Moderatori: *S. Parisi (Padova), C. Torti (Catanzaro)*

15:40 - 16:00 **Uno sguardo oltre gli antibiotici: immunoglobuline, terapia fagica e monoclonali?** - *C. Tascini (Udine)*

Prof Carlo Tascini

Direttore Clinica Malattie Infettive

Università di Udine – ASUFC

c.tascini@gmail.com

Conflict of interest Disclosure

prof. Carlo Tascini has received in the last two years grants as a speaker at symposia from:

- Astrazeneca
- AVIR Pharma
- Merck
- Pfizer
- Astellas
- Angelini
- Gilead
- Novartis
- Biotest
- Thermofischer
- Correvio/Advanz Pharma
- Basilea
- Biomerieux
- Hikma
- Zambon

Spoke Hospital, Udine Province, Italy

- 67-year old male, previous pneumococcal meningitis
- Fever, headache, Glasgow coma scale: 9, lumbar puncture: purulent CSF
- Centralized to Udine Hospital
- Started on intravenous ceftriaxone 2 g, and ampicillin 2 g

Time 13:38 spoke Hospital –Time 20:08 Udine Hub Hospital after antibiotics without steroid administration

Esame Emocromocitometrico				
Globuli Bianchi	13.25	>	x10^3/µL	4.00 - 11.00
Globuli Rossi	5.42		x10^6/µL	4.60 - 5.60
Emoglobina	16.7		g/dL	14.0 - 18.0
Ematocrito	51.5	>	%	40.0 - 50.0
MCV	95.1	>	fL	80.0 - 94.0
MCH	30.8		pg	27.0 - 32.0
MCHC	32.4		g/dL	32.0 - 35.0
RDW (CV Distrib. Vol. Eritrocitari)	13.9		%	11.0 - 14.0
Piastrine	197		x10^3/µL	150 - 400

Proteina C reattiva	19.00	>	mg/L	0.00 - 5.00
Procalcitonina	0.60		ng/mL	< 0.10

Rischio per sepsi:
0.10 - 0.50 basso
0.50 - 2.00 moderato
2.00 - 10.00 alto
> 10.00 molto alto

Esame Emocromocitometrico				
Globuli Bianchi	31.24	>	x10^3/µL	4.00 - 11.00
Globuli Rossi	5.12		x10^6/µL	4.60 - 5.60
Emoglobina	16.1		g/dL	14.0 - 18.0
Ematocrito	48.6		%	40.0 - 50.0
MCV	94.9	>	fL	80.0 - 94.0
MCH	31.4		pg	27.0 - 32.0
MCHC	33.1		g/dL	32.0 - 35.0
RDW (CV Distrib. Vol. Eritrocitari)	13.8		%	11.0 - 14.0
Piastrine	191		x10^3/µL	150 - 400
Formula Leucocitaria				
Neutrofili %	87.8		%	
Linfociti %	1.7		%	
Monociti %	10.2		%	
Eosinofili %	0.0		%	
Basofili %	0.2		%	
Neutrofili	27.44	>	x10^3/µL	2.00 - 7.50
Linfociti	0.54	<	x10^3/µL	1.00 - 4.00
Monociti	3.19	>	x10^3/µL	0.10 - 1.00
Eosinofili	0.01	<	x10^3/µL	0.04 - 0.65
Basofili	0.06		x10^3/µL	0.00 - 0.20

Formula Strumentale non verificata al Microscopio; Presenza di aggregati piastrinici. Conteggio sottostimato.

Proteina C reattiva	63.99	>	mg/L	0.00 - 5.00
Procalcitonina	34.55		ng/mL	< 0.10

INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

The Journal of Clinical Investigation REVIEW

Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

jci.org Volume 126 Number 1 January 2016

Matthew J. Delano[1] and Peter A. Ward[2]

[1]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, Michigan, USA. [2]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

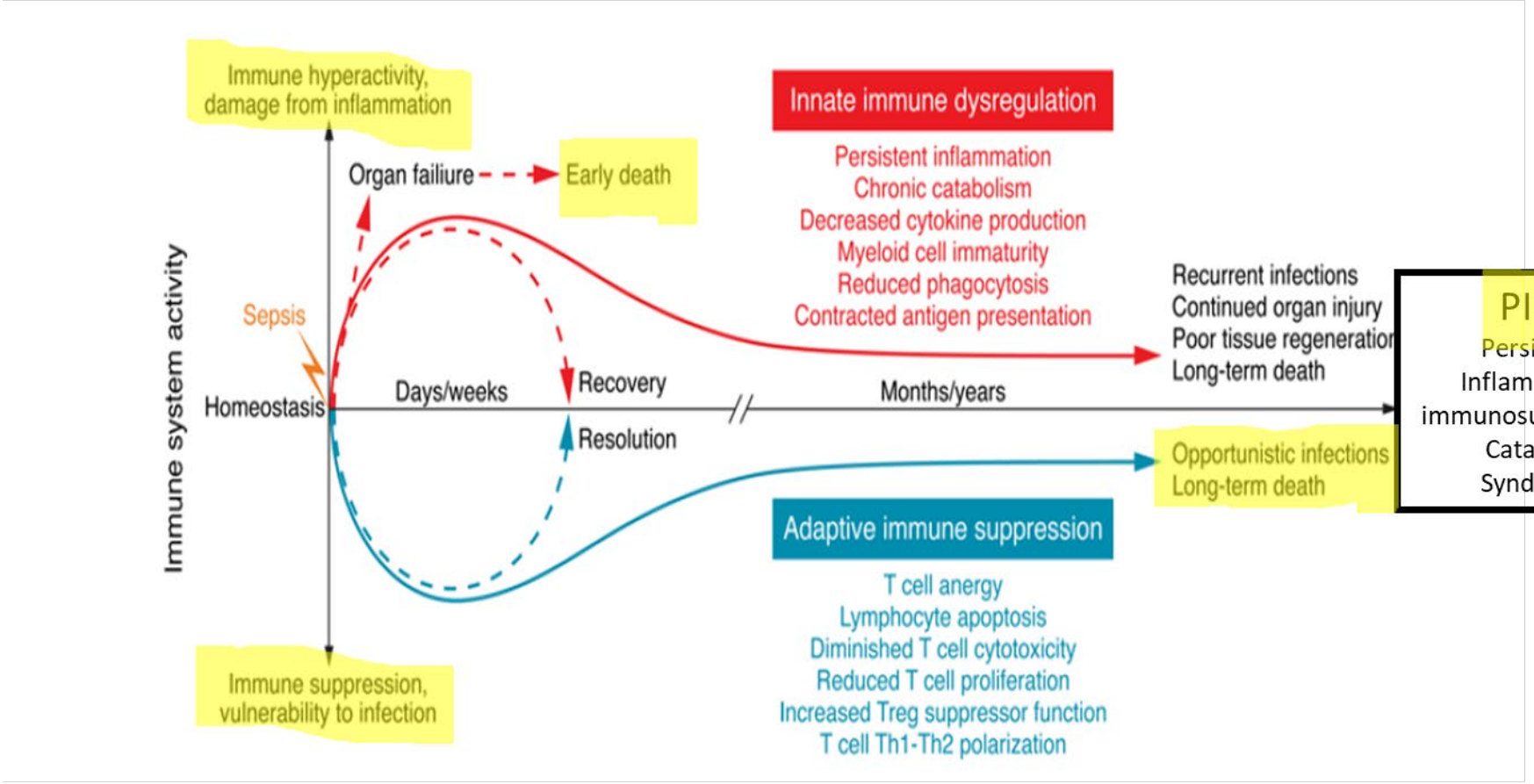
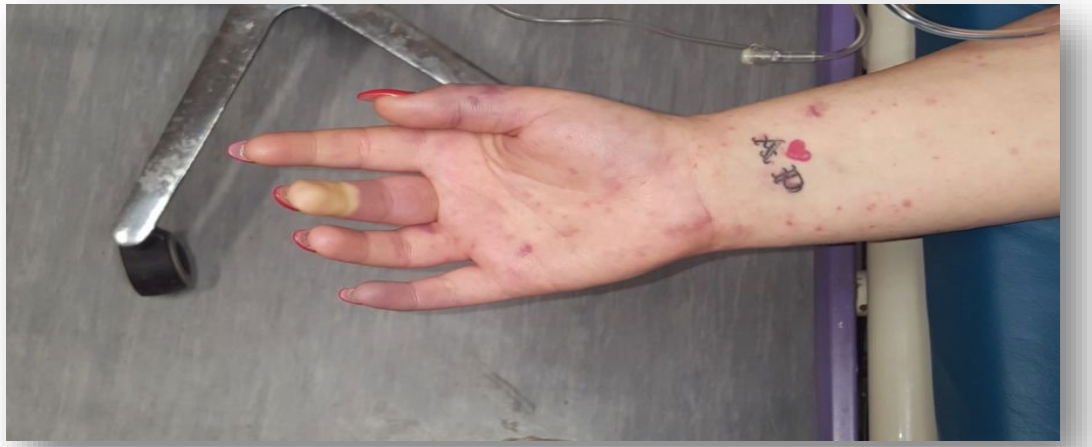


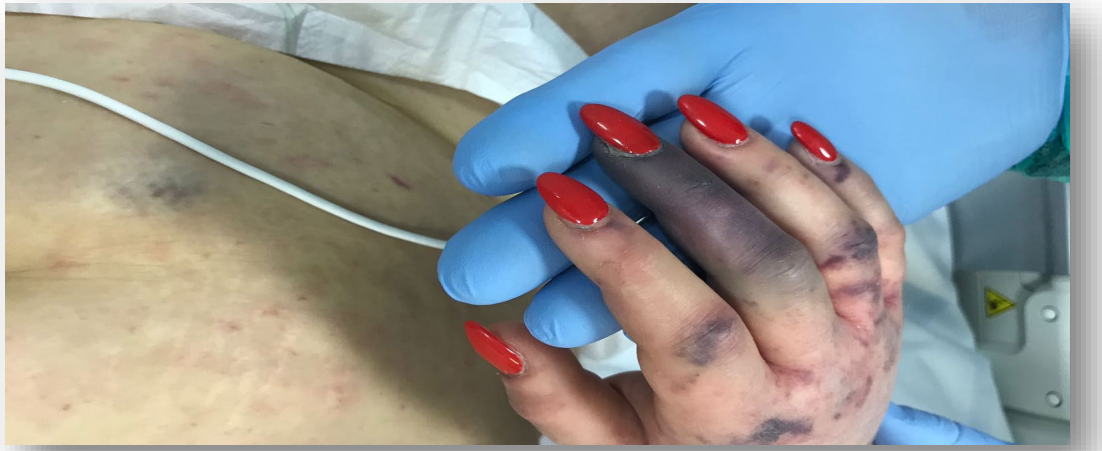
Figure 2. Immune dysregulation in sepsis. New insights into immune dysregulation have been gained using samples from deceased septic patients as well as from severely injured trauma patients. These studies demonstrate an enduring inflammatory state driven by dysfunctional innate and suppressed adaptive immunity that culminates in persistent organ injury and death of the patient. Although the initial inflammatory process, if unabated, contributes to organ failure and early mortality, this process is largely ameliorated by improvements in patient management protocols. However, considering that the vast majority of sepsis survivors are elderly with highly comorbid conditions, the short-term gains in survival have merely been pushed back by several months to a year. Although theories about the processes underlying this observation are numerous, the widespread consensus is that persistent derangements in innate and adaptive immune system cellular function are the main culprits driving long-term mortality.

Courtesy of Prof M. Girardis

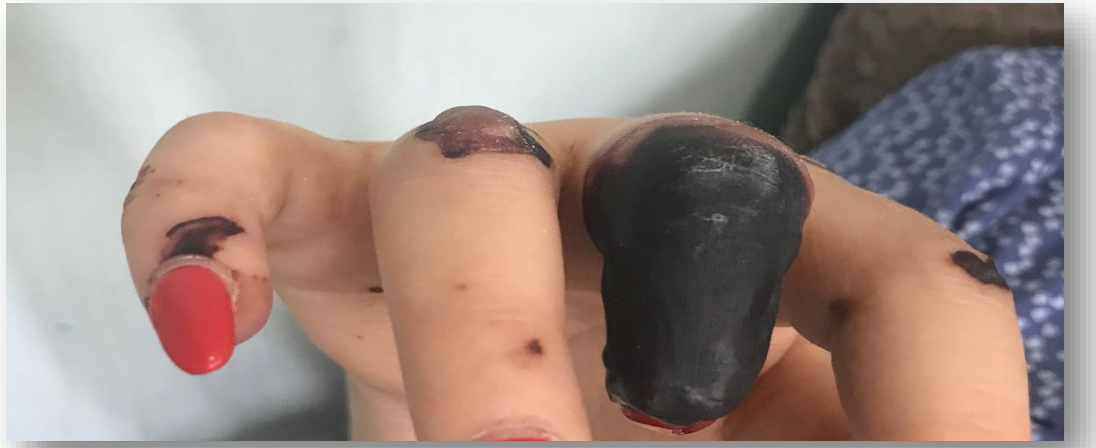
N. meningitidis: Purpura fulminans



Dismissed from ED: Doppler advised



After 12 hrs back to ICU



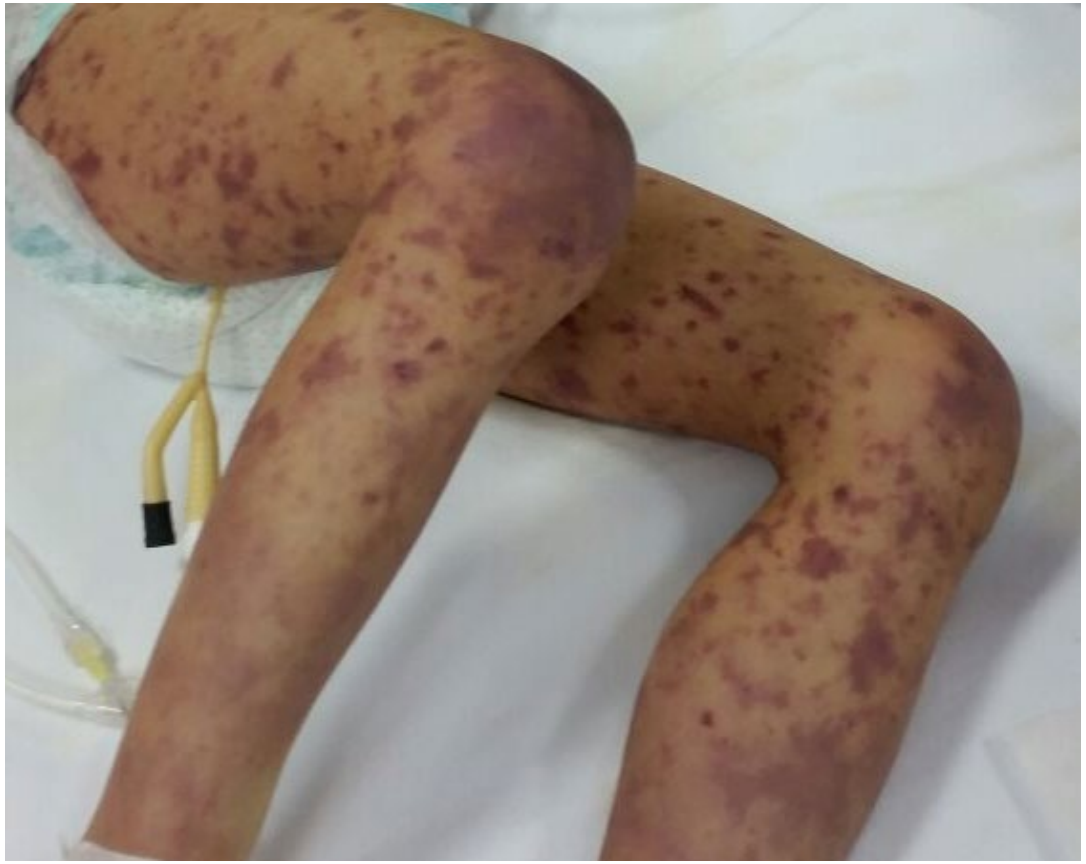
After two months

After one year

Purpura fulminans

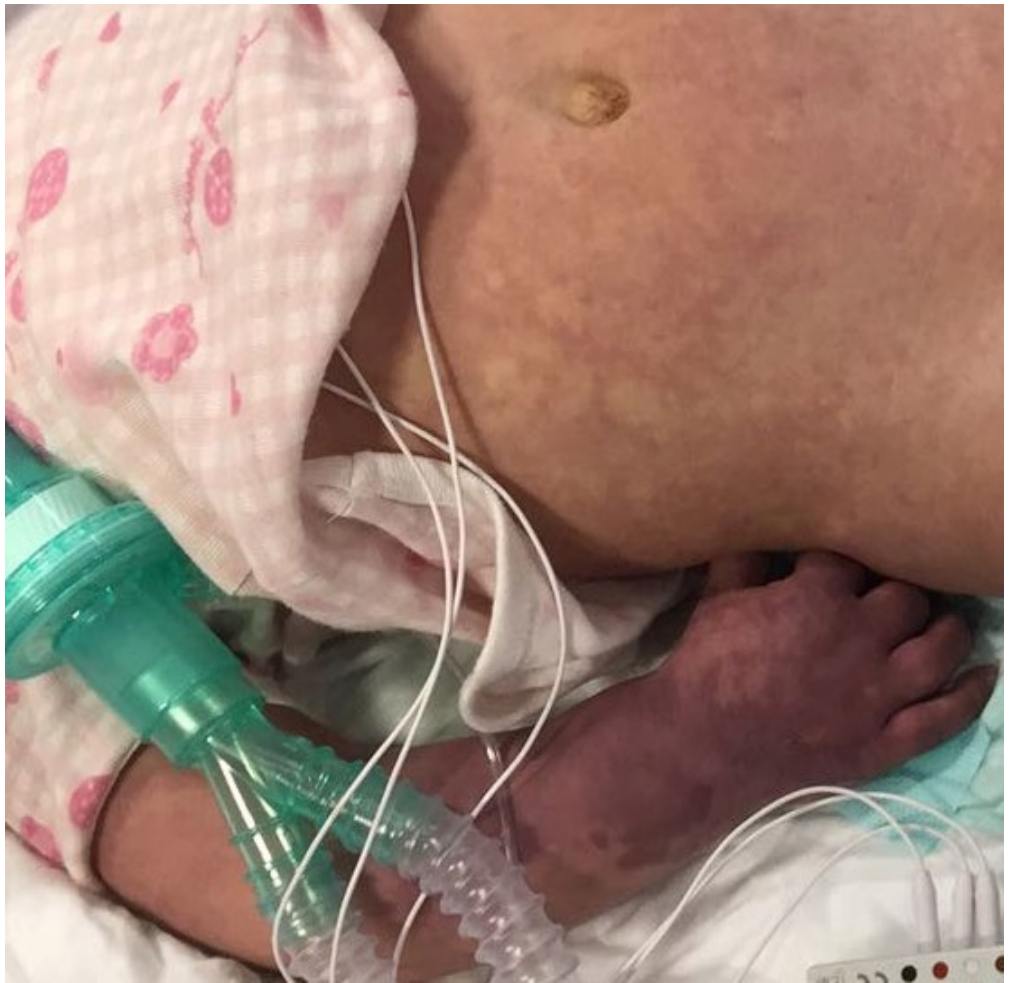
- Cotugno Hospital, Naples, Italy
- Admitted to ICU, sedated and intubated
- **Therapy**: Dexamethasone, rifampicin 600 mg, than ceftriaxone 2 g slowly, IGAM 5 mL/kg Continuous Infusion (CI) for the first 3 days

Case - 2018: *N. meningitidis* group C, ST11; unvaccinated 5-year-old boy, cardiac arrest after steroid and during antibiotic ceftriaxone therapy: endotoxin 1 EU/ml, procalcitonin 80 ng/ml.



