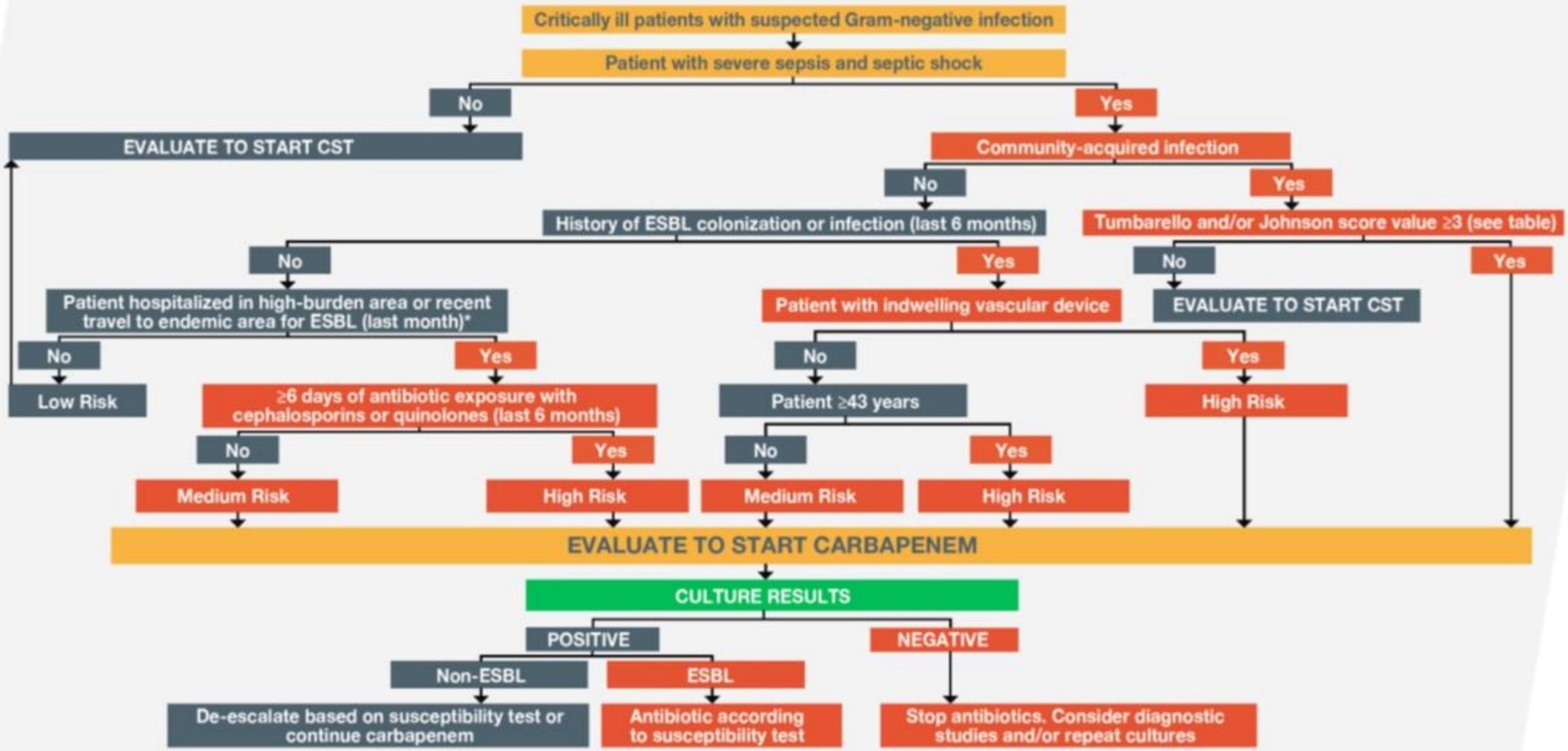
Reporting ECCMID 2019

L'essentiel de ce que nous avons vu en diapos

Sur 28 thématiques

