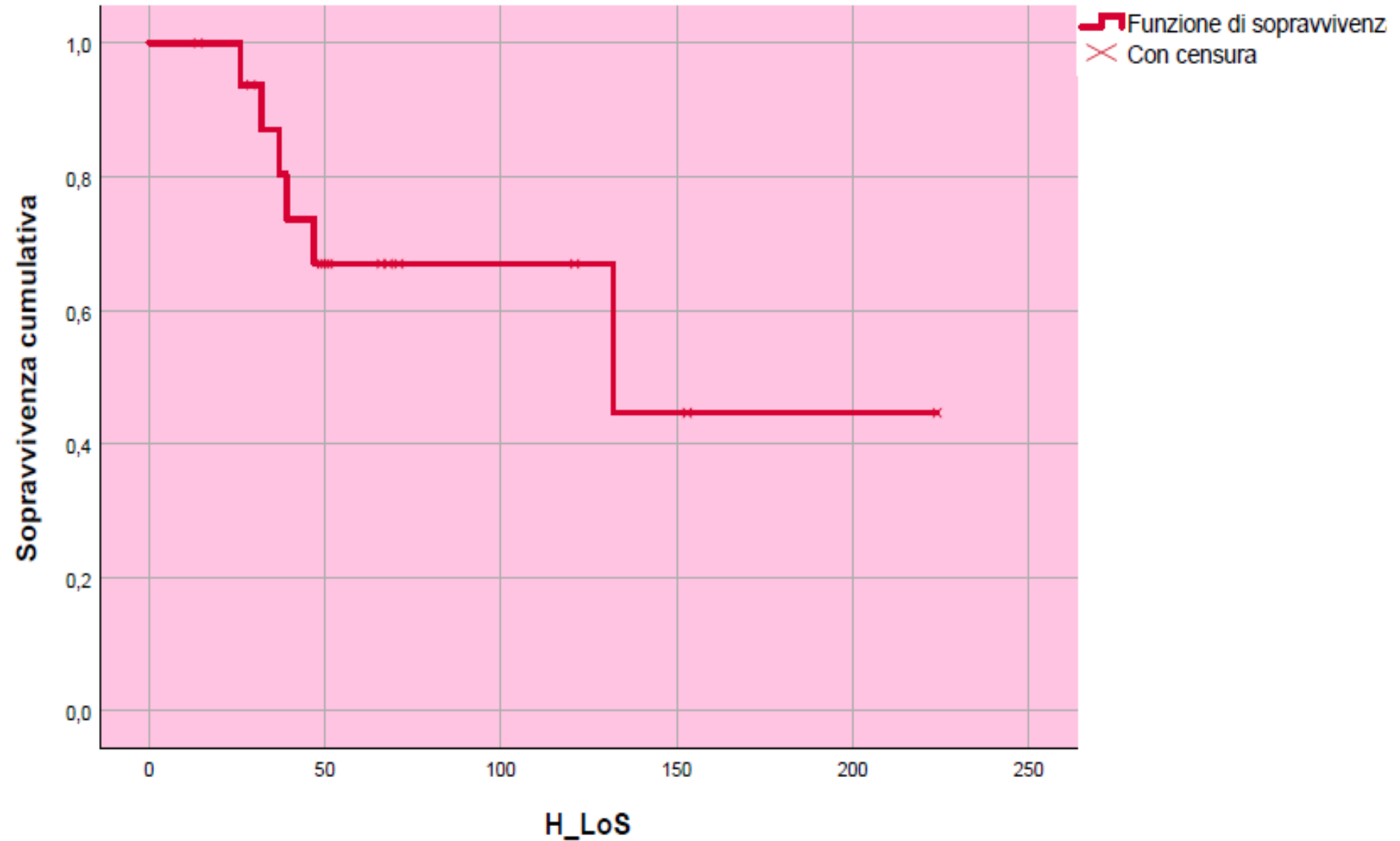
Suscettibilità alla Colistina
Rideterminata
Con metodo della
microdiluizione

Suscettibilità al
Ceftazidime/Avibactam
Kirby Bauer Method
NO MIC



Results-3: Susceptibility
Pattern's

Funzione di sopravvivenza



HIV/HCV+ in cART
CAZ-AVY: 13 days
Gentamicin 7 days

(Colangitis)
 HIV+ in C-ART
CAZ-AVY: 14 days

#	Severità di Malattia	Esito	Gg Terapia	Risposta Clinica	Risposta Microbiologica
2	Shock Settico	dimesso da H	13	si	si
11	Sepsi	dimesso da H	14	si	transitoria
16	Shock Settico	deceduto	13	si	transitoria
18	Shock Settico	dimesso da H	12	si	transitoria