Courtesy Prof. Tascini

2018: *N. meningitidis* group W, st type 11,
12 month old girl
Expired following cortisone and ceftriaxone administration:
endotoxin values= 1,2, PCT=100



Intensive Care Med (2018) 44:1502–1511
https://doi.org/10.1007/s00134-018-5341-3

ORIGINAL

Clinical spectrum and short-term outcome of adult patients with purpura fulminans: a French multicenter retrospective cohort study

Damien Contou[1,2*], Romain Sonneville[3], Florence Canoui-Poitrine[4,5], Gwenhaël Colin[6], Rémi Coudroy[7,8], Frédéric Pène[9], Jean-Marc Tadié[10], Martin Cour[11], Gaëtan Béduneau[12], Antoine Marchalot[13], Laurent Guérin[14], Sébastien Jochmans[15], Stephan Ehrmann[16], Nicolas Terzi[17], Sébastien Préau[18], François Barbier[19], Guillaume Schnell[20], Damien Roux[21], Olivier Leroy[22], Claire Pichereau[23], Elodie Gélisse[24], Lara Zafrani[25], Richard Layese[4], Christian Brun-Buisson[1], Armand Mekontso Dessap[1] and Nicolas de Prost[1] for the Hopeful Study Group

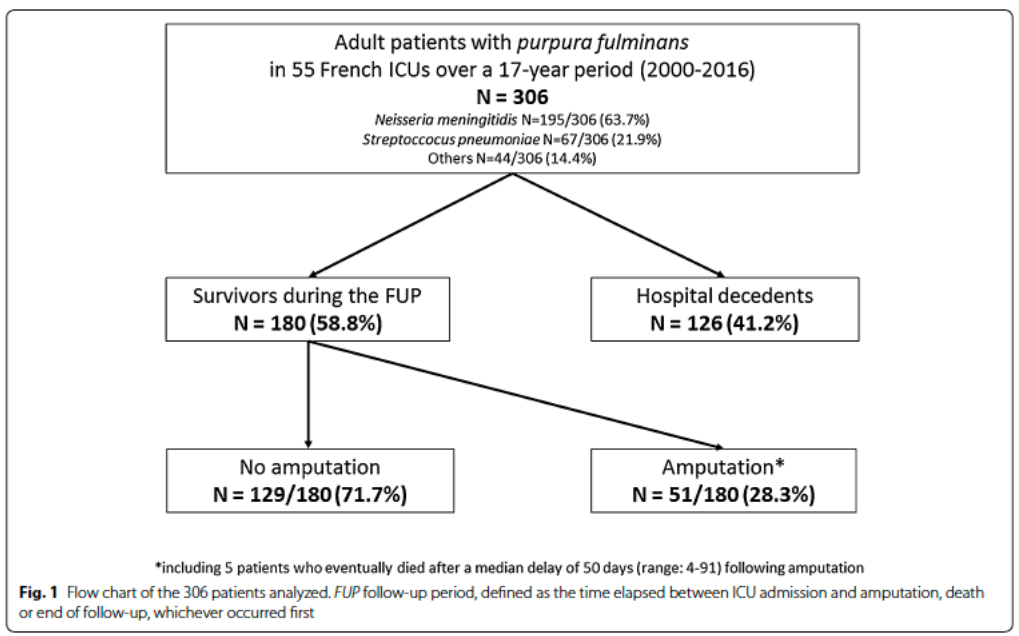


Fig. 1 Flow chart of the 306 patients analyzed. *FUP* follow-up period, defined as the time elapsed between ICU admission and amputation, death or end of follow-up, whichever occurred first

Intensive Care Med (2018) 44:1502–1511
https://doi.org/10.1007/s00134-018-5341-3

ORIGINAL

Clinical spectrum and short-term outcome of adult patients with purpura fulminans: a French multicenter retrospective cohort study

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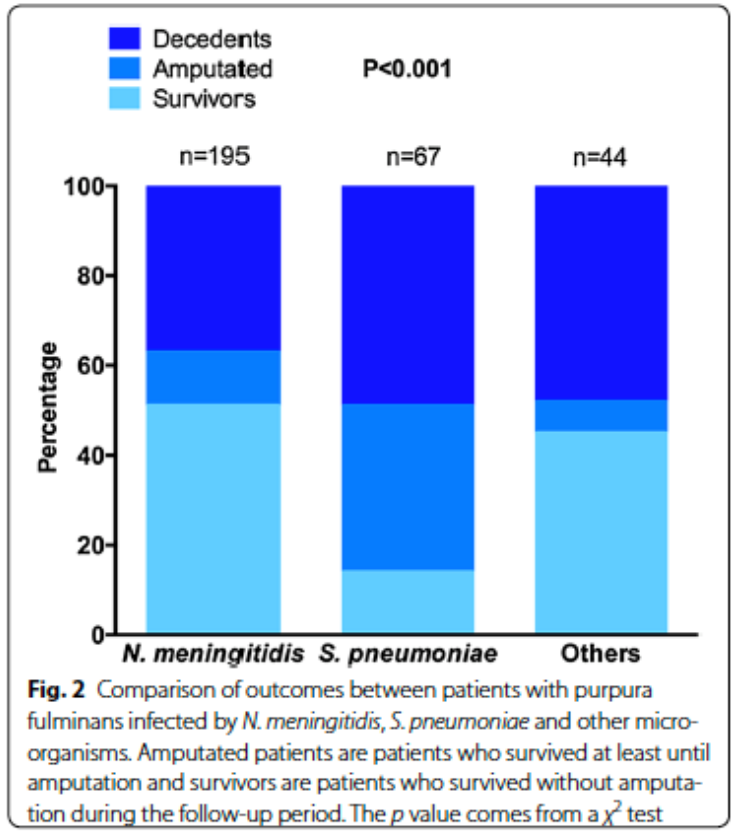


Fig. 2 Comparison of outcomes between patients with purpura fulminans infected by *N. meningitidis*, *S. pneumoniae* and other micro-organisms. Amputated patients are patients who survived at least until amputation and survivors are patients who survived without amputation during the follow-up period. The *p* value comes from a χ^2 test

Table 3 Multivariable Cox model for hospital death (censored at day 30) after multiple imputations and adjustment for center size and year of admission ($n = 301$)

	Hospital death ($n = 301$, number of events = 114)	
	HR (95% CI)	*p*
SAPS II	1.03 (1.02–1.04)	< 0.001
Neck stiffness	0.51 (0.28–0.92)	0.026
Leukocytes count, 10^3 mm^{-3}	0.83 (0.69–0.99)	0.034
Arterial lactate, mmol/L[a]	2.71 (1.68–4.38)	< 0.001
Platelets count, 10^3.mm^{-3} [a]	0.77 (0.60–0.91)	0.007
Center size ≥ 4 patients	0.45 (0.27–0.97)	0.028
Year of admission		0.52
2000–2004	1.00	
2005–2008	1.11 (0.64–1.94)	0.71
2009–2012	0.75 (0.43–1.32)	0.32
2013–2016	0.97 (0.55–1.72)	0.93

HR adjusted hazard-ratio, *CI* confidence interval

[a] Log-transformed variables and expressed for one unit of the log

Vaccine 36 (2018) 5962–5966

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Invasive Meningococcal Disease due to group C N. meningitidis ST11 (cc11): The Tuscany cluster 2015–2016

Francesco Menichetti [a,*], Simona Fortunato [a], Andrea Ricci [a], Francesca Salani [a], Andrea Ripoli [b], Carlo Tascini [c], Francesco Maria Fusco [d], Jessica Mencarini [e], Alessandro Bartoloni [e], Massimo Di Pietro [f]

Table 2
Patient outcome according to demographic, clinical and management variables.

	Recovered (n = 38)	Sequelae or death (n = 15)	P value univariate analysis	OR[b]
Males	17 (45%)	9 (60%)	0.486	–
Mean age (range)	33.9 (3–70)	35.5 (17–75)	0.799	**1.003**
Previous Vaccination[a]	9 (24%)	2 (13%)	0.645	–
Meningitis	6 (16%)	2 (13%)	1	–
Meningitidis + meningococcemia	16 (42%)	7 (47%)	1	–
Meningococcemia	16 (42%)	6 (40%)	1	–
Septic shock	**14 (37%)**	**12 (80%)**	**0.011**	**1.211**
Multi-organ failure	11 (29%)	8 (53%)	0.177	–
Disseminate intravascular coagulophaty	**7 (18%)**	**9 (60%)**	**0.008**	**–**
Purpura fulminans	**6 (16%)**	**9 (60%)**	**0.004**	**6.641**
Adequate Antibiotic therapy	38 (100%)	15 (100%)	**1**	**–**
Steroid treatment	28 (74%)	11 (74%)	1	–
Pentaglobin®	8 (21%)	2 (13%)	0.797	–
ICU	25 (66%)	14 (93%)	0.089	–
Tertiary-care Universitary Hospital	**13 (34%)**	**0 (0%)**	**0.024**	**0.111**

[a] Previous receipt of a serogroup C-containing meningococcal conjugate vaccine.
[b] OR were calculated with a multivariate analysis on a total of 53 patients with the availability of all the listed variables.

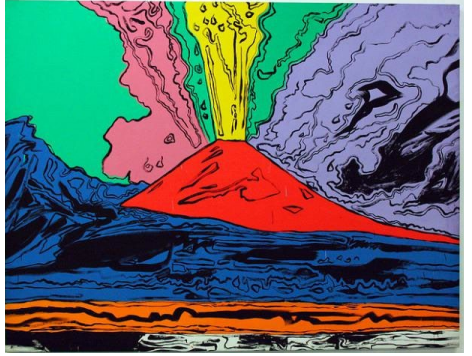
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Community-Acquired Bacterial Meningitis in Adults

Diederik van de Beek, M.D., Ph.D., Jan de Gans, M.D., Ph.D.,
Allan R. Tunkel, M.D., Ph.D., and Eelco F.M. Wijdicks, M.D., Ph.D.



- Purulent meningitis: dexamethasone NNT 1:10
- Mortality drop from 15 to 7%
- Glasgow score: 8-11
- Pneumococcus: dexamethasone NNT 1:4
- Mortality from 34% to 14%
- **Steroids should be administered within 4 hours from antibiotic administration**

Adjunctive dexamethasone in adults with meningococcal meningitis

Sebastiaan G.B. Heckenberg, MD*
Matthijs C. Brouwer, MD, PhD*
Arie van der Ende, PhD
Diederik van de Beek, MD, PhD

Dexamethasone, 10 mg IV, given every 6 hours for 4 days was started before or with the first dose of parenteral antibiotics in 78 of 96 episodes (81%). In 6 patients (6%), dexamethasone was discontinued after cultures grew meningococci. Dexamethasone was prescribed in 35 of 39 patients (90%) with a rash on admission. Adjunctive dexamethasone was administered in 43 episodes (17%) in the 1998–2002 cohort. Twelve of these patients were included in the European dexamethasone in adulthood bacterial meningitis study and received dexamethasone 10 mg IV, given every 6 hours for 4 days, started before or with first dose of parenteral antibiotics; dexamethasone was initiated after clinical deterioration in all other episodes.[4,13]

Steroid use in non-pneumococcal and non-Haemophilus bacterial meningitis

Lancet 2022 Feb 19;399(10326):717-718.

To conclude, dexamethasone should be initiated with the first dose of antibiotics in all patients with community-acquired bacterial meningitis beyond the neonatal age. On the basis of available evidence, we advise to continue dexamethasone treatment in this patient group for 4 days regardless of microbial cause, except in patients with *Listeria monocytogenes*.

We declare no competing interests.

*Diederik van de Beek,
Matthijs C Brouwer, Uwe Koedel,
Emma C Wall
d.vandebeek@amsterdamumc.nl

Adjunctive dexamethasone treatment in adults with listeria monocytogenes meningitis: a prospective nationwide cohort study

Matthijs C. Brouwer* and Diederik van de Beek**

dexamethasone. The case fatality rate was 51 of 162 (31%) and an unfavourable outcome occurred in 91 of 162 patients (56%). Age and the standard regimen of adjunctive dexamethasone were independent predictors for an unfavourable outcome and mortality. The adjusted odds ratio of dexamethasone treatment for unfavourable outcome was 0.40 (95% confidence interval 0.19–0.81).

Interpretation Adjunctive dexamethasone is associated with an improved outcome in patients with *L. monocytogenes* meningitis and should not be withheld if *L. monocytogenes* is suspected or detected as causative pathogen.

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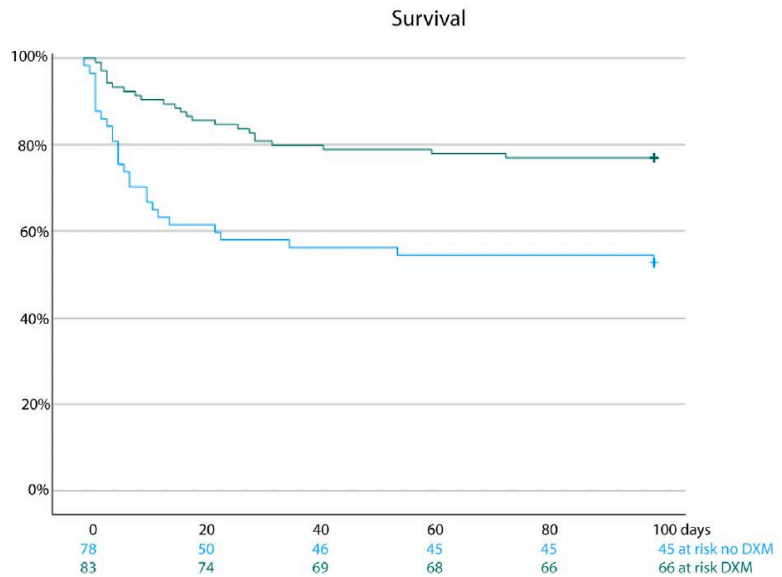


Fig. 2: Kaplan-Meijer estimates of survival for listeria meningitis patients receiving standard dexamethasone treatment and those receiving no dexamethasone or a non-standard regimen (log-Rank test P < 0.001).

Materiale: Liquor

Ag Cryptococcus neoformans test IC	**Negativo**
Ricerca diretta molecolare multiplex	
BATTERI	
Escherichia coli K1	**Negativa**
Haemophilus influenzae	**Negativa**
Listeria monocytogenes	**Negativa**
Neisseria meningitidis	**Negativa**
Streptococcus agalactiae	**Negativa**
Streptococcus pneumoniae	**Positiva**

Dato comunicato il 03/12/2022 alle ore 14:08, mediante modalità read back.

Glucosio	**160** >	mg/dL	74 - 109

Indagini su Liquido Cefalo-Rachidiano

Liquido cefalo rachidiano			
Aspetto	**Limpido**		
Aspetto dopo centrifugazione	**Limpido**		
Colore	*LEGG XANTOCROMICO*		
Volume	**0.5**	mL	
Glucosio	**<2**	mg/dL	
Proteine totali	**3551** >	mg/L	150 - 450
Lattato	**14.6** >	mMol/L	0.0 - 2.8
Conta leucociti	**14.0** >	/µL	0.0 - 3.0
Polimorfonucleati	**24**	%	
Linfociti	**12**	%	
Mononucleate	**64**	%	
	RARE EMAZIE		

Richiesta: **55333178** del: **03/12/2022** Ore: 12:17
(UD)-2° piano, Pad. 9

Off-Label
CSF Pro ADM

Esame	*Esito*	*U.M.*	*Intervalli di riferimento*

Indagini su Liquido Cefalo-Rachidiano

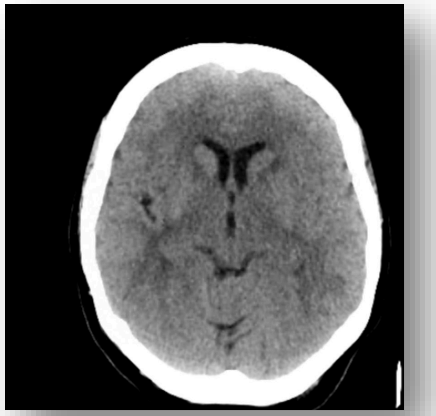
Pro-adrenomedullina liquido cefalo rachidiano	**16.77**	nMol/L
Ratio pro-adren.liquor/sangue	**7.7**	

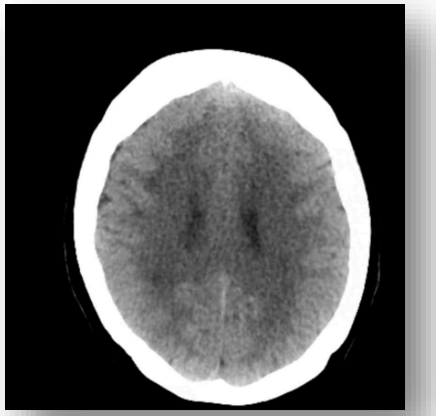
Proadrenomedullina eseguita su richiesta n. 55331420

Plasma Pro-ADM: 2,17 mMol/L

Clinical case: patient Z.A.