Anne Lise Beaumont
Michaël Thy

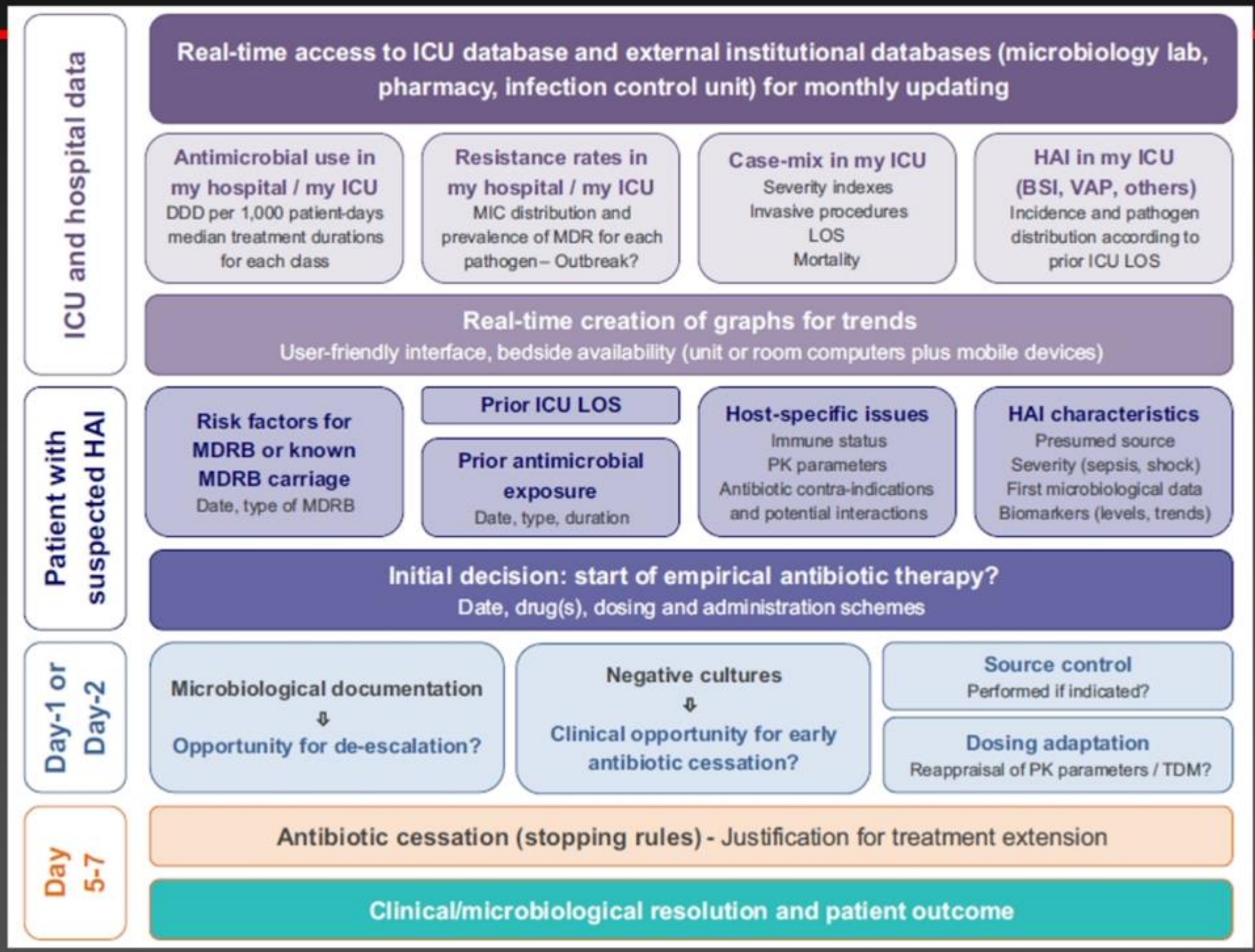
Should we take into account ESBLs in empirical antibiotic treatment?