CAZ-AVY:13 days
Aztreonam: 13 days

Kidney TX
CAZ-AVY: 12 days

Results-5a: Treatment

Results-5a:

Pancreatitis
CAZ-AVY: 14 days
Colistin: 22 days
Fosfomicin: 5 days

Results-5b:
 Treatment

Pancreatitis
CAZ-AVY: 14 days

#	Severità di Malattia	Patologia	Esito	Gg	Risposta	Risposta
1	Shock Settico	Peritonite II stercoracea batteriemica	deceduto			
4	Shock Settico	Peritonite II stercoracea	dimesso da H			
5	Sepsi	Peritonite II stercoracea	dimesso da H	14	si	si
6	Sepsi	Peritonite II stercoracea	dimesso da H	14		
8	Sepsi	Peritonite II stercoracea	dimesso da H	14		
9	Sepsi	Peritonite II stercoracea	deceduto	13	no	no
12	Shock Settico	Peritonite II stercoracea batteriemica	dimesso da H	17(*)	si	transitoria

Hirschprung Disease
 Colectomy
CAZ-AVY: 14 days
Fosfomicin: 14 days

Gastric AdenoK
CAZ-AVY: 14 days

IBD Colic Resection
CAZ-AVY: 14 days

Colovesical fistula
CAZ-AVY: 14 days

DCP
CAZ-AVY: 14 days

UTI / Ureterostomy
Infection
CAZ-AVY: 14 days

UTI / Ureterostomy
Infection
CAZ-AVY: 14 days
Colistin; 10 days

#	Severità di Malattia	Patologia	Esito	Gg Terapia	Risposta Clinica	Risposta microbiologica
8	Shock Settico	Idronefrosi / IVU in ureterostomia	dimesso da H	14	si	transitoria
10	Shock Settico	Idronefrosi / IVU	dimesso da H	14	si	transitoria
13	Sepsi	Idronefrosi / IVU	dimesso da H	14	si	si

Results-5c: Treatment

Results-5c: Treatment

(SVA + CABG)
CAZ-AVY: 14 days

Mediastinitis (ECMO)
CAZ-AVY: 14 days
Colistin: 22 days
Fosfomycin: 5 days

Results-5d: Treatment

Results-5d: Treatment

#	Sede Isolamento KPC	Malattia	Patologia	Esito	Gg Terapia	Risposta Clinica	Risposta microbiologica
2	sangue materiale mediastinico	Shock Settico	Mediastinite batteriemia	deceduto	14	no	no
14	sangue materiale mediastinico	Sepsi	Mediastinite batteriemia	deceduto	14	si	no
15	BAL	Shock Settico	VAP	deceduto	12	si	si

Aortic Dissection
CAZ-AVY: 12 days
Fosfomycin: 12 days

**Mediastinitis
(SVA + CABG)**
CAZ-AVY: 14 days

Results-5e: Treatment

Terapia:

• Monotherapy :

• Main Association

• Fosfomicin + Colistin

• Fosfomicin + Aztreonam

• Fosfomicin + Gentamicin

• Fosfomicin

• Colistin



Emerging Gram negativ X + v

https://www.ncbi.nlm.nih.gov/pubmed/?term=fosfomicin+synergy+ceftazidime-avibactam

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NCBI Resources How To Sign in to NCBI

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[Expert Rev Anti Infect Ther](#). 2018 Mar 21;1-18. doi: 10.1080/14787210.2018.1453807. [Epub ahead of print]

Emerging Gram negative resistance to last-line antimicrobial agents fosfomicin, colistin and ceftazidime-avibactam - epidemiology, laboratory detection and treatment implications.

[Sherry N](#)^{1,2}, [Howden B](#)^{1,2}.