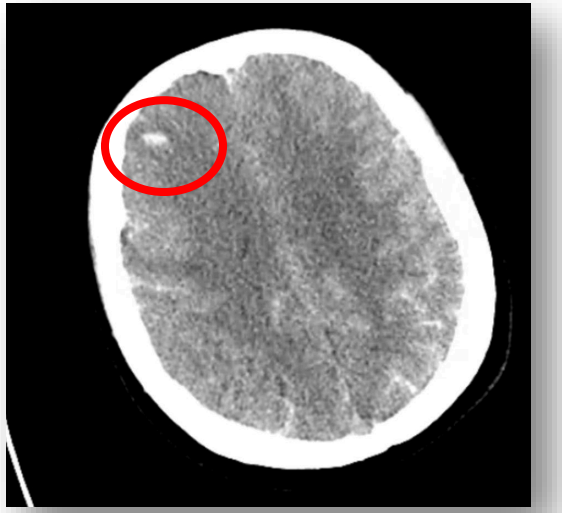
- Ampicillin and acyclovir therapy discontinued. Ceftriaxone and dexamethasone continued.
- On the 5th of December 2022: patient locked her gaze and no longer replied if not with the emission of incomprehensible sounds; presented deviation of buccal line and flattening of the nasolabial fold with flaccid paresis on the right side (ischemic stroke)

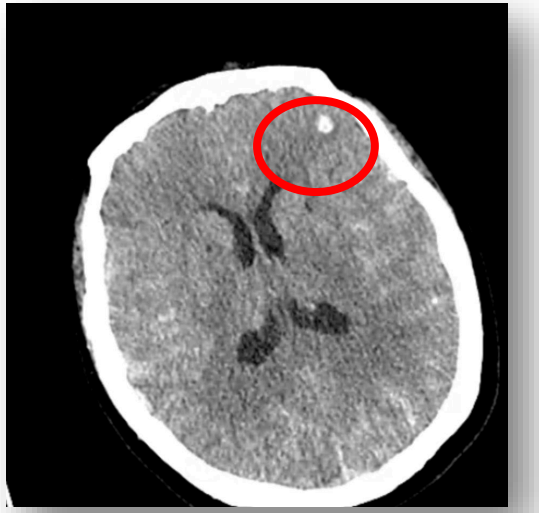




Clinical case: patient Z.A.

- CT scan: negative. Started fibrinolysis with alteplase.
- Approximately 30 mins following the end of alteplase infusion, further neurological deterioration was observed: the patient appeared no longer responsive to the call. She presented afinalistic movements of the upper left limb alternating with a state of drowsiness with snoring breath with respiratory pauses. Normally reactive myotic pupils (haemorragic stroke)

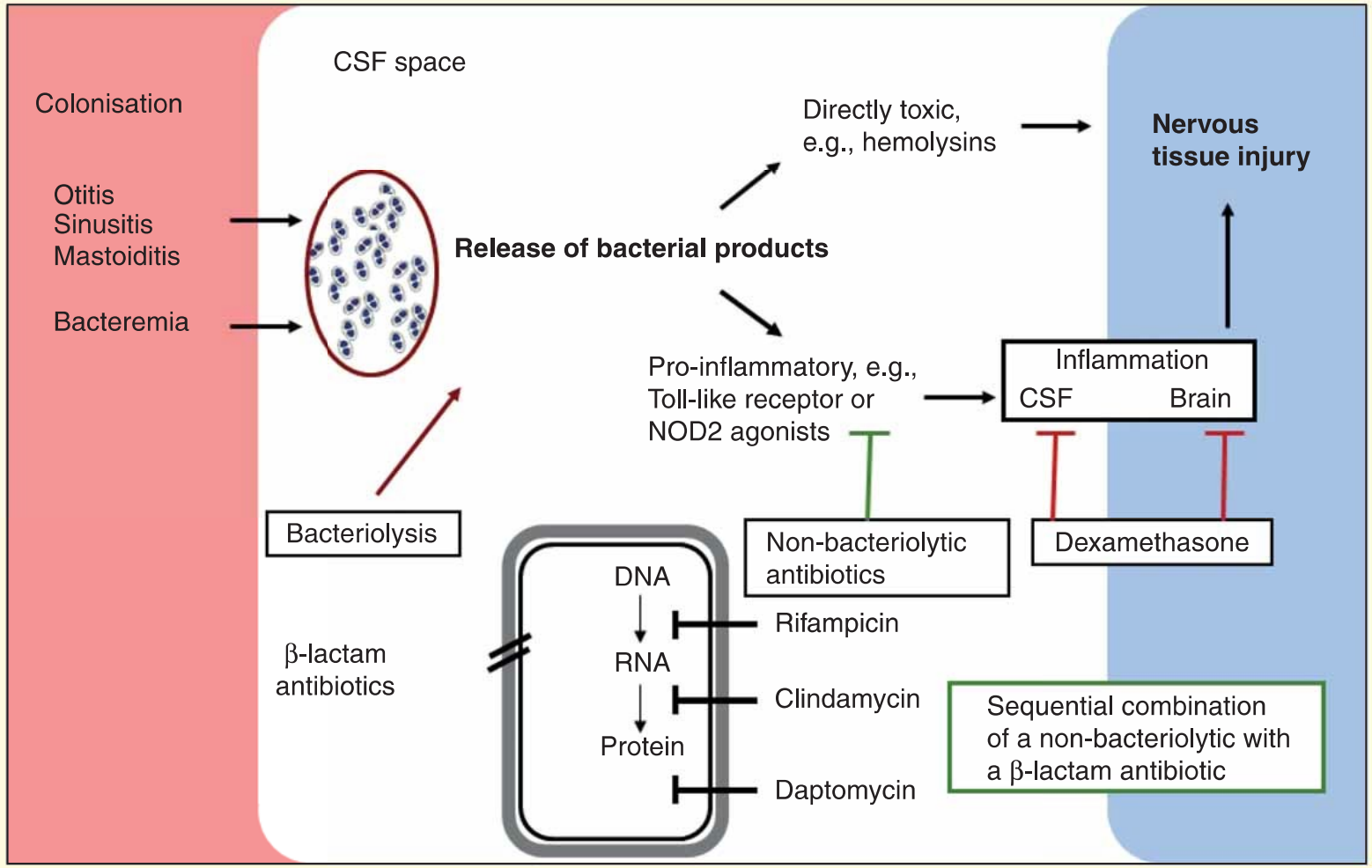




Med Intensiva. 2014;38(6):356–362

medicina *intensiva*

Quick and dirty versus killing bacteria softly



Bretonnière et al. Critical Care (2015) 19:303
DOI 10.1186/s13054-015-1021-7

RESEARCH Open Access

Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study

Cédric Bretonnière[1,2*], Mathieu Jozwiak[1,3], Christophe Girault[4,5], Pascal Beuret[6], Jean-Louis Trouillet[7], Nadia Anguel[3], Jocelyne Caillon[2,8], Gilles Potel[2,9], Daniel Villers[1], David Boutoille[2,10] and Christophe Guitton[1]

Table 2 Correlation between ICU mortality and rifampin treatment in critically ill patients admitted with bacterial meningitis

Rifampin use	Non-survivors		Survivors		*p* Value
Entire population	n=23		n=134		
Rifampin during hospitalization	2/23	8.7 %	30/134	22.4 %	NS
Rifampin during first 48 h of hospitalization	1/23	4.3 %	23/134	17.2 %	NS
Rifampin during first 24 h of hospitalization	0/23	0.0 %	19/134	14.2 %	0.078
Streptococcus pneumoniae meningitis	n=18		n=58		
Rifampin during hospitalization	2/18	11.1 %	18/58	31.0 %	NS
Rifampin during first 48 h of hospitalization	1/18	5.6 %	15/58	25.9 %	0.097
Rifampin during first 24 h of hospitalization	0/18	0.0 %	13/58	22.4 %	**0.031**

NS not significant
Data are proportions of patients. They were compared with Fisher's exact test
p Values <0.1 are detailed. *p* Values <0.05 were considered significant (bold)

Intensive Care Med
DOI 10.1007/s00134-017-4957-z

LETTER

Potential role of IgM-enriched immunoglobulin as adjuvant treatment for invasive meningococcal disease

Carlo Tascini[1], Fiorentino Fraganza[2], Francesca Salani[3], Emanuela Sozio[4], Marco Rossi[1], Francesco Sbrana[5], Novella Carannante[1], Maria Daniela Chiesa[2], Andrea Ripoli[5], Giacomo Bertolino[6], Massimo Di Pietro[7], Alessandro Bartoloni[8,9] and Francesco Menichetti[3*], on behalf of GISA/SIMIT Meningitis Study Group

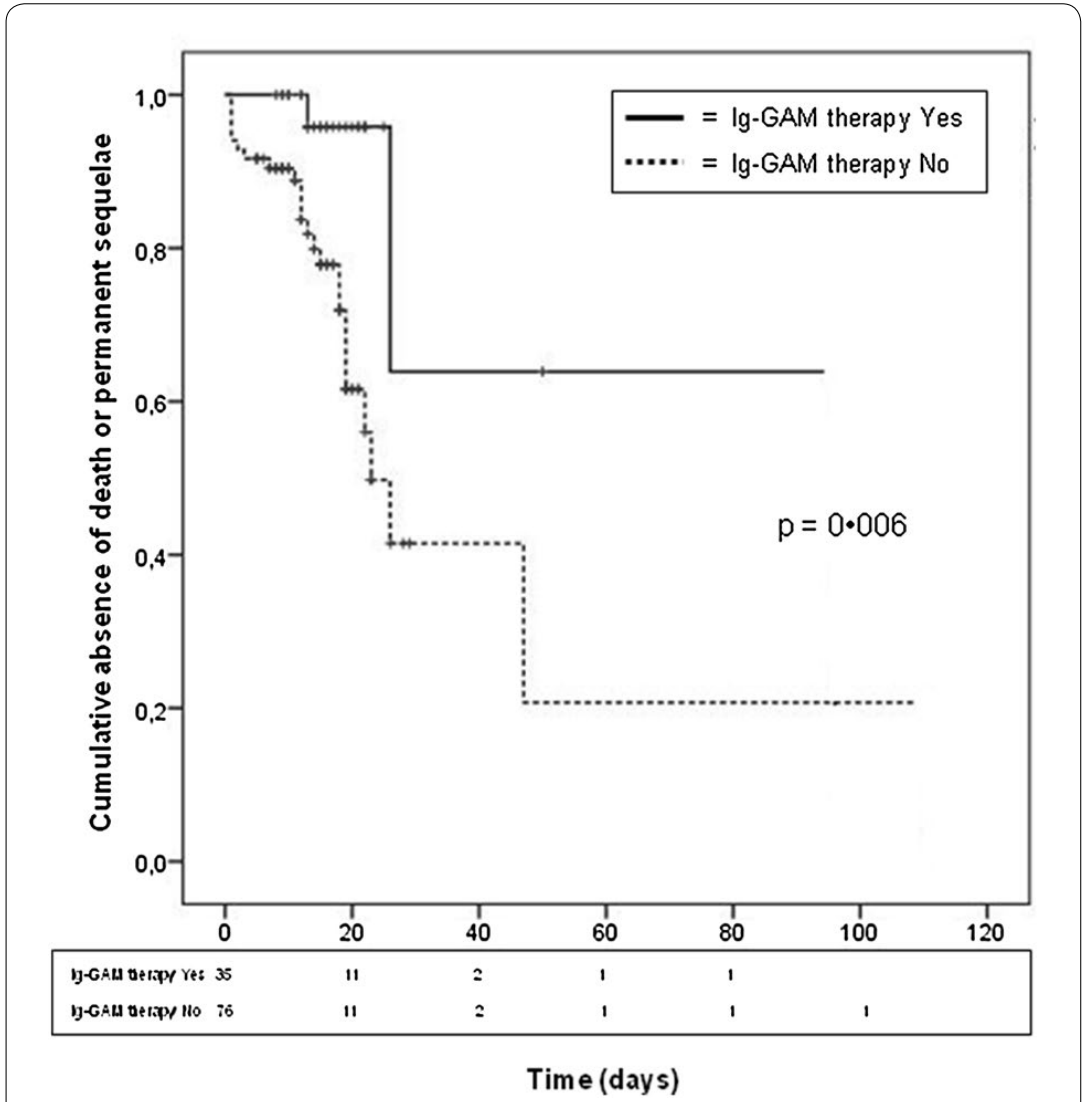
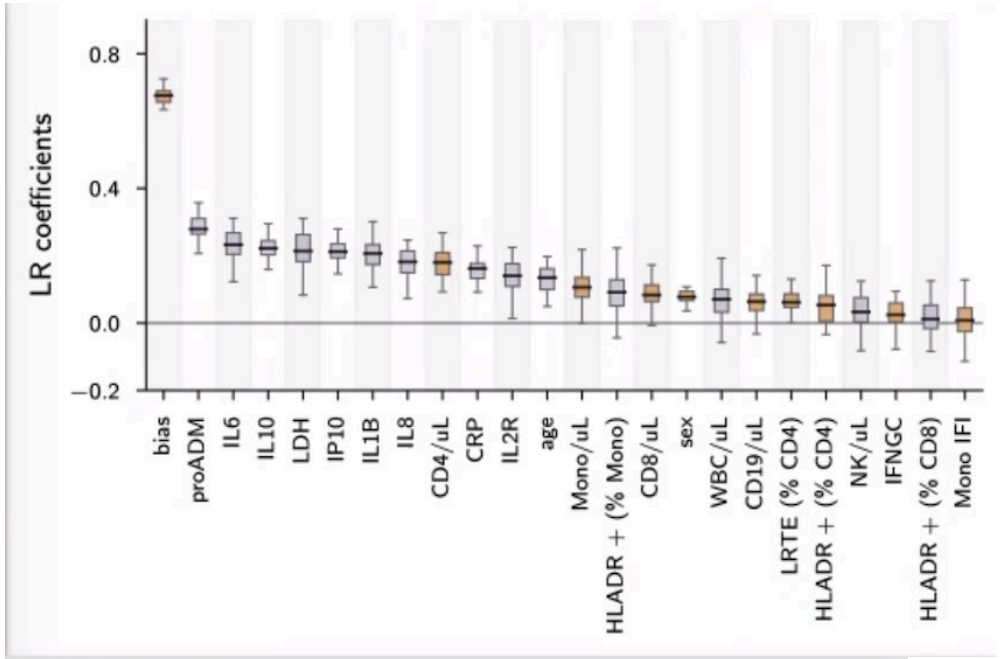
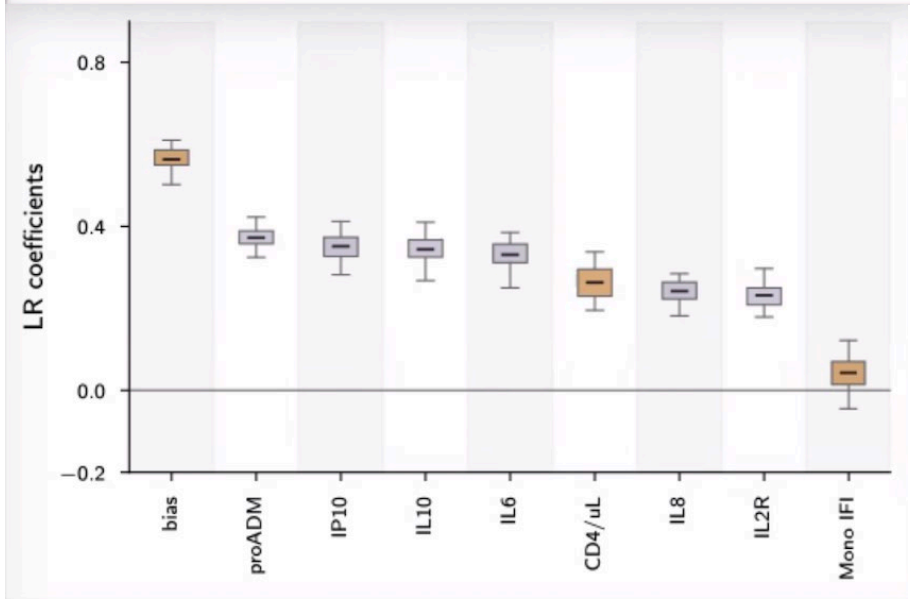


Fig. 1 Kaplan–Meier analysis of aggregated data on death and permanent sequelae in patients treated or not with Ig-GAM

article to be published, confidential data

Multivariate models - Coefficients logistic regression. Negative sign in yellow.





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Minerva Anestesiologica 2023 mese;89(0):000–000
DOI: 10.23736/S0375-9393.23.17244-0

ORIGINAL ARTICLE

Potential role of IgM-enriched immunoglobulin as adjuvant treatment in severe SARS-CoV-2 infection

Carlo TASCINI [1, 2] *, Marco COTRUFO [1], Emanuela SOZIO [1, 2], Matteo FANIN [1], Fabiana DELLAI [1], Agnese ZANUS FORTE [1], Daniela CESSELLI [3], Paola DE STEFANIS [4], Andrea RIPOLI [5], Francesco SBRANA [6], Simone GIULIANO [1], Martina FABRIS [3], Massimo GIRARDIS [7], Francesco CURCIO [3], Flavio BASSI [3]

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TABLE IV.—*Multivariable logistic regression for death outcome. In order to try to balance treated and controls for all non-treatment variables, each observation has been weighted by the computed propensity score.*

Parameters	OR [95% CI]	P value
Pentaglobin® treatment	0.820 [0.698-0.963]	0.016
P/F	0.999 [0.998-1.001]	0.277
SOFA	1.032 [0.981-1.086]	0.220
D-Dimer	1.000 [0.999-1.001]	0.225
CRP	1.001 [1.000-1.002]	0.031
ProADM	1.055 [0.941-1.183]	0.359
Oncological disease	1.112 [0.871-1.419]	0.391
Lymphocytes	1.000 [0.999-1.000]	0.268
Onset-hospitalization delay	0.983 [0.967-0.999]	0.041

225 pazienti della prima e seconda ondata: 119 decessi, 106 sopravvissuti

IgM-enriched Immunoglobulins in Septic Shock
Cavazzuti I et al ICM 2014

- **IgM-treated patients had**
  - Greater percentage of unidentified microorganisms
  - Significantly higher SAPS II ($p<0.05$)
  - More likely to have their blood collected for culture before receiving antibiotic therapy ($p<0.05$)
  - In patients with ALI/ARDS, the plateau inspiratory pressure less than 30 cmH2O was more frequently completed ($p<0.05$)
- **21.1% reduction of mortality**

New Microbiologica, 42, 3, 176-180, 2019, ISSN 1121-7138

FULL PAPER

A Position Paper on IgM-Enriched Intravenous Immunoglobulin Adjunctive Therapy in Severe Acute Bacterial Infections: The TO-PIRO SCORE Proposal

Francesco Giuseppe De Rosa[1], Silvia Corcione[1], Carlo Tascini[2], Daniela Pasero[3], Andrea Rocchetti[4], Massimo Massaia[5], Giorgio Berlot[6], Paolo Solidoro[7*], Massimo Girardis[8]

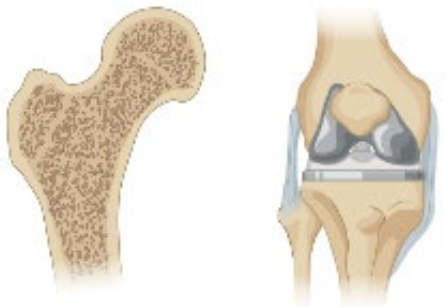
Table 1 - *Evaluation criteria of the TO-PIRO score.*

Items	*Criteria*	*Score*
Predisposition	• Uncontrolled cancer	1
	• Colonization by MDR bacteria and/or candida	1
	• Neutropenia or immunosuppressive drugs (monoclonal/steroids/micophenolate/cyclosporin) or allogenic stem cell transplant or splenectomy	2
Insult	• Necrotizing fasciitis, invasive meningococcal/ pneumococcal diseases, *Streptococcus pyogenes*; CA-MRSA	5
	• MDR infections or nosocomial infections	2
	• Secondary/tertiary peritonitis	2
Response	• Leucocytes < 600/ul	2
	• IgM < 60 mg/dl	2
	• PCT > 10 ng/l and CRP >20 mg/dl	1
	• PCT > 100 ng/l or endotoxin > 0.6 or IL-6>1000 pg/ml or adrenomedullin > 4 nm/l *or* presepsin 1400 ng/l	2
	• Disseminated intravascular coagulation	1
Organ	• Septic shock	3
	• Sepsis with ≥ 1 organ failure	2
	• Infection without sepsis	1

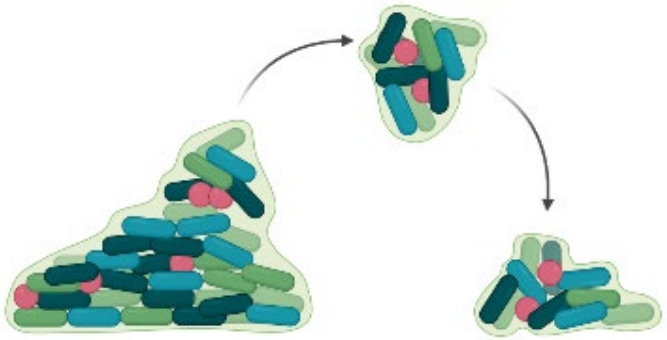
CA-MRSA, methicillin-resistant *Staphylococcus aureus*; CRP, C-reactive protein; IgM, immunoglobulins M; IL, interleukin; MDR, multi-drug resistant; PCT, procalcitonin.