	Tumbarello et al. Score	Johnson et al. Score
Recent use of β-lactams or fluoroquinolones (<3 months)	2	3
Recent hospitalization (<3 months)	3	2
Transfer from healthcare facility	3	4
Charlson index >3	2	--
Recent history of urinary catheter (<1 months)	2	5
Age ≥70 years	2	--
Immunosuppression (<3 months)	--	2

Bassetti M et al. *Intensive Care Medicine* 2016; **42**:2059–2062

Rationalized approach to antimicrobial treatment



Timsit JF et AL, Intensive Care Med. 2019 Feb;45(2):172-189

Impact PK/PD de la dysfonction d'organes

Applying pharmacokinetic/pharmacodynamic principles in critically-ill patients

Chairs: Maya Hites
Jordi Rello

11:07
Saturday, 13 April 2019
HALL E

ESCMID

ISAP

Spectrum of organ function

CRITICAL ILLNESS				
Hyperdynamic ↑ Cardiac output	**Altered fluid balance** Third spacing &/or altered protein binding	**No organ dysfunction**	**Renal &/or hepatic dysfunction**	**Organ support** RRT &/or ECMO
↑ CL	↑ Vd	Unchanged Vd and CL	↑ Vd & ↓ CL	↑ Vd and ?CL ↑
↓ Plasma concentrations	↓ Plasma concentrations	'Normal' plasma concentrations	↑ Plasma concentrations	↓ Or ↑ Plasma concentrations

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Need for altered dose depends on concentration and MIC of pathogen

Jason Roberts

How to optimise antibiotic administration in critically ill patients: from PK/PD to TDM

29th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Amsterdam, Netherlands
13 – 16 April 2019
ESCMID

Indices PK/PD optimaux par antibiotique

10:00 - 12:00
Applying pharmacokinetic/pharmacodynamic principles in critically-ill patients

Chairs: Maya Hites
Jordi Rello

11:14
Saturday, 13 April 2019
HALL E

The University Of Queensland

Antibacterial PK/PD

Table 1: Optimal PK/PD indices and the magnitudes associated with antibiotic clinical efficacy and toxicity

Antibiotic class	Optimal PK/PD index	PK/PD magnitude for pre-clinical efficacy	PK/PD magnitude for clinical efficacy	PK/PD threshold for toxicity
Aminoglycosides				
Amikacin	AUC_{0-24}/MIC		• C_{max}/MIC ≥8–10	C_{max} >5 mg/L
Gentamicin/tobramycin	AUC_{0-24}/MIC	• AUC_{0-24}/MIC: 80–100	• AUC_{0-24}/MIC ≥110 • C_{max}/MIC ≥8–10	C_{min} >1 mg/L
Beta-lactams				
Carbapenems	% $fT_{>MIC}$	• 40% $fT_{>MIC}$	• 50% $fT_{>MIC}$	• C_{min} >44.5 mg/L
Cephalosporins	% $fT_{>MIC}$	• 60–70% $fT_{>MIC}$	• 45–100% $fT_{>MIC}$	• C_{min} >20 mg/L
Penicillins	% $fT_{>MIC}$	• 50% $fT_{>MIC}$	• 50–100% $fT_{>MIC}$	• C_{min} >361.4 mg/L
Co-trimoxazole	Unclear	Unclear	Unclear	Unclear
Daptomycin	AUC_{0-24}/MIC	•	• AUC_{0-24}/MIC ≥668 mg/L	• C_{min} >24.3 mg/L
Fluoroquinolones	AUC_{0-24}/MIC	• AUC_{0-24}/MIC ≥100 • C_{max}/MIC ≥8	• AUC_{0-24}/MIC ≥125–250 • C_{max}/MIC ≥12.2	Unclear
Glycopeptides				
Teicoplanin		•	• C_{min} ≥10 mg/L	Unclear
Vancomycin	AUC_{0-24}/MIC	•	• AUC_{0-24}/MIC ≥400 • C_{min} >10–20 mg/L	• C_{min} >20 mg/L
Linezolid	AUC_{0-24}/MIC	• AUC_{0-24}/MIC ≥100	• AUC_{0-24}/MIC: 80–120 • ≥85% $T_{>MIC}$	• AUC_{0-24} >300 • C_{min} >7
Polymyxins				•
Colistin	AUC_{0-24}/MIC	•	Not available	• C_{min} >2.4 mg/L
Polymyxin B	AUC_{0-24}/MIC	• fAUC$_{0-24}$/MIC: 3.7–28.0	Not available	• AUC_{0-24} >100