Author information

Abstract

Multidrug-resistant (MDR) and extensively-drug-resistant (XDR) Gram-negative bacteria have emerged as a major threat to human health globally. This has resulted in the 're-discovery' of some older antimicrobials and development of new agents, however resistance has also rapidly emerged to these agents. Areas covered: Here we describe recent developments in resistance to three of the most important last-line antimicrobials for treatment of MDR and XDR Gram negatives: fosfomicin, colistin and ceftazidime-avibactam. Expert commentary: A key challenge for microbiologists and clinicians using these agents for treating patients with MDR and XDR Gram negative infections is the need to ensure appropriate reference methods are being used to test susceptibility to these agents, especially colistin and fosfomicin. These methods are not available in all laboratories meaning accurate results are either delayed, or potentially inaccurate as non-reference methods are employed. Combination therapy for MDR and XDR Gram negatives is likely to become more common, and future studies should focus on

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Laboratory diagnosis, clinical management and infection con [Clin Microbiol Infect. 2016]

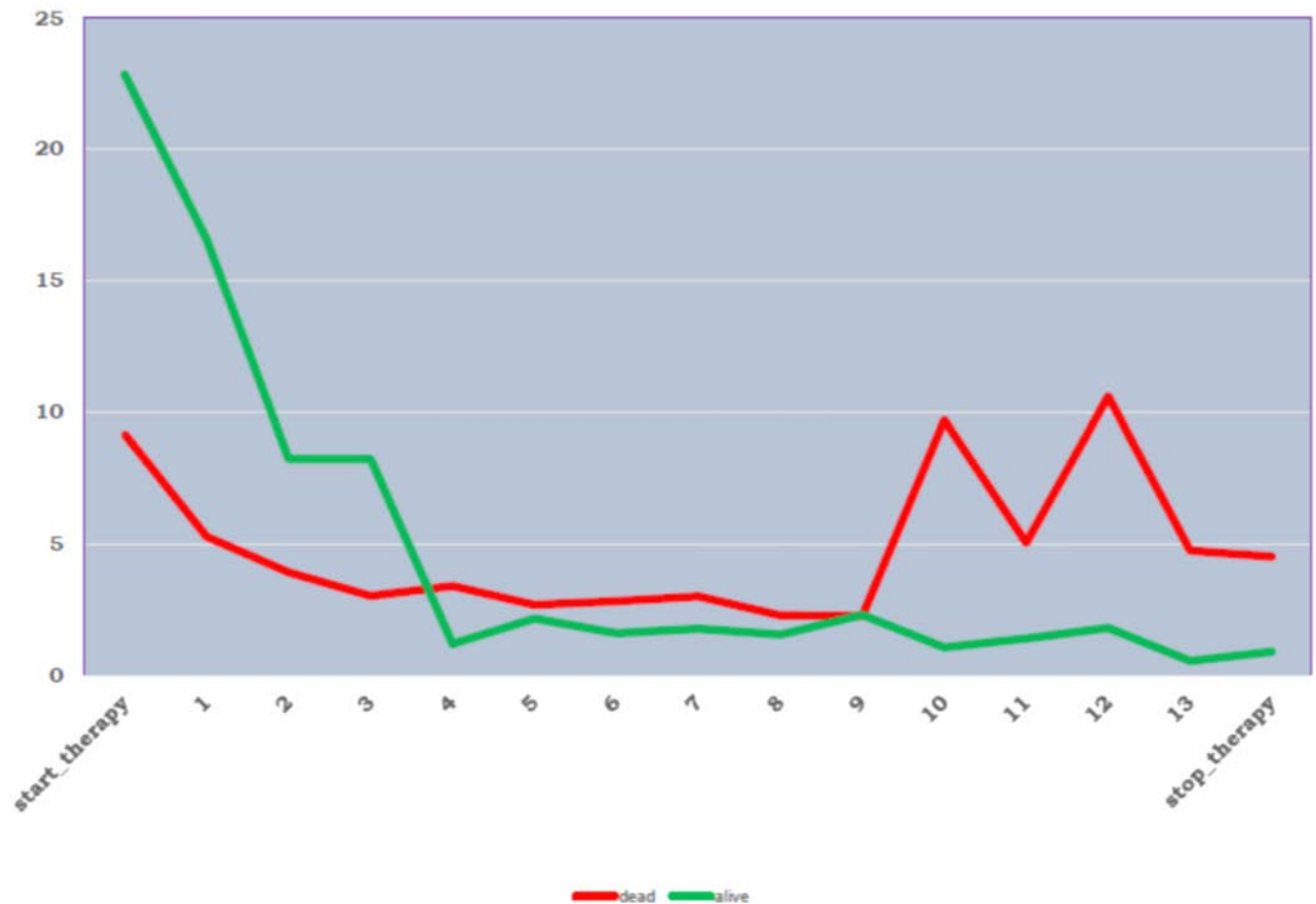
[1 patient with IVU complicated by ureteronefroscopy infection (previous fosfomicin)]