Difficult to treat infection: a big challenge

Deep-seated infections
(poor antibiotic penetration)

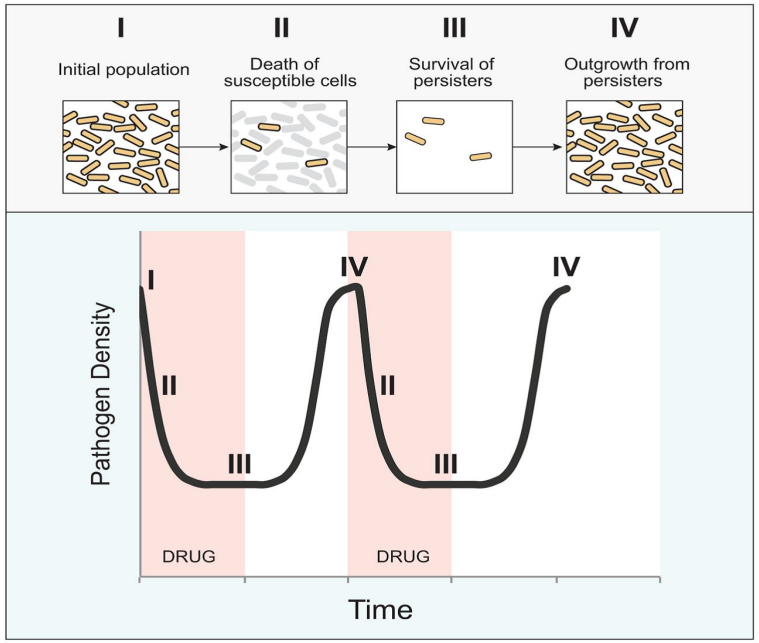


Biofilm associated-infections



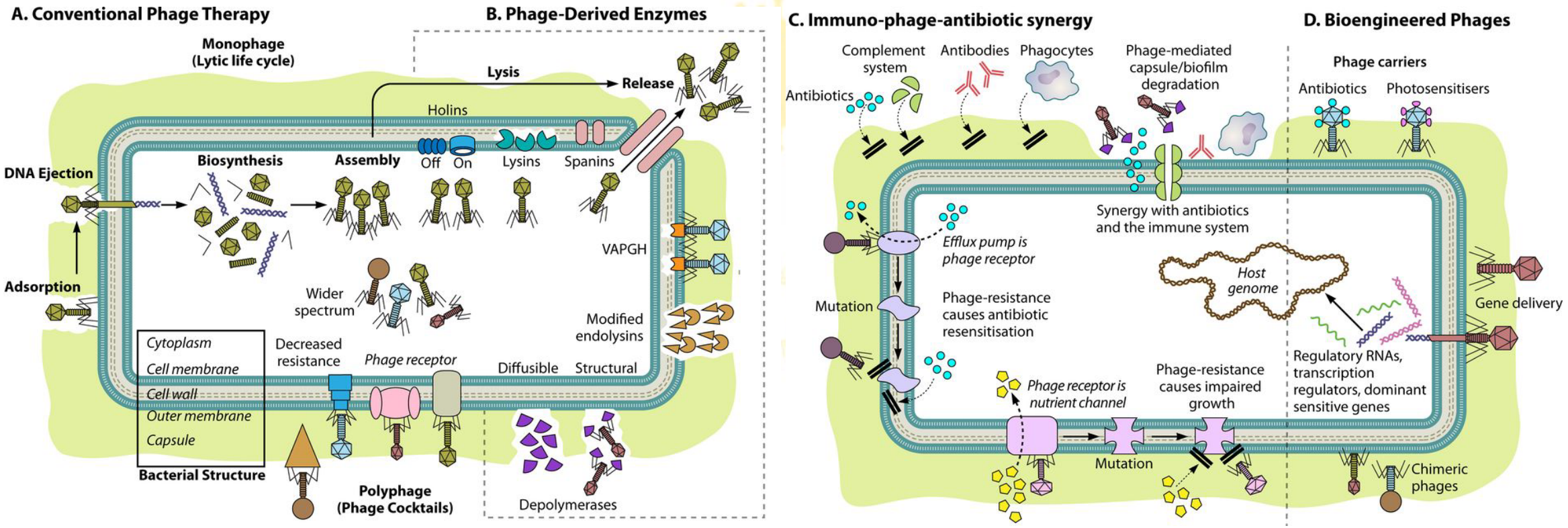
- Biofilm matrix
- Persister cells

Infection relapse after antibiotic therapy



Fauvart M. *et al* (2011), *Journal of Medical Microbiology*, 60: 699-709

Phage therapy as promising solution

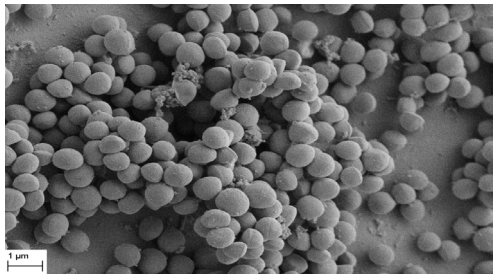


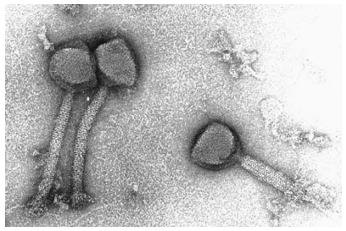
- Active against antibiotic-resistant bacteria
- Safe for humans
- Do not interfere with the microbiome

- Isolating the bacterium before starting therapy
- Reduced host spectrum
- Development of resistance

Sb-1 enhances the antibiotic activity against biofilm-embedded MRSA

24h-old biofilm of MRSA ATCC43300 on porous glass beads





Staphylococcal bacteriophage – Sb-1

	Antibiotic	Antibiotic + Sb-1	Sb-1 followed by antibiotic	Antibiotic followed by Sb-1
	MBEC (µg/ml)	MBEC (µg/ml) +(PFU/ml)	MBEC (PFU/ml)/(µg/ml)	MBEC (µg/ml)/(PFU/ml)
FOS	>4096	>($1024+10^5$)	10^5/64 S	>(1024/10^5)
RIF	256	64+10^5 S	10^5/16 S	64/10^5 S
VAN	2048	>($512+10^5$)	10^5/32 S	512/10^5 S
DAP	128	32+10^5 S	10^5/4 S	32/10^5 S
CIP	>256	>($128+10^5$)	10^5/32 S	>(32/10^5)

24h-old biofilm of MRSA ATCC43300 on porous glass beads

MBEC: minimum biofilm eradicating concentration
S: synergistic effect

Sb-1 followed by the antibiotic treatment exhibits a synergistic effect

Tkhilaishvili T, Lombardi L, Klatt AB, Trampuz A, Di Luca M. Int J Antimicrob Agents. 2018 Dec;52(6):842-853

Phage antibiotic synergism vs Gram-negative bacteria

E. coli

Table 2
Antibiofilm effects of simultaneous or staggered phage–antibiotic combinations against *Escherichia coli* EC1 and ATCC 25922.

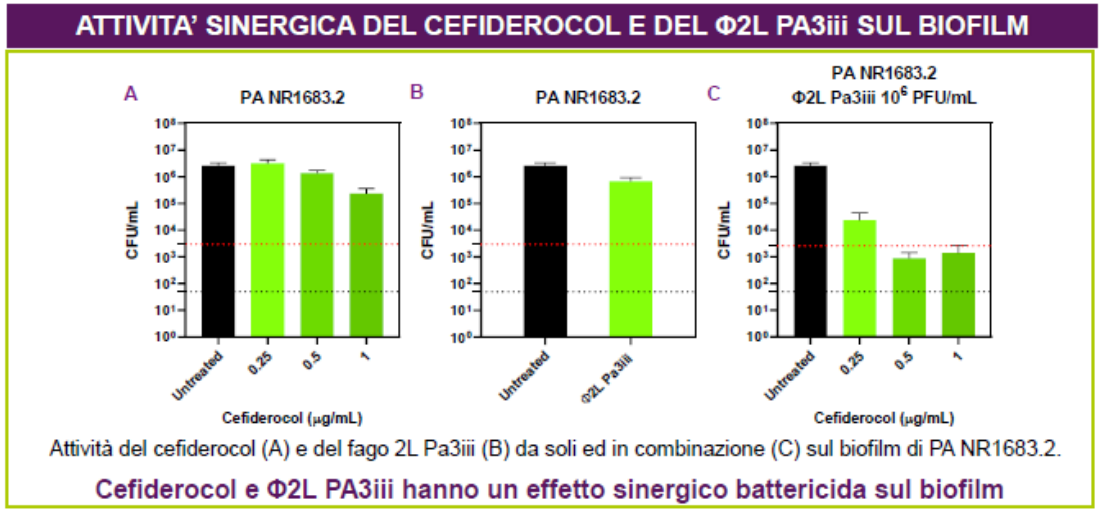
Antibiotic	Simultaneous exposure		Staggered exposure	
	MBEC (μg/mL)	Ratio [interpretation]	MBEC (μg/mL)	Ratio [interpretation]
EC1				
CIP	>1024[a]	1 [NE]	4	0.004 [SYN]
FOS	4	0.004 [SYN]	2	0.002 [SYN]
GEN	8	0.25 [SYN]	8	0.25 [SYN]
MER	4	0.125 [SYN]	1	0.03 [SYN]
CEF	>1024[a]	1 [NE]	>1024[a]	1 [NE]
ATCC 25922				
CIP	8	0.5 [NE]	0.25	0.016 [SYN]
FOS	64	0.125 [SYN]	32	0.06 [SYN]
GEN	8	0.5 [NE]	8	0.5 [NE]
MER	64	0.5 [NE]	16	0.128 [SYN]
CEF	>1024 [a]	8 [ANT]	32	0.25 [SYN]

MBEC, minimum biofilm eradication concentration; CIP, ciprofloxacin; FOS, fosfomycin; GEN, gentamicin; MER, meropenem; CEF, ceftriaxone; NE, no effect; SYN, synergism; ANT, antagonism.

[a] MBEC of the single antibiotic was considered equal to 1024 μg/mL for $MBEC_{phage}/MBEC_{alone}$ ratio calculations.

Wang L, et al Int J Antimicrob Agents. 2020 Dec;56(6)

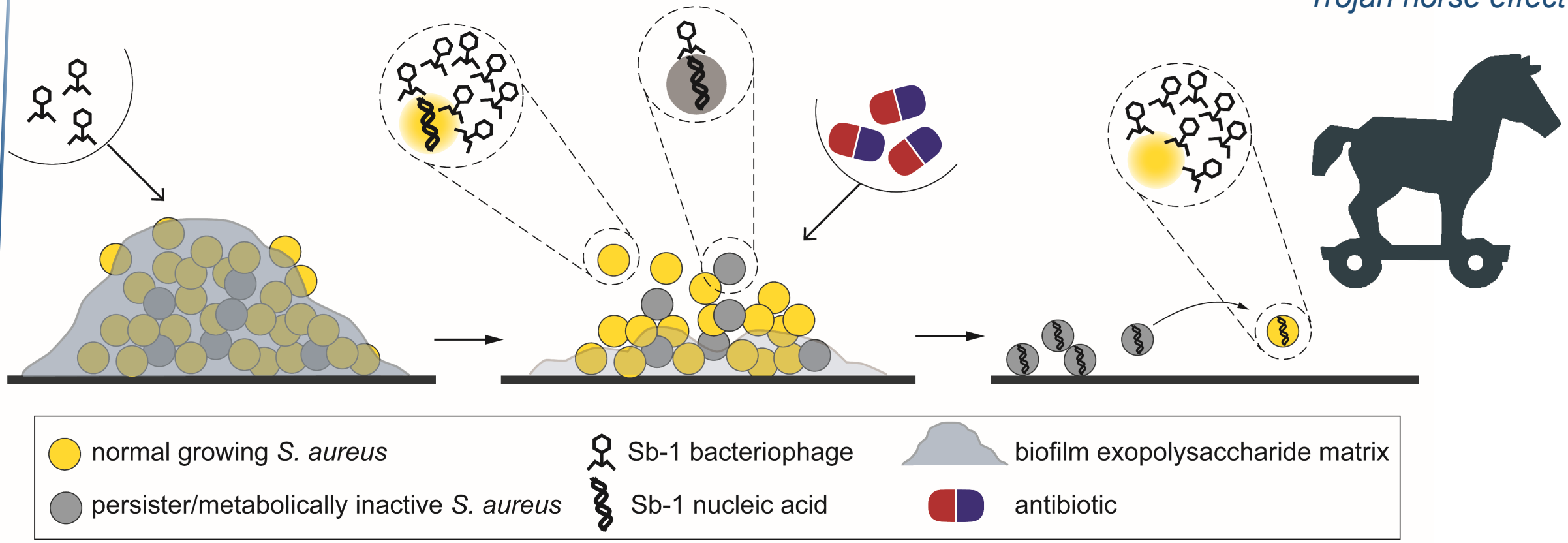
P. aeruginosa



Ferretti et al, 2023 (Manuscript in preparation), Poster 16 IDiPaC4

Proposed model for *in vitro* interaction

"Trojan horse effect"



Sb-1 might be used as an adjuvant to antibiotic therapy against biofilm-associated infections due to multi-drug resistant *S. aureus*

Tkhilaishvili T, Lombardi L, Klatt AB, Trampuz A, Di Luca M. Int J Antimicrob Agents. 2018 Dec;52(6):842-853

Patients are already looking for **alternatives to antibiotics**

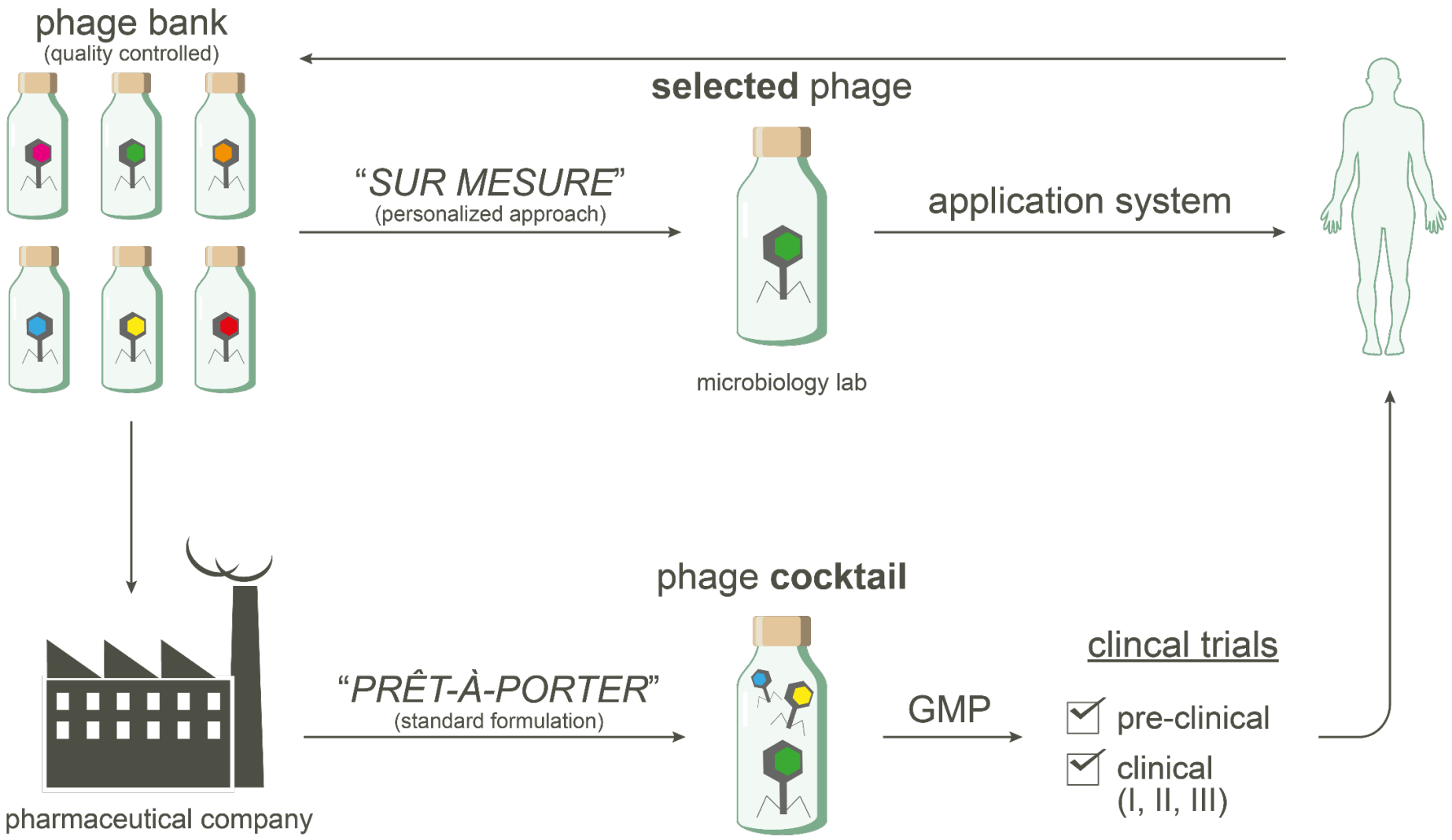
- **General Chapter on Phage Therapy in European Pharmacopeia (March 2023)**

- **No product on the market yet**, except in former Soviet Union Countries

- **Magistral preparation** at Queen Astrid Military Hospital in Bruxelles, Belgium and in France.