Jason Roberts

How to optimise antibiotic administration in critically ill patients: from PK/PD to TDM

29th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Amsterdam, Netherlands
13 – 16 April 2019
ESCMID

Indices PK/PD optimaux par antiviral

Applying pharmacokinetic/pharmacodynamic principles in critically-ill patients

Jordi Rello

11:16
Saturday, 13 April 2019
HALL E

Antiviral PK/PD

Optimal PK/PD indices and the magnitudes associated with antiviral clinical efficacy and toxicity

Antivirals	Optimal PK/PD index	PK/PD magnitude for pre-clinical efficacy	PK/PD magnitude for clinical efficacy	PK/PD threshold for toxicity
Acyclovir/valacyclovir				**Neurotoxicity** • C: 10 mg/L [1] • C: 18 mg/L [2] • C_{max} :51.8 mg/L [3] **Mixed** • C_{max} >25 mg/L [4]
Ganciclovir/valganciclovir			**Solid-organ transplant recipients receiving ganciclovir/valganciclovir prophylaxis** • AUC: 40–50 mg·h/L [5]	
Ribavirin			**Chronic hepatitis C patients** • AUC_{0-12} >1755 mg/L [6] • AUC_{0-12} >3014 mg/L [6]	Anemia • C >2.8 mg/L [7] • C_{12h} >3.5 mg/L [8] Mixed • C ≥3.5 mg/L [9]

Jason Roberts

How to optimise antibiotic administration in critically ill patients: from PK/PD to TDM

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Impact clinique d'une PK/PD optimale d'antibiotique

10:00 - 12:00
Applying pharmacokinetic/pharmacodynamic principles in critically-ill patients

Chairs: Maya Hites
Jordi Rello

THE UNIVERSITY OF QUEENSLAND

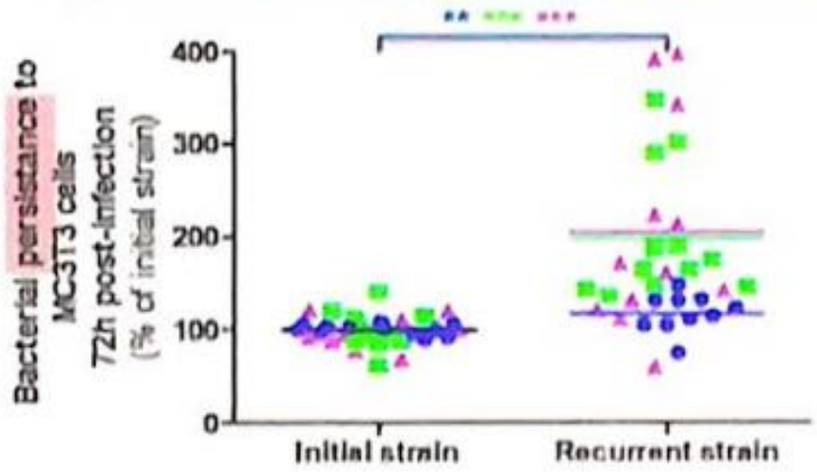
Clinical outcomes with achieving PK/PD targets