Results-5a: Monitoring of Therapy Efficacy

Results-5a: Monitoring
of Therapy Efficacy

Trend PCT



Results-5b: Monitoring
of Therapy Efficacy

Colonisation
Index (CI)

Numero dei campioni di sorveglianza positivi per KP-cp

Numero totale dei campioni di sorveglianza eseguiti

probabilità
dipendente
da CI

Infection
Index (II)

= CI *

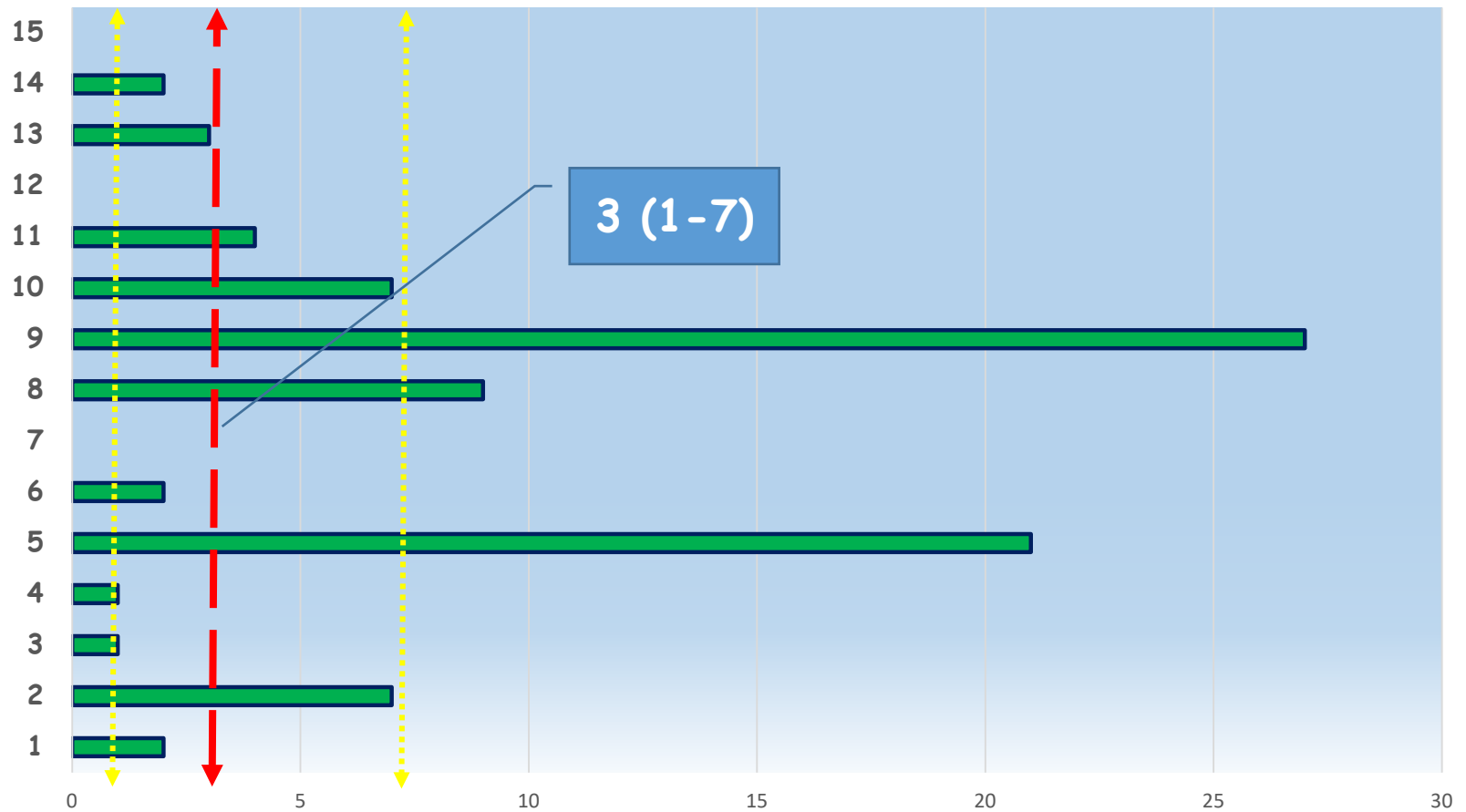
Numero delle colture diagnostiche positive per
KP-cp