- **Compassionate use**

Phage therapy products



Phage therapy for PJI treatment

	Patient population	Causative pathogen	Phage preparation	Administration	Dose (PFU/mL)	Regimen	Concomittant treatment	Adverse events	Efficacy	
									Clinical improvement	Bacterial eradication
Case reports										
Fish et al[26]	Diabetic foot ulcer complicated by osteomyelitis (n=1)	*Staphylococcus aureus*	Single phage Sb-1	Local injection	NS	0·7 mL once a week for 7 weeks	Antibiotics	NS	Improvement, reossification	NS
Ferry et al[28]	Relapsing PJI of the hip (n=1)	*Pseudomonas aeruginosa** and *S aureus*	Two customised cocktails†	Intra-articular injection	1×10^{10}	10 mL of each cocktail during surgery	Antibiotics and surgery	No	Improvement, wound closure	NS
Nir-Paz et al[33]	Fracture-related infection of the tibia (n=1)	*Acinetobacter baumannii** and *Klebsiella pneumoniae**	Single phages ϕabkt21phi3 and ϕkpkt21phi1	Intravenous	5×10^{7}	1 mL of each phage for 11 days	Antibiotics	No	Improvement, wound closure, prevention of amputation	Yes, negative cultures at 8-month follow-up
Cano et al[29]	Chronic PJI of the knee (n=1)	*K pneumoniae*	Single phage kpjh46	Intravenous	$6\cdot3\times10^{10}$	50 mL daily, 40 applications	Antibiotics	No	Improvement	NS
Doub et al[30]	Chronic PJI of the knee (n=1)	MRSA*	Single phage sagr51ϕ1	Intravenous and intra-articular	$2\cdot7\times10^{9}$ intravenous, $5\cdot4\times10^{9}$ intra-arterial	4 doses of 10 mL intravenously, 50 mL per day intra-articularly	Antibiotics and surgery	Yes¶	Improvement, second-stage prosthesis	Yes, negative intra-operative cultures 2 months after treatment
Tkhilaishvili et al[31]	Chronic PJI of the knee (n=1)	*P aeruginosa**	Customised cocktail, NS	Intra-articular	1×10^{8}	5 mL every 8 h for 5 days	Antibiotics and surgery	No	Improvement, second-stage prosthesis	Yes, negative cultures 4 weeks after treatment
Ramirez-Sanchez et al[32]	Chronic PJI of the knee (n=1)	*S aureus*	AB-SA01, AB-SA01, and SaGR51ø1	Intra-articular and intravenous	$5\cdot3–5\cdot9\times10^{8}$, $2\cdot89\times10^{10}$	One intra-articular dose (10 mL) plus intravenous infusions every 6 h for 8 weeks	Antibiotics plus surgery	No	Improvement, improved C-reactive protein concentrations	Yes, negative cultures at 2-month follow-up

Increase of Alanine and aspartate aminotransferase concentration, after 3 intravenous doses. Then, intra articular application.

Saartje Uyttebroek, et al 2022 Lancet

Cesta N, et al. **Application of Phage Therapy in a Case of a Chronic Hip-Prosthetic Joint Infection due to *Pseudomonas aeruginosa*: An Italian Real-Life Experience and *In Vitro* Analysis**. Open Forum Infect Dis. **2023** Feb 1;10(2):ofad051.

Clinical and microbiological follow up (since 2020

Patient ID	Infection/ colonization	Isolate	Standard of care	Phage	Provider	Outcome
001_MM	Osteomyelitis	*P. aeruginosa*	DAIR	PYO	Eliava Biopreparation (Georgia)	No infection sign 1 year follow up
002_GMS	Prostatitis	*E. coli*	Doxycycline 100 mg q12h OS	SES and PYO 10 ml each q12h OS	Eliava Biopreparation (Georgia)	No recalcitrant infection 1 year follow up
003_MAR*	Hip Prosthetic Joint	*P. aeruginosa*	Meropenem 2 gr q12h EV and DAIR	Pa 53	Eliava Biopreparation (Georgia)	No sign of infection 2 year follow up
004_VC*	Lung (PCD)	*P. aeruginosa*	Cefepime 2gr q8h EV	PT07	Queen Astrid Military Hospital Bruxelles (Belgium)	No eradication
005_ND	Osteomyelitis	*S. aureus*	No antibiotic no surgery	Sb-1	Eliava Biopreparation (Georgia)	No eradication
006_RP	Rhinosinusitis	*S. aureus*	Linezolid 600mg q12h OS no surgery	Sb-1	Eliava Biopreparation (Georgia)	Under treatment

** Informed consent signed to the phage provider*

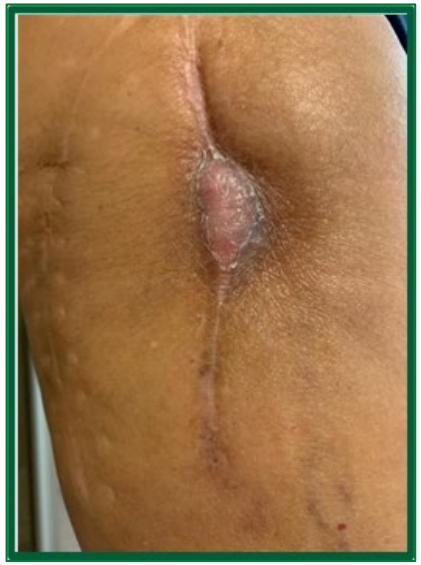
PCD: Primary ciliary dyskinesia

A 62- year-old woman affected by hip PJI

- 2015 total right-hip artroplasty
- 2016 – Infection by *P. aeruginosa*
- *P. aeruginosa* (cipro-S) 2017-2019 two DAIR for failure of previous treament
- Antibiotic iv therapy (with β-lact, carbapenem) Oral suppressive therpy with ciprofloxacin

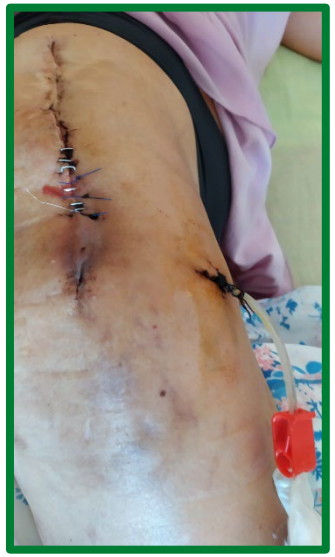
March 2020
Patient sent the *P. aeruginosa* strain to Eliava Institute

August 2020
Patient received custom phage preparation



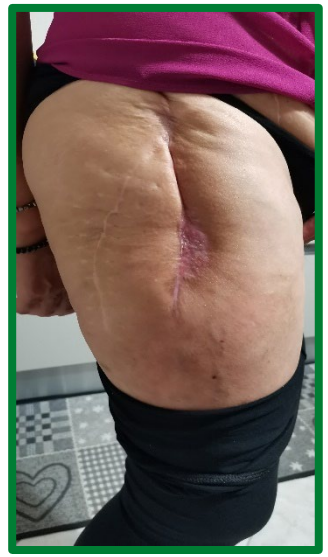
August 2020
DAIR surgery.
Meropenem 2g q12h
+ start PT (2W)

10 ml x 10^3 PFU/ml q8h the 1° day, then 5ml x 10^3 PFU/ml q8h from day 2 to 15 Into a drainage



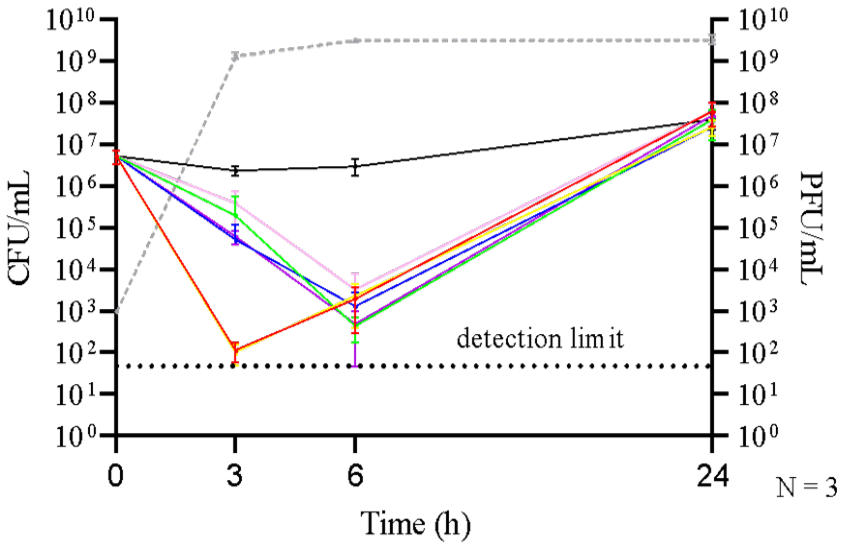
July 2022
No sign of relapse of infection (medical examination)

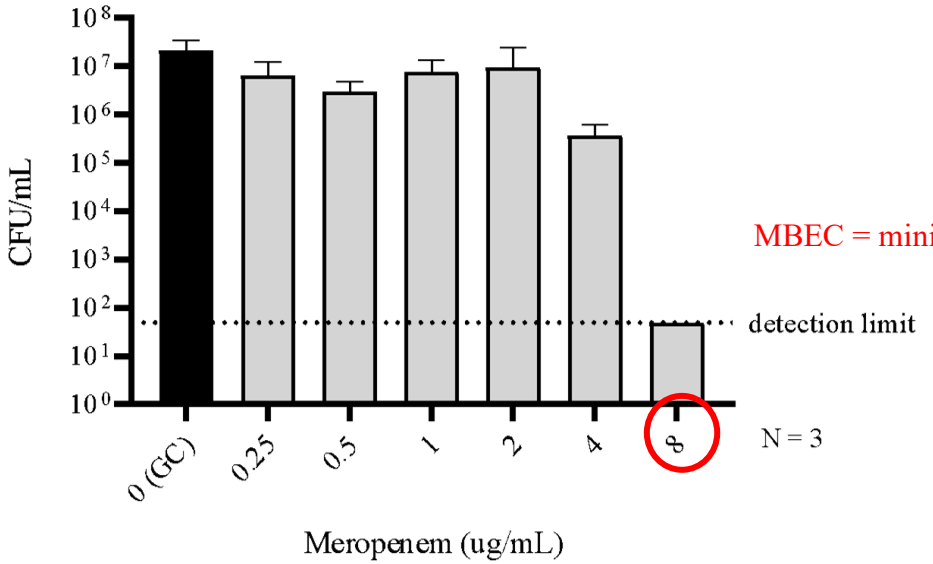
September 2021
No sign of relapse of infection (medical examination + radiological exam)



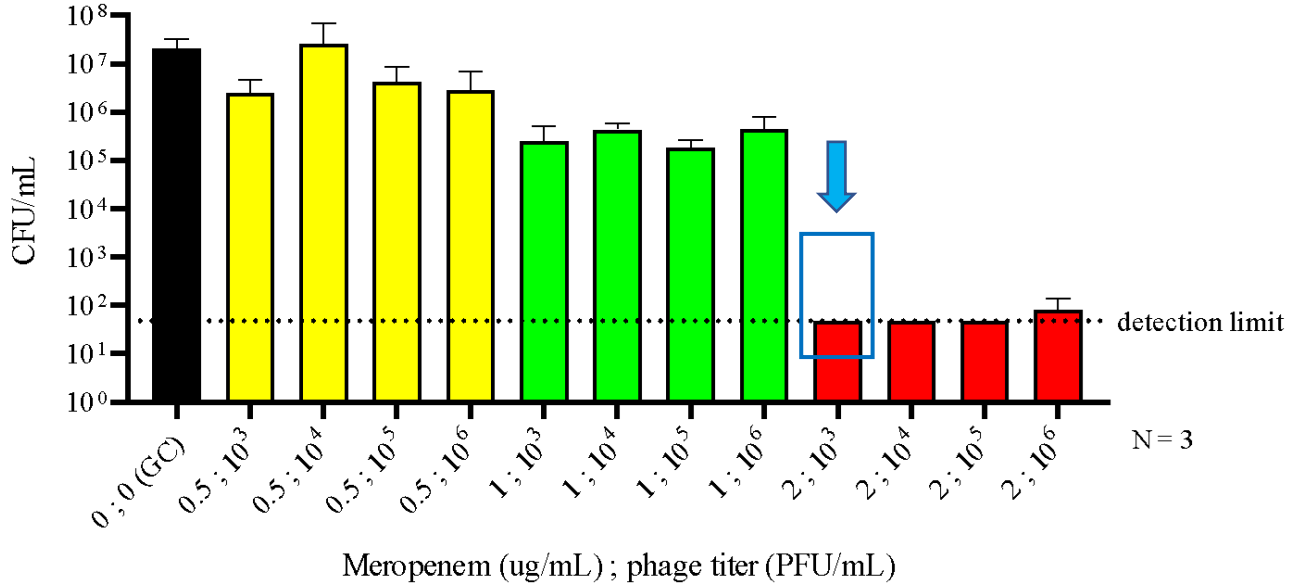
(N. Cesta, et al Open Forum Infectious Diseases, 2023)

Meropenem-phage synergy (24h) vs *P. aeruginosa* biofilm





MBEC = minimal biofilm-eradication concentration



Phages resulted effective in combination with antibiotics after DAIR

JOURNAL ARTICLE EDITOR'S CHOICE

Application of Phage Therapy in a Case of a Chronic Hip-Prosthetic Joint Infection due to *Pseudomonas aeruginosa*: An Italian Real-Life Experience and *In Vitro* Analysis

Novella Cesta ✉, Marco Pini, Tiziana Mulas, Alessandro Materazzi, Ernesto Ippolito, Jeroen Wagemans, Mzia Kutateladze, Carla Fontana, Loredana Sarmati, Arianna Tavanti, Rob Lavigne, Massimo Andreoni, Mariagrazia Di Luca ✉

Author Notes

Open Forum Infectious Diseases, Volume 10, Issue 2, February 2023, ofad051,
https://doi.org/10.1093/ofid/ofad051

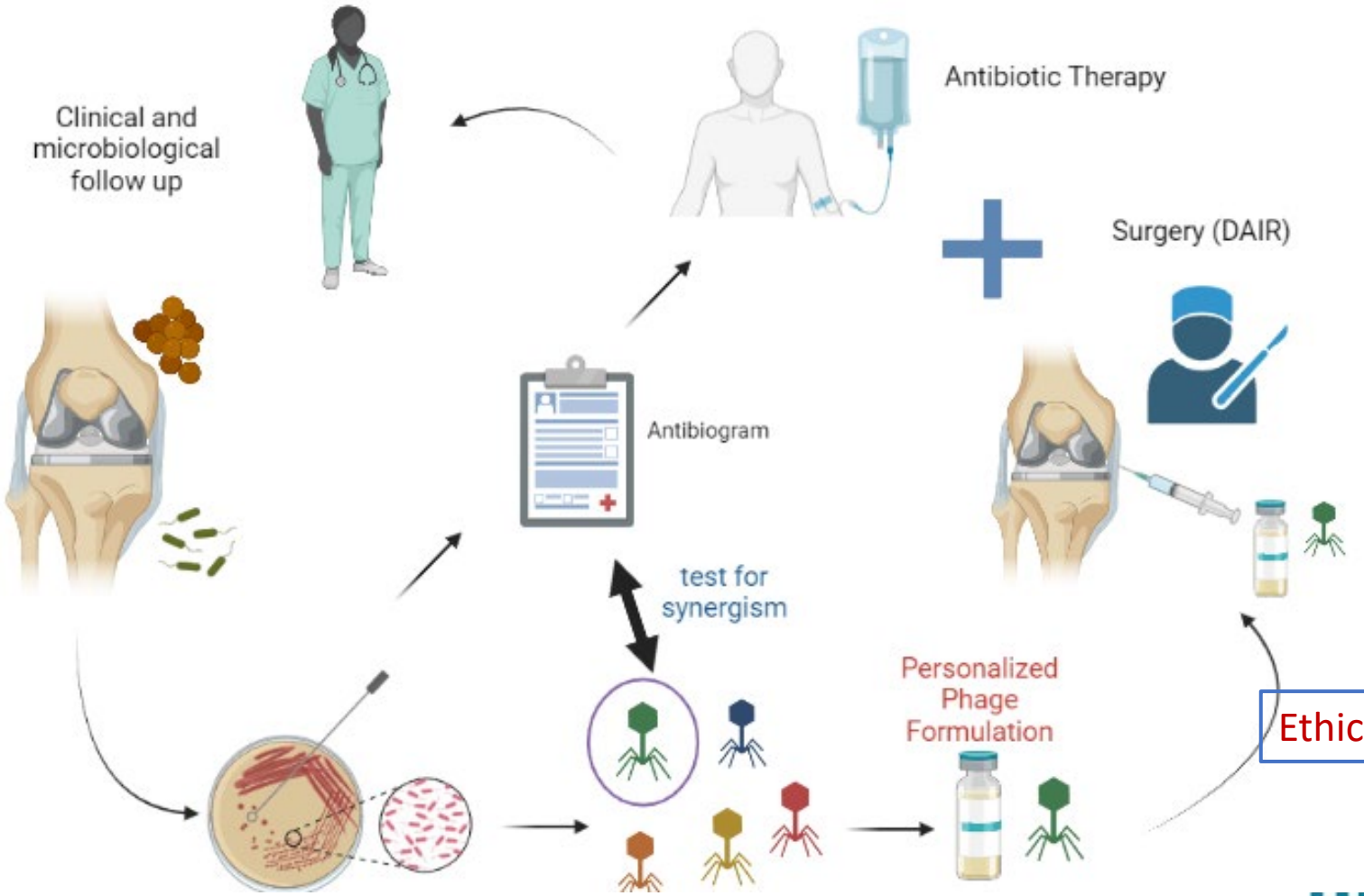
Published: 01 February 2023 **Article history** ▾

Open Forum Infectious Diseases

IDSA hivma

Tomorrow…

- Phages might be one solution among others which is available in the toolbox of the ID doctor
- A multidisciplinary task force is required to develop phage therapy



mariagrazia.diluca@unipi.it

Varianti

- Omicron
- BA.1
- BA.2 - BA.2.75 (Centaurus), XBB.1.5 (Kraken), XBB.1.16 (Arcuturus)
- BA.3
- BA.4
- BA.5
- EG.5 Eris

viruses

MDPI

Editorial

How SARS-CoV-2 Big Data Are Challenging Viral Taxonomy Rules

Daniele Focosi [1,*] and Fabrizio Maggi [2]