Drug class	Patient group	Target Exposure	Ref
Aminoglycosides	C_{max}/MIC ≥8	Increased clinical cure for Pseudomonas aeruginosa blood stream infections	JAC 2003;52(4): 668-674
	AUC_{0-24}/MIC ≥72	Increased clinical cure for lower respiratory tract infections	JAC 1999;43 Suppl A:55-63
Carbapenem	C_{min}/MIC > 5	Increased clinical & microbiological cure in lower respiratory tract infections	AAC 2007;51(5): 1725-1730
Cephalosporins	100% $T_{>MIC}$	Increased microbiological & clinical cure in serious infections	IJAA 2008;31(4): 345-351
Quinolones	AUC_{0-24}/MIC ≥ 125	Increased microbiological & clinical cure in critically ill patients	AAC 1993;37(5): 1073-1081
Vancomycin	AUC_{0-24}/MIC ≥ 451	Increased survival in critically ill patients associated with MRSA septic shock	IJAA 2013;41(3): 255-260
Linezolid	AUC_{0-24}/MIC ≥ 85	Increased clinical cure in severely ill patients with blood stream infections	Clin Pharmacokin 2003;42(15): 1411-1423
Tigecycline	f AUC_{0-24}/MIC ≥ 0.9	Increased clinical success in hospital acquired pneumonia	AAC 2012;56(1): 130-136

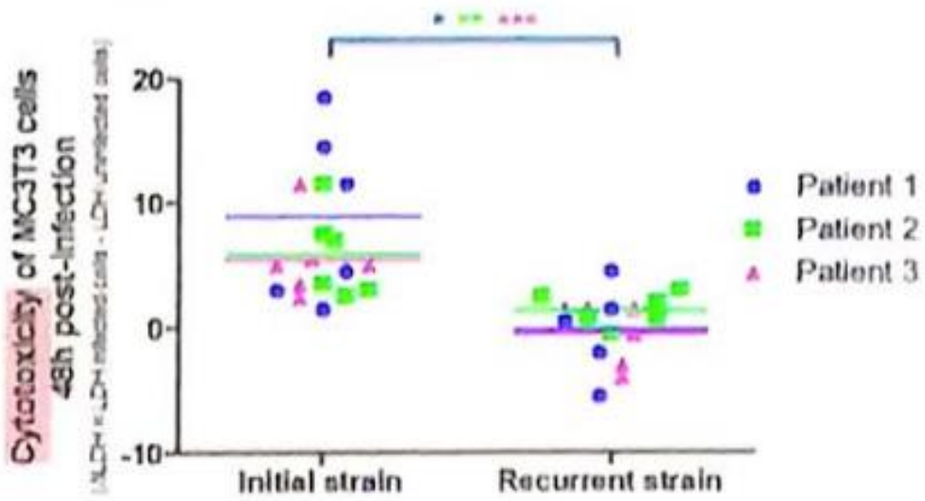
Infections ostéo-articulaires (IOA) : aigues vs chroniques

Osteoblast invasion: acute isolate *vs* persistent isolate

Chronic isolates = more persistent

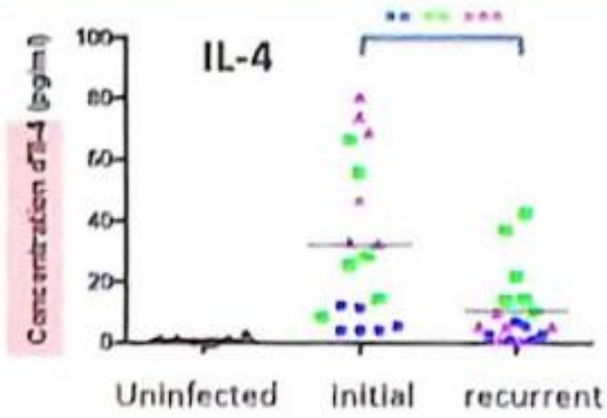


Chronic isolates = less cytotoxic



Chronic isolates =

↘ inflammatory response



Same profile for IL-4, IL-5, IL-6, IL-12, TNF-α, IFN-γ

Chronic isolates are adapted to intracellular life

IOA : Potentiels anti-« persistants »

Potential anti-Persisters

Basic science > Pre-clinical > Clinical > Market approval > Marketing

New small molecules
NH125 Nitroxoline TN-5 ADEP4S SAR2
2D-24 NCK-10 Piscidin p3 XF-73
SPI009 IDR1018 QAC-10 PLGP-0206