Numero totale delle colture diagnostiche
eseguite

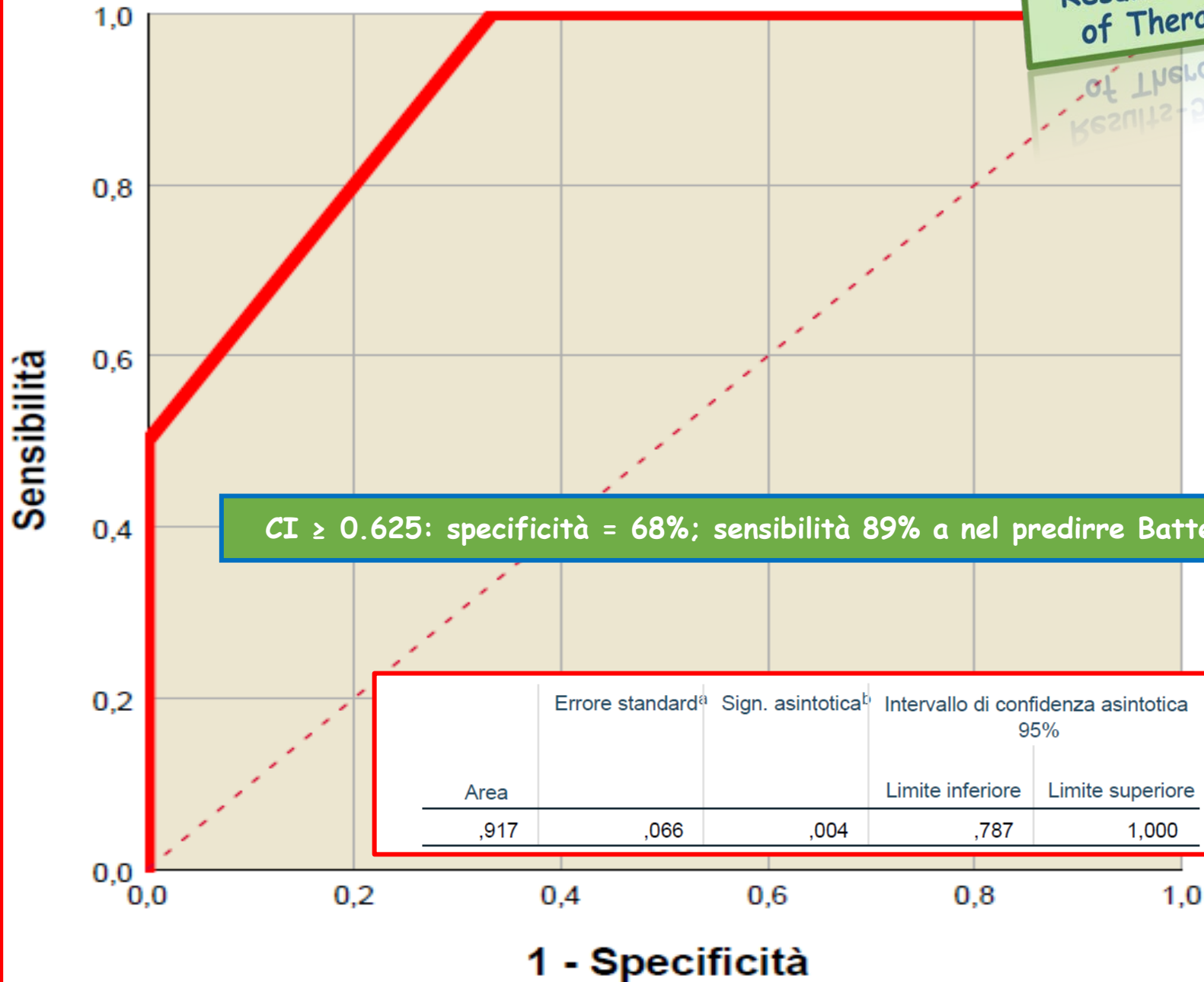
Results-2c: Risk factors

Results-2c: Risk factors

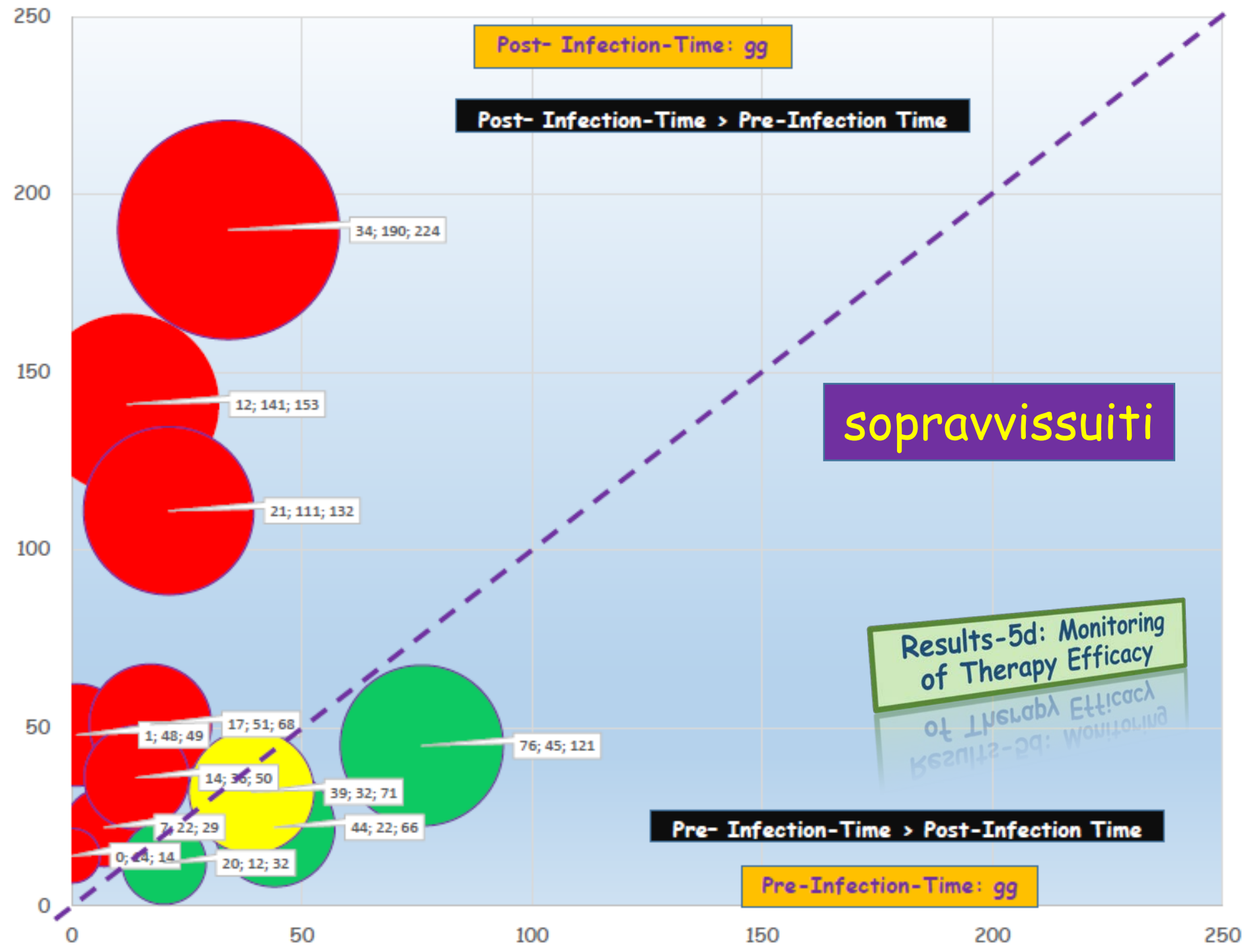
Timing Colonizzazione-Infezione



Curva ROC



Results-5c: Monitoring of Therapy Efficacy



Conclusions

Ceftazidime/avibactam

- resulted in a proper rescue therapy for KP-cp severe infections with a clinical cure rate of 77.8%
- was associated with a good tolerance by patients (only a case of ipoK+); no impairment of renal failure was recorded (1/2 of dose for CVVH)
- recorded of di- undirectly related mortality due to KC-cp seems to be lower if compared to the literature data



Thanks!

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