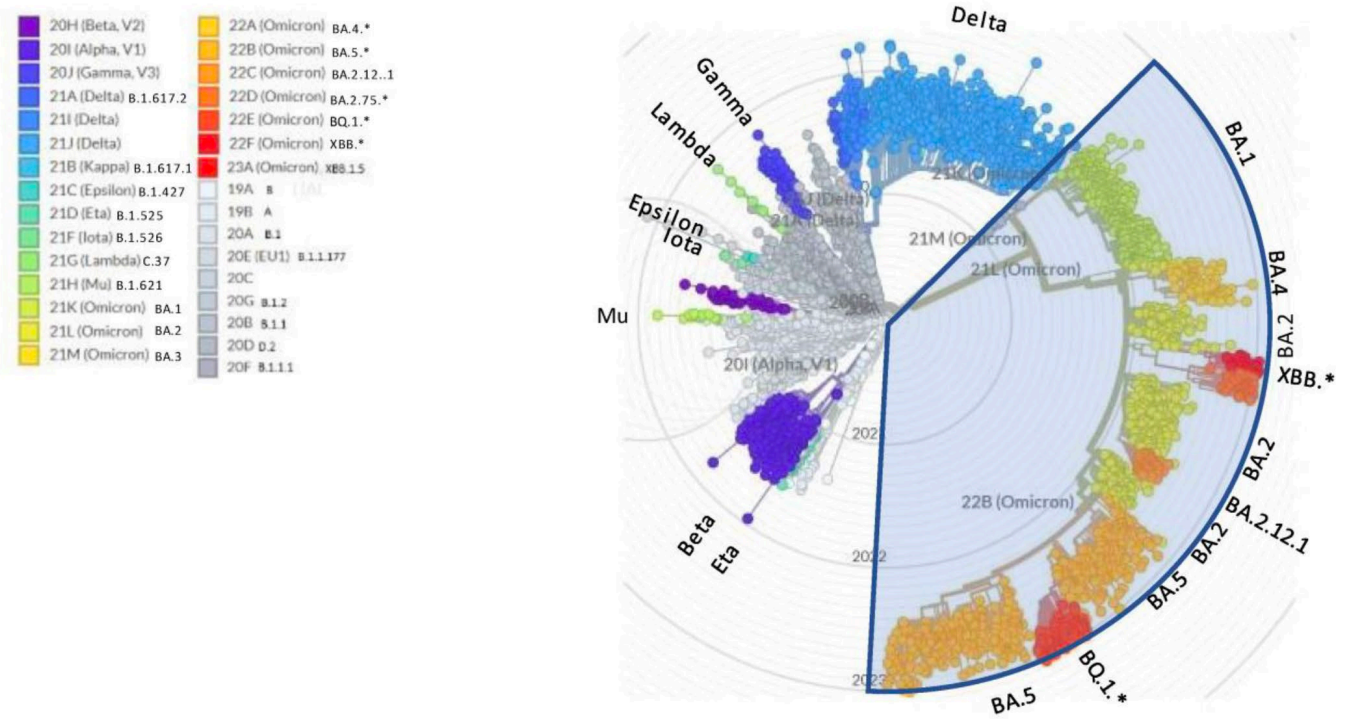


Figure 1. NextStrain radial view of SARS-CoV-2 phylogenetic tree. The legend shows the corresponding WHO variants of concern (VOC) and PANGOLIN names. * asterisk indicates that sublineages are included in the variant.

Tabella 2a.

REGIONE/PA	N. Lab	N. campioni positivi in RT-PCR	N. campioni sequenziati	N. di sequenze ottenute per analisi
ABRUZZO	1	29	11	11
BASILICATA	1	6	1	1
CALABRIA	3	45	12	8
CAMPANIA	3	nd**	20	20
EMILIA ROMAGNA	3	21	21	21
FRIULI VENEZIA GIULIA	5	22	22	21
LAZIO	1	67	67	67
LIGURIA	5	112	15	15
LOMBARDIA	12	103	103	102
MARCHE	1	6	6	6
MOLISE	1	23	3	3
PA BOLZANO	1	15	15	15
PA TRENTO	1	5	5	5
PIEMONTE	11	10	10	10
PUGLIA	9	56	53	52
SARDEGNA	3	20	20	20
SICILIA	4	25	25	25
TOSCANA	3	66	66	64
UMBRIA	4	59	31	31
VALLE D'AOSTA	1	1	0	0
VENETO	10	82	82	82
ITALIA	**83**	**773**	**588**	**579**

**Non disponibile

Agosto 2023

Tabella 2b.

REGIONE/PA	Numero †								Prevalenza (%) †							
	XBB.1.5 §	XBB.1.16 §	EG.5 §	XBB.1.9 ^	XBB.2.3 §	XBB ^	CH.1.1 §	Altro ~	XBB.1.5 §	XBB.1.16 §	EG.5 §	XBB.1.9 ^	XBB.2.3 §	XBB ^	CH.1.1 §	Altro ~
ABRUZZO	1	7	1	0	1	1	0	0	9,1	63,6	9,1	0,0	9,1	9,1	0,0	0,0
BASILICATA	0	0	0	0	0	0	1	0	0,0	0,0	0,0	0,0	0,0	0,0	100,0	0,0
CALABRIA	2	2	1	0	1	1	1	0	25,0	25,0	12,5	0,0	12,5	12,5	12,5	0,0
CAMPANIA	2	2	11	2	1	2	0	0	10,0	10,0	55,0	10,0	5,0	10,0	0,0	0,0
EMILIA ROMAGNA	2	0	11	4	3	0	0	1	9,5	0,0	52,4	19,0	14,3	0,0	0,0	4,8
FRIULI VENEZIA GIULIA	2	4	10	3	2	0	0	0	9,5	19,0	47,6	14,3	9,5	0,0	0,0	0,0
LAZIO	9	10	25	11	6	5	0	1	13,4	14,9	37,3	16,4	9,0	7,5	0,0	1,5
LIGURIA	2	7	2	2	2	0	0	0	13,3	46,7	13,3	13,3	13,3	0,0	0,0	0,0
LOMBARDIA	15	20	46	9	8	2	2	0	14,7	19,6	45,1	8,8	7,8	2,0	2,0	0,0
MARCHE	1	0	3	0	2	0	0	0	16,7	0,0	50,0	0,0	33,3	0,0	0,0	0,0
MOLISE	1	1	0	0	1	0	0	0	33,3	33,3	0,0	0,0	33,3	0,0	0,0	0,0
PA BOLZANO	0	2	8	1	3	1	0	0	0,0	13,3	53,3	6,7	20,0	6,7	0,0	0,0
PA TRENTO	0	1	1	1	0	0	1	1	0,0	20,0	20,0	20,0	0,0	0,0	20,0	20,0
PIEMONTE	1	0	5	4	0	0	0	0	10,0	0,0	50,0	40,0	0,0	0,0	0,0	0,0
PUGLIA	8	8	16	2	0	11	7	0	15,4	15,4	30,8	3,8	0,0	21,2	13,5	0,0
SARDEGNA	3	3	11	1	0	0	1	1	15,0	15,0	55,0	5,0	0,0	0,0	5,0	5,0
SICILIA	6	1	6	4	4	4	0	0	24,0	4,0	24,0	16,0	16,0	16,0	0,0	0,0
TOSCANA	6	16	31	6	3	1	1	0	9,4	25,0	48,4	9,4	4,7	1,6	1,6	0,0
UMBRIA	6	1	19	1	2	0	1	1	19,4	3,2	61,3	3,2	6,5	0,0	3,2	3,2
VALLE D'AOSTA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
VENETO	13	9	42	9	5	3	0	1	15,9	11,0	51,2	11,0	6,1	3,7	0,0	1,2
ITALIA	80	94	249	60	44	31	15	6	13,4	16,5	41,9	12,0	7,8	5,1	2,3	1,1

† Classificazione in accordo con le più recenti indicazioni di ECDC (ref.3) e WHO (ref. 4).
§ Include i relativi sotto-lignaggi.
^ Include i relativi sotto-lignaggi non soggetti a classificazione specifica.
~ Include BA.5.1, BF.7.24, GL.1, HW.1.1, XBC.1.6.3

Check for updates

The BMJ
Cite this as: *BMJ* 2023;382:p1964
http://dx.doi.org/10.1136/bmj.p1964
Published: 24 August 2023

Covid-19: Scientists sound alarm over new BA.2.86 "Pirola" variant

Mun-Keat Looi

- Pirola ha più di 35 mutazioni da BA.2, compare spontaneamente, forse ha circolato per mesi a bassi livelli
- Il livello di mutazioni di Kraken rispetto all'omicron originale
- Immunità cellulare proteggerà dalle forme gravi, ma molti casi di infezioni con sintomi ci saranno
- **Probabilmente si sarà selezionata in immunodepresso dove si è replicata per mesi**
- Capire l'infettività ed immunoescape

Riepilogo nazionale e regionale per principio attivo – trattamenti per milione di residenti (periodo: apertura monitoraggio – 30 giugno 2023)*

Regione	Popolazione residente al 01/01/2023	Bamlanivimab	Bamlanivimab + etesevimab	Ronapreve (casirivimab + imdevimab)	Xevudy (sotrovimab)	Evusheld (tixagevimab e cilgavimab), precoce	Totale per regione	Evusheld (tixagevimab e cilgavimab), profilassi	Totale per regione
ABRUZZO	1.275.950	0,0	554,9	696,7	1.467,1	288,4	3.007,2	234,3	3.241,5
BASILICATA	541.168	5,5	144,1	290,1	365,9	49,9	855,6	157,1	1.012,6
CALABRIA	1.855.454	0,0	91,1	249,0	560,5	237,7	1.138,3	215,0	1.353,3
CAMPANIA	5.624.420	27,9	175,1	345,8	637,4	149,2	1.335,4	157,4	1.492,8
EMILIA ROMAGNA	4.425.366	0,2	278,4	240,9	190,9	51,3	761,7	297,6	1.059,3
FRIULI VENEZIA GIULIA	1.194.647	33,5	241,1	734,1	927,5	179,1	2.115,3	501,4	2.616,7
LAZIO	5.714.882	3,7	466,3	698,9	874,7	157,1	2.200,8	317,4	2.518,2
LIGURIA	1.509.227	30,5	739,5	858,1	621,5	157,0	2.406,5	246,5	2.653,0
LOMBARDIA	9.943.004	2,6	132,9	146,3	217,0	80,7	579,5	305,1	884,6
MARCHE	1.487.150	24,9	574,9	810,3	1.188,2	98,9	2.697,1	172,8	2.869,9
MOLISE	292.150	41,1	3,4	239,6	400,5	0,0	684,6	229,3	913,9
PIEMONTE	4.256.350	3,3	182,3	453,9	394,0	93,3	1.126,8	451,8	1.578,6
PROV. AUTON. BOLZANO	532.616	0,0	24,4	92,0	338,0	30,0	484,4	212,2	696,6
PROV. AUTON. TRENTO	540.958	7,4	77,6	223,7	273,6	3,7	586,0	99,8	685,8
PUGLIA	3.922.941	18,4	137,4	229,4	406,8	82,9	874,9	254,9	1.129,8
SARDEGNA	1.587.413	0,0	23,3	252,0	587,8	68,7	931,7	81,9	1.013,6
SICILIA	4.833.329	15,1	135,5	314,1	520,1	69,1	1.053,9	200,5	1.254,4
TOSCANA	3.663.191	8,7	466,5	556,4	415,2	117,1	1.563,9	393,1	1.957,0
UMBRIA	858.812	59,4	125,8	331,9	556,6	31,4	1.105,0	87,3	1.192,3
VALLE D'AOSTA	123.360	267,5	1.021,4	2.885,9	640,4	64,9	4.880,0	24,3	4.904,4
VENETO	4.847.745	41,5	790,3	686,5	868,2	114,5	2.501,0	280,3	2.781,3
ITALIA	**59.030.133**	**13,9**	**292,3**	**412,4**	**541,5**	**108,5**	**1.368,5**	**274,3**	**1.642,8**

* I numeri indicano le prescrizioni anticorpi monoclonali (RF=richieste farmaco) al netto di quelle senza dispensazione

Test\mAb	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	BEB	ADI
Alpha	1_{23}	13_{20}	1.3_{9}	1_{32}	0.6_{33}	0.9_{14}	0.6_{15}	1.5_{14}	0.8_{14}	1.8_{30}	0.9_{6}	1.3_{6}
Beta	$>1000_{29}$	516_{25}	990_{12}	91_{38}	0.6_{38}	1.6_{19}	1.1_{16}	5.8_{17}	1.7_{16}	1_{31}	1_{8}	2.8_{6}
Gamma	$>1000_{16}$	348_{16}	404_{4}	124_{24}	0.4_{24}	1_{9}	0.5_{12}	3.7_{11}	0.9_{10}	1_{23}	1_{5}	2.2_{6}
Delta	$>1000_{25}$	0.4_{25}	1_{9}	0.7_{33}	1.5_{34}	1.3_{14}	2.4_{15}	1.0_{16}	1_{17}	1.1_{31}	1_{12}	1.5_{8}
Omicron/BA.1	$>1000_{42}$	459_{42}	980_{17}	$>1000_{50}$	$>1000_{51}$	$>1000_{23}$	263_{48}	264_{50}	63_{35}	3.8_{64}	1_{27}	108_{20}
Omicron/BA.2	$>1000_{24}$	515_{24}	744_{15}	$>1000_{34}$	219_{33}	387_{23}	1.8_{39}	928_{38}	8_{35}	21_{52}	1_{33}	$>1000_{15}$
Omicron/BA.2.12.1	$>1000_{12}$	515_{12}	794_{8}	$>1000_{13}$	125_{13}	250_{9}	2.8_{15}	410_{15}	9.1_{10}	20_{18}	1_{13}	968_{6}
Omicron/BA.2.75	$>1000_{9}$	383_{9}	554_{5}	477_{11}	$>1000_{11}$	$>1000_{7}$	14_{15}	29_{15}	24_{11}	12_{15}	3.1_{15}	437_{7}
Omicron/BA.2.75.2	556_{2}	489_{2}	$>1000_{1}$	589_{4}	588_{4}	$>1000_{3}$	$>1000_{7}$	$>1000_{7}$	$>1000_{7}$	8_{9}	2.8_{7}	509_{2}
Omicron/XBB	$>1000_{1}$	$>1000_{1}$	-	589_{2}	588_{2}	200_{1}	$>1000_{3}$	$>1000_{3}$	738_{2}	14_{4}	$>1000_{4}$	$>1000_{1}$
Omicron/XBB.1	$>1000_{1}$	$>1000_{1}$	$>1000_{1}$	880_{3}	$>1000_{3}$	887_{3}	$>1000_{6}$	$>1000_{6}$	$>1000_{6}$	15_{8}	900_{6}	-
Omicron/XBB.1.5	Krachen	-	-	650_{2}	572_{2}	751_{2}	433_{3}	$>1000_{3}$	867_{3}	18_{5}	475_{4}	-
Omicron/XBB.1.16	-	-	-	420_{1}	143_{1}	615_{1}	127_{1}	448_{1}	488_{1}	5.3_{1}	149_{1}	-
Omicron/BA.4/5	$>1000_{19}$	504_{19}	588_{11}	$>1000_{26}$	143_{26}	387_{17}	8.1_{33}	$>1000_{33}$	25_{27}	22_{39}	1_{29}	$>1000_{13}$

centaurus

13%

16%

Differential serum neutralisation of omicron sublineages in patients receiving prophylaxis with tixagevimab–cilgavimab

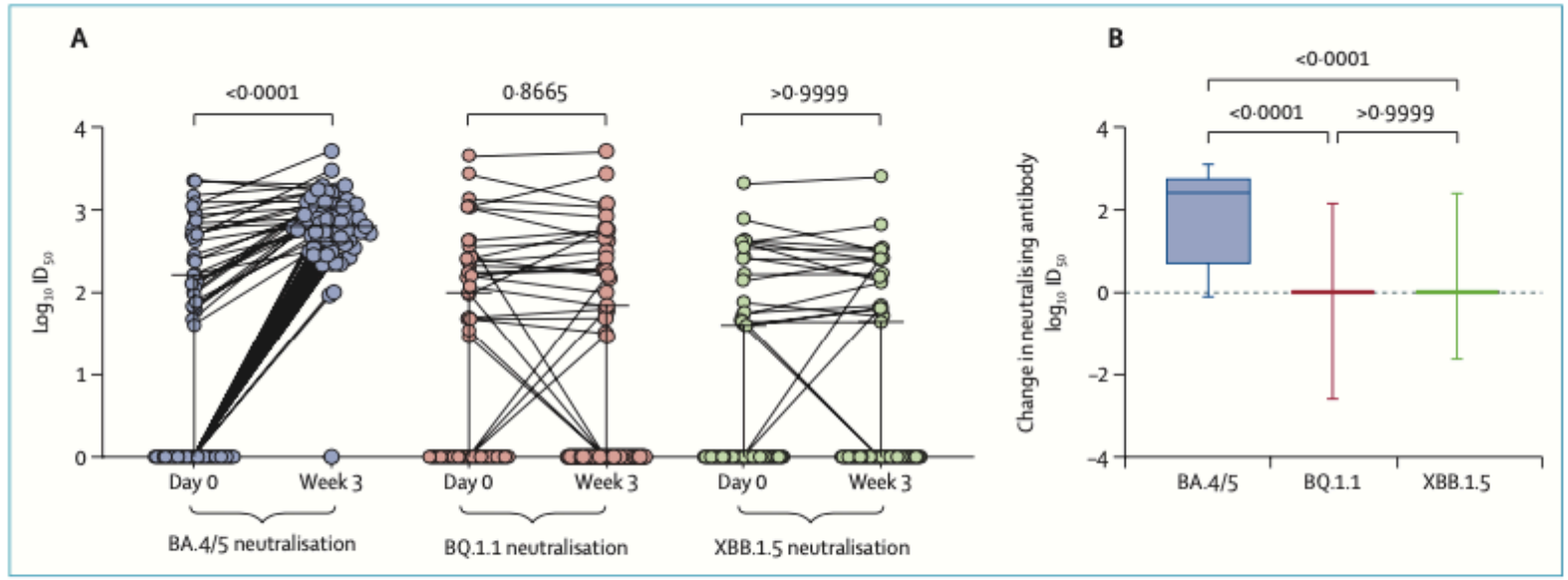


Figure: **Variant-specific neutralising antibody to tixagevimab–cilgavimab**
(A) Dot plots with connectors of the neutralising antibody titre against omicron BA.4/5, BQ.1.1, and XBB.1.5 at day 0 and at 3 weeks after receiving 300 mg tixagevimab–cilgavimab. Each dot represents one patient and connector lines join each patient's antibody titre before and after receiving tixagevimab–cilgavimab. Horizontal lines represent median and interquartile range. The p value was estimated using Wilcoxon matched-paired signed-rank test. (B) Box and whiskers plot of the change in the neutralising antibody titre against omicron sublineages BA.4/5, BQ.1.1, and XBB.1.5 after receiving tixagevimab–cilgavimab. Horizontal lines represent median and interquartile range. The p value was estimated using Wilcoxon matched-paired signed-rank test.

www.thelancet.com/infection **Vol 23 May 2023**

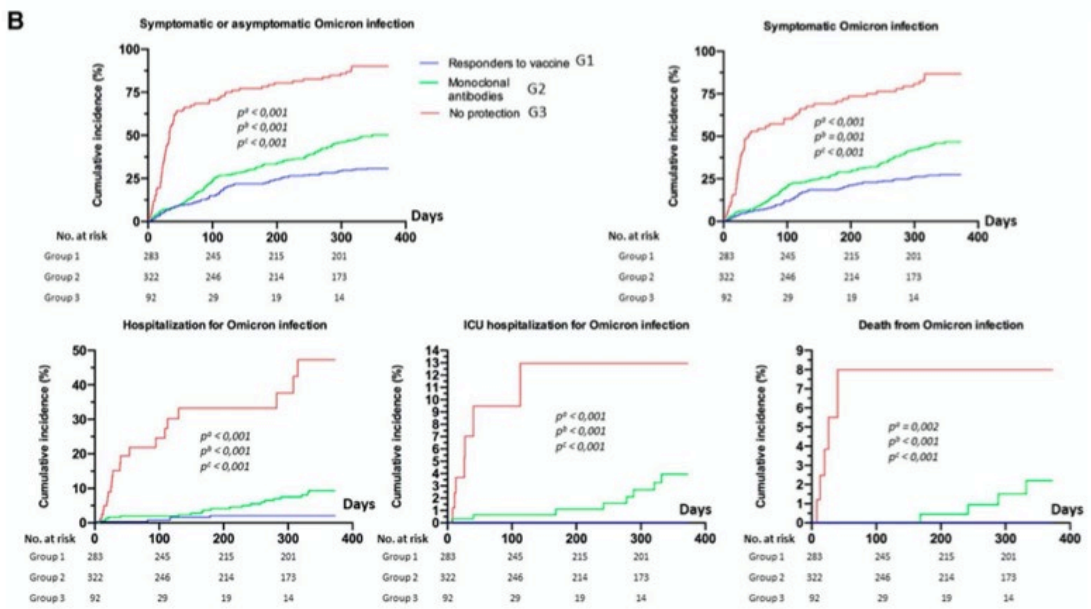
79 trapiantati di organo solido, profilassati con T+C, prelievo tempo 0 e 3 settimane
Test fenotipico con pseudovirus

Efficacy of Tixagevimab/Cilgavimab Prophylaxis and Vaccination on Omicron Variants (BA.1, BA.2, BA.5, and BQ.1.1) in Kidney Transplant Recipients

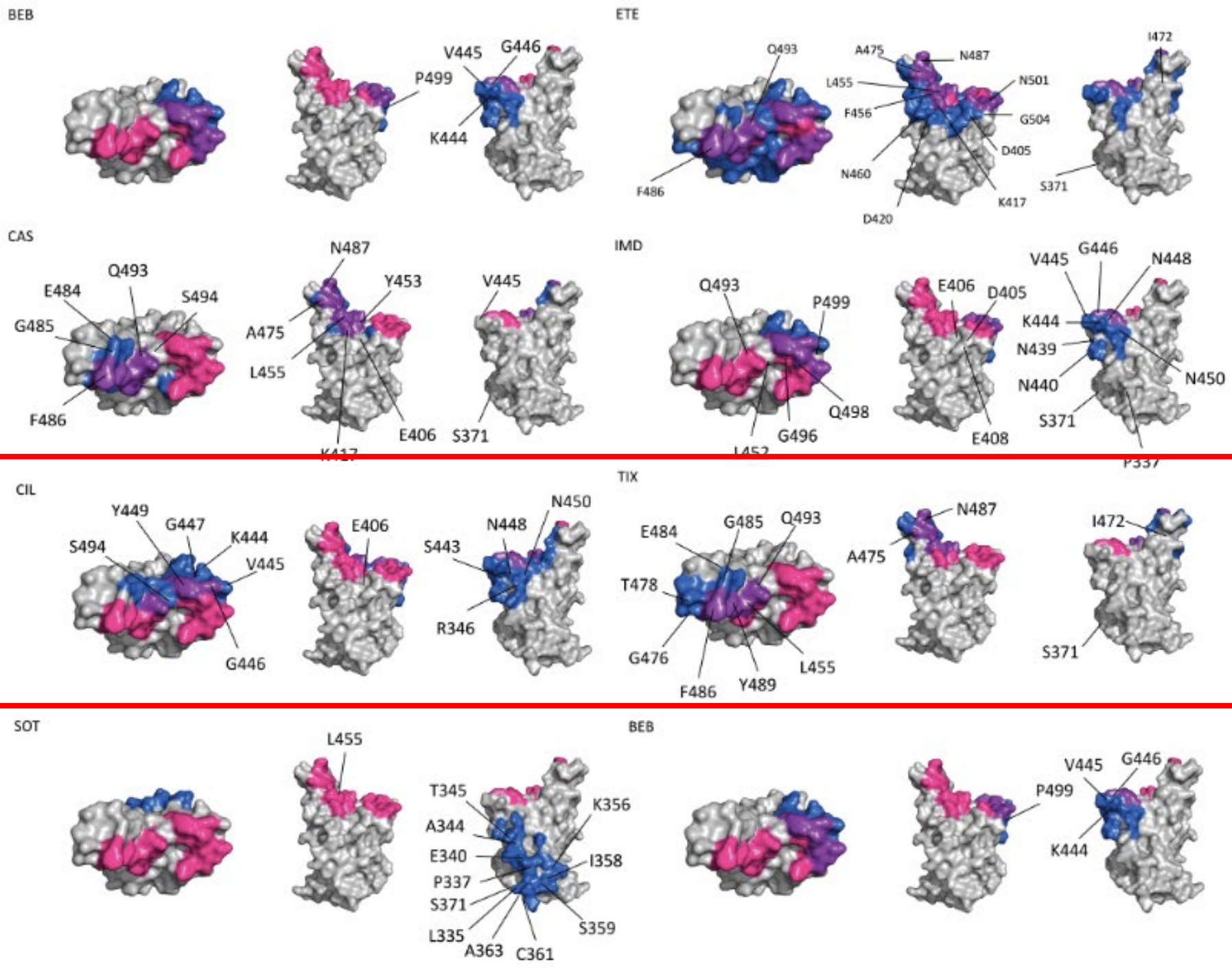
Dominique Bertrand,[1] *Charlotte Laurent*,[1] *Veronique Lemée*,[2] *Ludivine Lebourg*,[1] *Mélanie Hanoy*,[1] *Frank Le Roy*,[1] *Dorian Nezam*,[1] *Diana Pruteanu*,[1] *Steven Grange*,[1] *Tristan de Nattes*,[1,3] *Mathilde Lemoine*,[1] *Sophie Candon*,[3,4] *and Dominique Guerrot*[1,5]

[1]Department of Nephrology

CJASN ■: 1–3, 2023. doi: https://doi.org/10.2215/CJN.0000000000000241



- Group 1: vaccine-induced immunization, 283 patients. Anti–SARS-CoV-2 antibody level was measured at least 1 month after the third dose of vaccine, and the median titer was 1344 BAU/ml, interquartile range, 648–2430.
- Group 2: insufficient vaccine-induced immunization but passive immunization with tixagevimab/cilgavimab, 322 patients. All kidney transplant recipients of group 2 received two intramuscular injections of 150 mg tixagevimab+150 mg cilgavimab between December 23, 2021, and February 2022, then two intramuscular injections of 150 mg tixagevimab+150 mg cilgavimab between April 2022 and May 2022, and then two intramuscular injections of 300 mg tixagevimab+300 mg cilgavimab between September and December 2022.
- Group 3: insufficient vaccine-induced immunization, 92 patients. In this group, kidney transplant recipients did not receive prophylaxis with tixagevimab/cilgavimab (patient refusal, patient on anticoagulant therapy, patient unreachable at the time of monoclonal antibodies proposal).


BEB
V445
G446
P499
K444
ETE
Q493
A475
N487
L455
N501
F456
G504
D405
N460
K417
D420
F486
I472
S371
CAS
N487
Q493
E484
Y453
S494
G485
A475
V445
L455
E406
F486
S371
IMD
Q493
P499
E406
D405
V445
G446
N448
K444
N439
N450
N440
Q498
G496
E408
S371
CIL
Y449
G447
K444
S494
V445
E406
N448
N450
S443
G446
R346
TIX
E484
G485
Q493
N487
A475
T478
I472
S371
G476
L455
F486
Y489
SOT
L455
T345
K356
A344
E340
I358
P337
S371
S359
L335
A363
C361
BEB
V445
G446
P499
K444

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

28 Gennaio 2022: Decreto Autorizzazione alla temporanea distribuzione

19 Febbraio 2022: Determina sulle definizione delle modalità e delle condizioni di impiego

Indicazioni

- ❑ **Profilassi Pre-esposizione dell'infezione da SARS-CoV2** in soggetti adulti e adolescenti (>12 anni) con perso corporeo >40kg.
- ❑ Soggetti con grave stato di compromissione del sistema immunitario e in presenza di sierologia negativa.

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2022 Apr 20. doi: 10.1056/NEJMoa2116620.

ORIGINAL ARTICLE

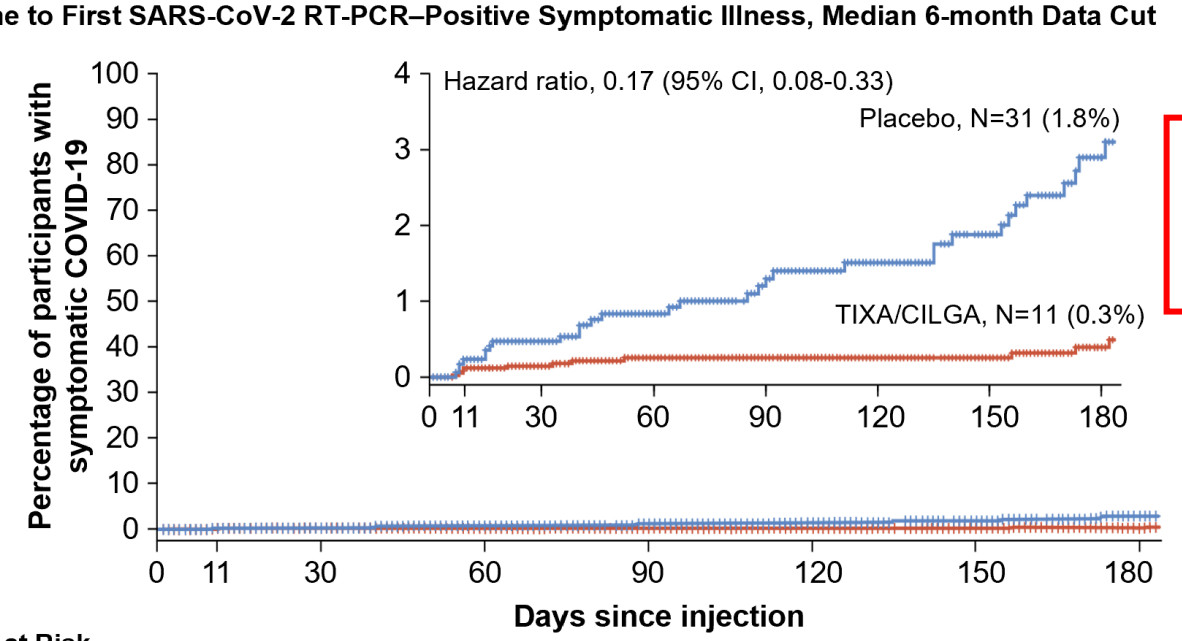
Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

M.J. Levin, A. Ustianowski, S. De Wit, O. Launay, M. Avila, A. Templeton, Y. Yuan, S. Seegobin, A. Ellery, D.J. Levinson, P. Ambery, R.H. Arends, R. Beavon, K. Dey, P. Garbes, E.J. Kelly, G.C.K.W. Koh, K.A. Near, K.W. Padilla, K. Psachoulia, A. Sharbaugh, K. Streicher, M.N. Pangalos, and M.T. Esser, for the PROVENT Study Group*

APPROVAZIONE ALL'UTILIZZO IN EMERGENZA DI EVUSHED in Italia

Primi di marzo 2022 *meeting* di reparto tra specialisti :

- confronto a partire dai dati,
- identificazione dei referenti,
- richiesta autorizzazione AIFA a prescrittori



Alfa
Delta
waves

Pazienti eleggibili:

- ✓ Assunzione nell'ultimo anno di terapie che comportano la deplezione dei linfociti B
- ✓ Trattamento con inibitori tirosin chinasi di Bruton
- ✓ Trattamento con CAR-T
- ✓ trapianto di cellule ematopoietiche con malattia da rigetto o assunzione di farmaci immunosoppressori
- ✓ malattia onco-ematologica in fase attiva
- ✓ trapianto di polmone
- ✓ trapianto di organo solido entro 1 anno
- ✓ trapianto di organi solidi con recente trattamento per rigetto acuto con agenti che riducono le cellule T o B
- ✓ immunodeficienze combinate gravi
- ✓ infezione da HIV non in trattamento e una conta dei linfociti T CD4 <50 cellule/mm3
- ✓ altra compromissione del sistema immunitario che ha determinato mancata sieroconversione (produzione di anticorpi IgG anti-Spike)

Da opportunità a realtà

✓28 marzo 2022 prima riunione infettivologi-ematologi (reparto e DH): aspetti conoscitivi, identificazione della popolazione a maggiore rischio e dei referenti, rivalutazione sierologica

✓29 marzo 2022 ricognizione degli spazi/percorsi/referenti; formazione del team: coinvolgimento ed istruzione del personale infermieristico della Clinica e della Farmacia Ospedaliera. Identificazione dei canali di segnalazione (mail e telefono del reperibile infettivologo).

✓30-31 marzo 2022 i Colleghi Ematologi contattano i loro pazienti ed espongono loro la strategia di profilassi

✓1 e 5 aprile 2022 gli Specialisti Infettivologi contattano i pazienti per i dettagli tecnici di procedura e di appuntamento

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio

| Clinical Microbiology | Research Article

Tixagevimab/cilgavimab for preventing COVID-19 during the Omicron surge: retrospective analysis of National Veterans Health Administration electronic data

Yinong Young-Xu,[1] Lauren Epstein,[2,3] Vincent C. Marconi,[2,3] Victoria Davey,[4] Caroline Korves,[5] Gabrielle Zwain,[5] Jeremy Smith,[5] Fran Cunningham,[1] Robert A. Bonomo,[6,7] Adit A. Ginde[8]

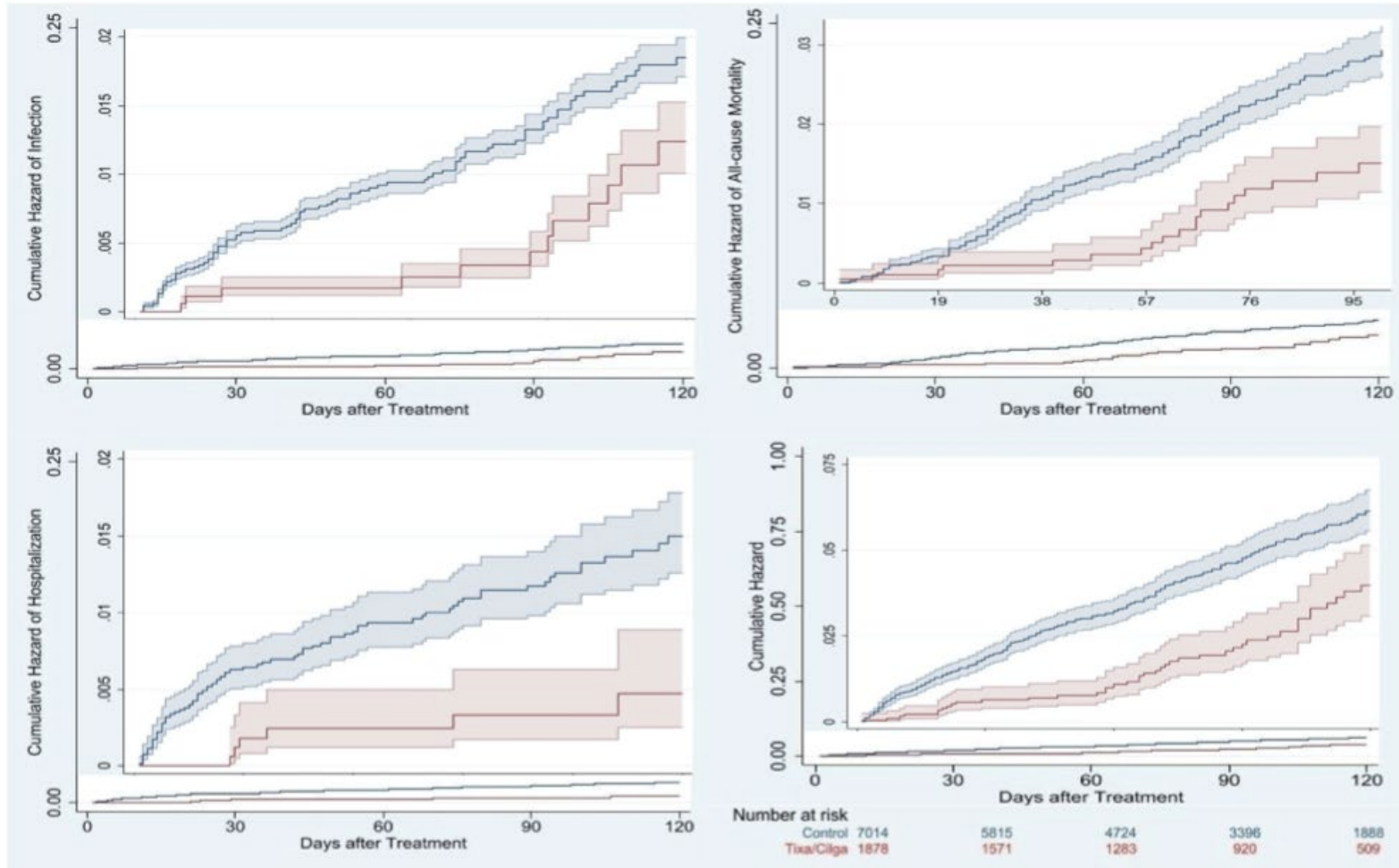
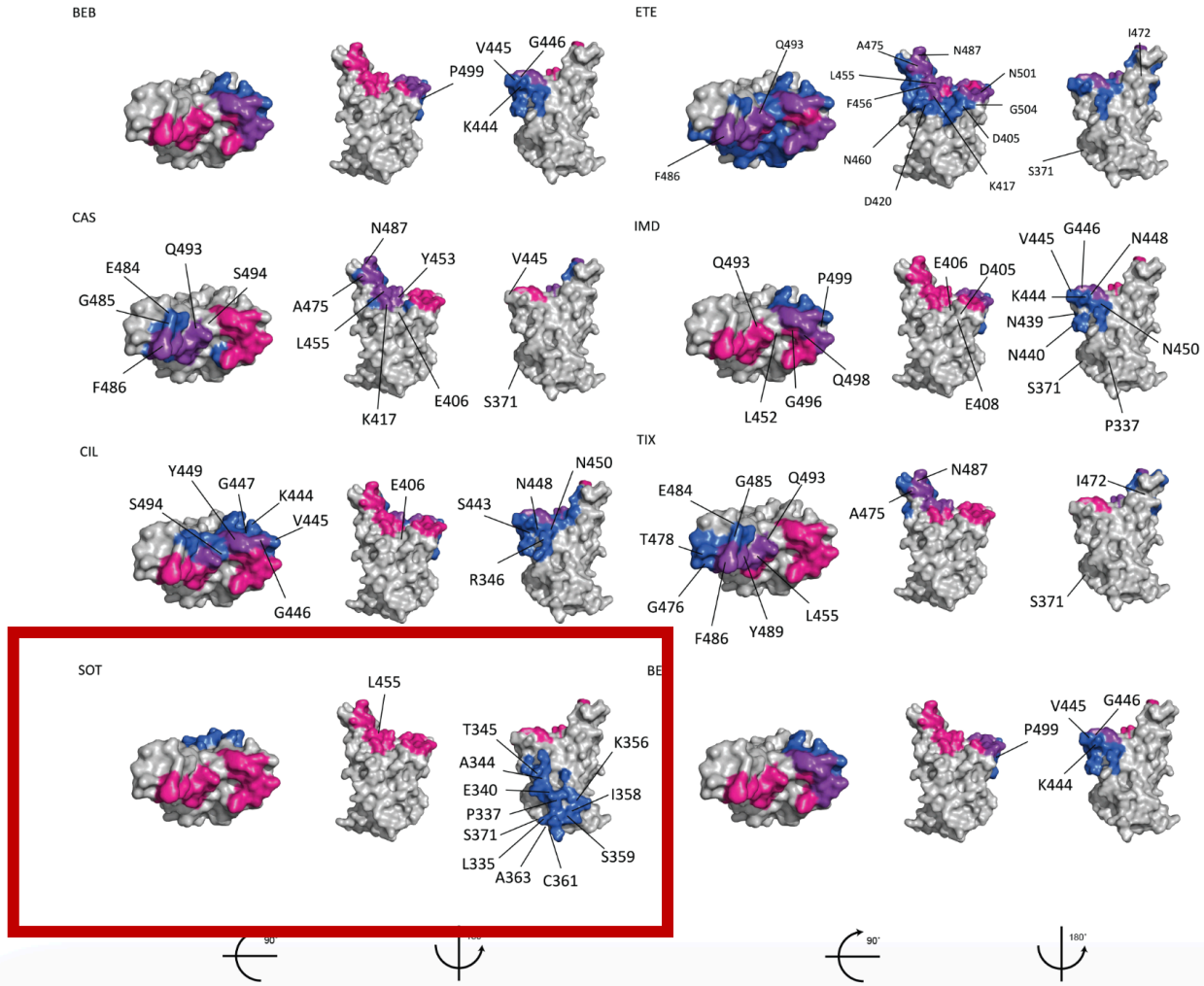


Figure 4: Monoclonal antibodies (mAbs) with EUAs or in advanced clinical development: receptor binding domain (RBD) epitopes and immune escape positions



For each mAb, the top of the RBD and two side views are depicted using coordinates from PDB 6M0J. ACE2 binding residues are shown in red; the mAb epitope defined as those residues within 4.5 angstroms of the RBD is shown in dark blue; and ACE2 binding residues within the mAb epitope are shown in purple. Those positions containing mutations that were either selected by the mAb in vitro ("SEL"), reduced binding in a deep mutational scanning assay ("DMS"), and/or reduced in vitro neutralizing susceptibility by a median of ≥4-fold in CoV-RDB (drug resistance; "DR") are also indicated. The mAb epitopes for BAM (bamlanivimab), ETE (etesevimab), CAS

Sotrovimab drives SARS-CoV-2 omicron variant evolution in immunocompromised patients

Sotrovimab is a monoclonal antibody used as monotherapy in outpatients at risk of developing severe COVID-19 disease. Indications include patients with respiratory, cardiac, metabolic, and immunosuppression comorbidities. Rockett and colleagues[1] have shown that, among 100 patients infected with the delta (B.1.617.2) variant and treated with sotrovimab monotherapy, four

E340 mutations (appendix p 5). Clinical data were available for eight patients, all of whom were immunocompromised and had been treated with sotrovimab at 0–10 days after symptoms onset (appendix pp 6–7). For six patients with a follow-up, mutations at positions 337 and 340 were absent before sotrovimab infusion and were detected at low relative frequency or high relative frequency (6–100%) at 5–18 days after sotrovimab infusion. Selection of resistant viral escape variants was associated with persistent SARS-CoV-2 excretion for up to 43 days, except for one patient who cleared their infection after convalescent plasma infusion at day 24 (appendix p 4). These results

Clinical Infectious Diseases® 2023;76(3):408–15

Clinical Infectious Diseases

MAJOR ARTICLE

Rapid Selection of Sotrovimab Escape Variants in Severe Acute Respiratory Syndrome Coronavirus 2 Omicron-Infected Immunocompromised Patients

Smaranda Gliga,[1,2,a] Nadine Lübke,[2,a] Alexander Killer,[1,a] Henning Gruell,[3] Andreas Walker,[2] Alexander T. Dilthey,[4] Alexander Thielen,[5] Carolin Lohr,[1] Charlotte Flaßhove,[1] Sarah Krieg,[1] Joanna Ventura Pereira,[1] Tobias Paul Seraphin,[1] Alex Zaufel,[1] Martin Däumer,[5] Hans-Martin Orth,[1] Torsten Feldt,[1] Johannes G. Bode,[1] Florian Klein,[3,6] Jörg Timm,[2] Tom Luedde,[1,a] and Björn-Erik Ole Jensen[1,a]

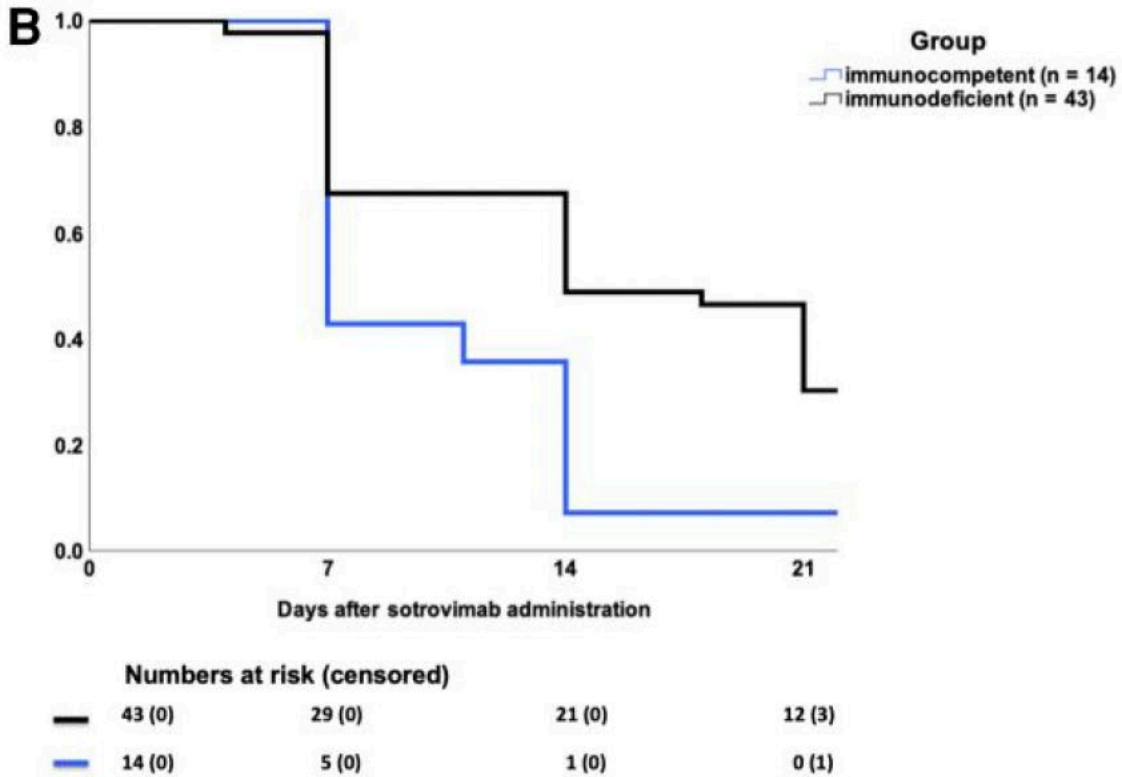


Table 1. Baseline Characteristics of Patients Grouped by Immunodeficiency

Variable	n
Total	57
Gender	
Male	36
Female	21
Groups	
Immunocompetent	14
Immunodeficient	43
Solid organ transplantation	
Kidney	18
Heart	2
Heart + kidney	1
Heart + lung	1
Kidney + pancreas	1
Stem cell transplantation	
Allogeneic	5
Autologous	2
Leukemia	
Acute lymphoblastic leukemia	2
AML[a]	2
AML + CMML	1
CMML	1
Lymphoma	
Diffuse large B-cell lymphoma	1
T-cell lymphoma[a]	1
AL amyloidosis/smoldering multiple myeloma[a]	1
Other malignancies	
Stage IV malignant melanoma and stage IV non-small cell lung cancer[b]	1
Common variable immune deficiency	1
Autoimmune diseases	
Cryoglobulinemic vasculitis	1
p-ANCA vasculitis	1
Rheumatoid arthritis	1
Systemic lupus erythematosus	1
Ulcerative colitis	1
Liver cirrhosis Child–Pugh A[c]	1
Liver fibrosis with portal hypertension[c]	1

Clinical Infectious Diseases® 2023;76(3):408–15

Clinical Infectious Diseases

MAJOR ARTICLE

Rapid Selection of Sotrovimab Escape Variants in Severe Acute Respiratory Syndrome Coronavirus 2 Omicron-Infected Immunocompromised Patients

Smaranda Gliga,[1,2,a] Nadine Lübke,[2,a] Alexander Killer,[1,a] Henning Gruell,[3] Andreas Walker,[2] Alexander T. Dilthey,[4] Alexander Thielen,[5] Carolin Lohr,[1] Charlotte Flaßhove,[1] Sarah Krieg,[1] Joanna Ventura Pereira,[1] Tobias Paul Seraphin,[1] Alex Zaufel,[1] Martin Däumer,[5] Hans-Martin Orth,[1] Torsten Feldt,[1] Johannes G. Bode,[1] Florian Klein,[3,6] Jörg Timm,[2] Tom Luedde,[1,a] and Björn-Erik Ole Jensen[1,a]

pository server, see Data availability section). This analysis revealed that mutations at spike protein residues associated with resistance to sotrovimab occurred in 14 of 57 patients (24.6%).

This group comprised 6 patients with SOT; 2 allogeneic SCT recipients; 2 patients with active hematologic malignancy who were receiving chemotherapy; 1 patient each with cryoglobulinemic vasculitis, systemic lupus erythematosus, and liver cirrhosis (Child–Pugh class A), each of whom received additional immunomodulatory therapies; and 1 patient with common variable immunodeficiency (Supplementary Table 2).

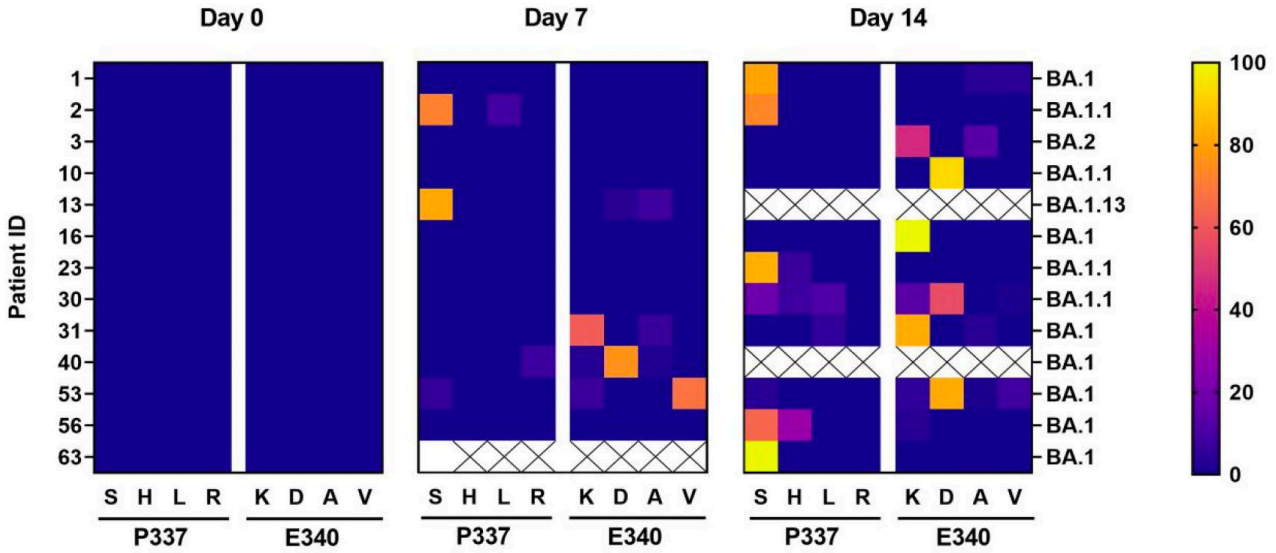


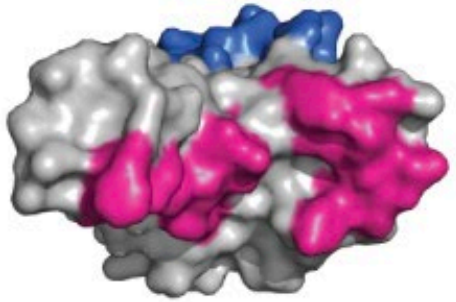
Figure 2. Prevalence and evolution of escape mutations in the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after sotrovimab treatment. Detected amino acid exchanges in the spike protein at positions 337 and 340 on day 0, day 7, and day 14 after sotrovimab administration. The frequency of reads in % is indicated by the color scale. The determined patient-related SARS-CoV-2 variant is shown. Only patients with detected mutations after sotrovimab treatment are indicated. Patients selecting a spike protein mutation after day 14 are not included in this figure (patient 51).

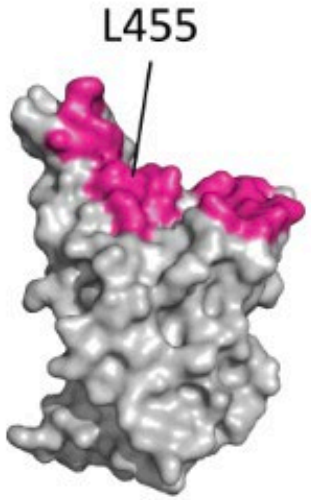
Esperienza di Udine: gennaio – marzo 2022

- Dati clinici e sequenza del virus in 43 pazienti trattati con sotrovimab, sempre in monoterapia
- 25 con infezione da Omicron Ba1 ….. e 18 con infezione da Omicron Ba2….
- Dei 43 pazienti , 23 con immunodepressione

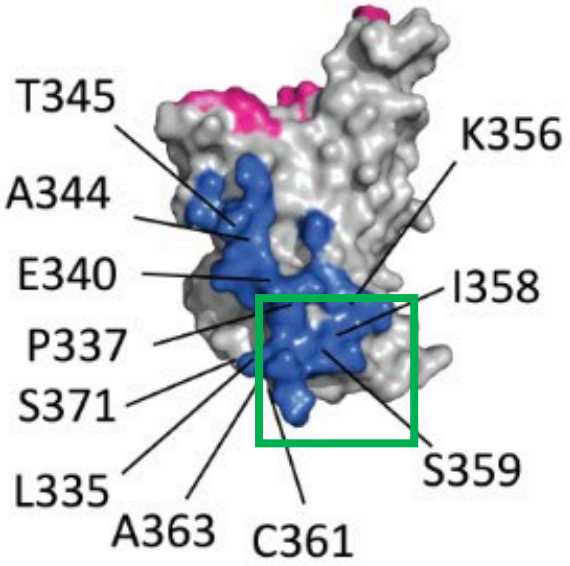
	Ba.1		Ba.2
M. ematologica	7	M. autoimmune	6
Trapianto	3	M. ematologica	1
M. oncologica	3	Trapianto	1
M. autoimmune	1		
Totale	14		8

SOT





BE



Mutazioni in un solo paziente

	S	T19I	SNP
	S	L24	deletion
	S	G142D	SNP
	S	G339D	SNP
	S	S371F	SNP
	S	S373P	SNP
	S	S375F	SNP
	S	T376A	SNP
	S	D405N	SNP
	S	R408S	SNP
	S	I410I	SNP_silent
	S	N440K	SNP
	S	S477N	SNP
	S	T478K	SNP
	S	E484A	SNP
	S	Q493R	SNP
	S	Q498R	SNP
	S	N501Y	SNP
	S	Y505H	SNP
	S	D614G	SNP
	S	H655Y	SNP
	S	N764K	SNP
	S	Q954H	SNP
	S	N969K	SNP
	S	D1146D	SNP_silent

- Posizioni di immuno-escape a sotrovimab:

335	345	361
337	356	363
340	358	371
344	359	455

Mutazioni virali in pazienti trattati con sotroviumab: 337, 340 (Udine)

- Due pazienti con mutazione maggiore, entrambi immunocompetenti: la prima P337H, la seconda P337S
- S371L in 14 pazienti: 10 immunodepressi e 4 immunocompetenti
- S371F in 8 pazienti: 4 immunodepressi e 4 immunocompetenti
- C361 delezione in 1 paziente ematologico
- Mutazioni in 15 immunodepressi e 10 immunocompetenti
- **Nessun aggravamento della patologia, nessun ricovero**

Conclusioni

- IGAM nella shock settico comunitario e nosocomiale (sono pronto come medico ad affrontarlo?) (le evidenze?)
- Fagi: laboratorio che li testa, sinergismo con gli antibiotici in vitro, legislazione
- Monoclonali: strumento utile che ci potrebbe ancora aiutare nei pazienti