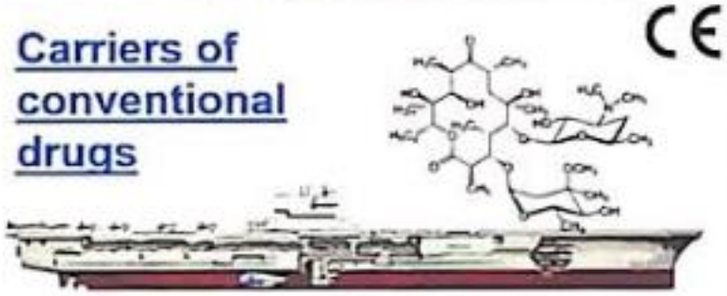
New antibiotics or drugs derived from antibiotics
TosufloxacinE HT61 C2DA ACH-702
Afabicin (FabI inhibitor)

WLBU2 **Matrix-targeting agents or mAB** DSTA4637S
Dispersin B Mucoid exopolysaccharide immune globulin

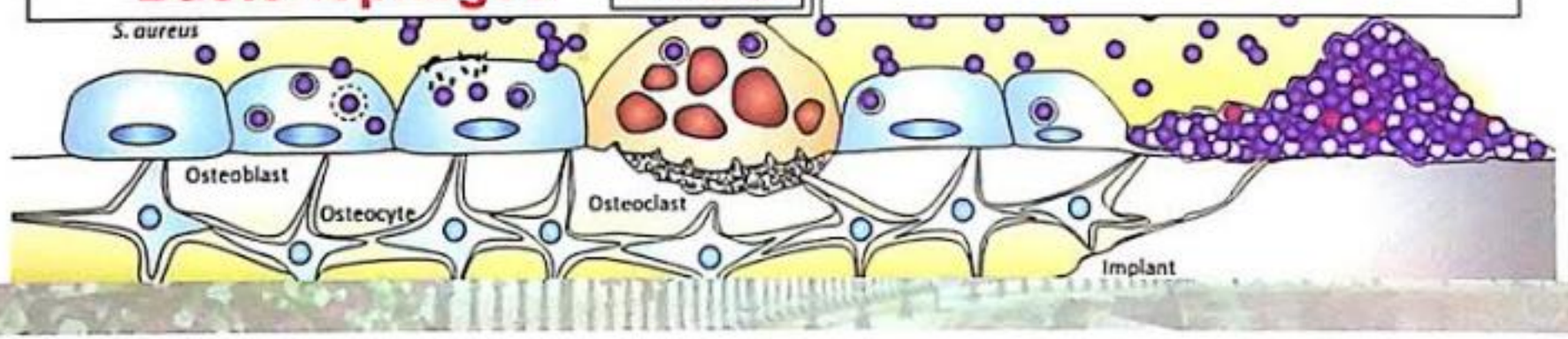
Bacteriophage Lysins LysK SAL200 CF-301

Bacteriophages GMP-like Bacteriophages

Carriers of conventional drugs



Local high doses and prolonged exposure
Nanotools
Liposomal carriers
Antibiotic-loaded hydrogel
Antibiotic-loaded ceramic tailored implants
Antibiotic-loaded bone substitutes (CaSO4)



IOA : Potentiels anti-« persistants »

Conclusion

- Crucial to **develop alternative options** in chronic BJI
- **Suppressive** antimicrobial therapy (oral; SC)
- **Carriers of conventional antibiotics in the market**
  - Huge local exposure and bone modeling (Genta CaSO4)
  - High potential for vectorisation of anti-persisters
- Several **promising antipersisters** (afabicin)
- Impressive potential efficacy of **bacteriophage lysins** (CF-301)
- A new horizon for **bacteriophage therapy (2.0)**
  - **GMP-like** Bacteriophages now available (*S. aureus; P. aeruginosa*)
  - Creation of a **local phage team (national phage team?)**
  - **Collaborations** with the industry and between researchers
  - Close relationship with the **national health authority**

Recommandations sur traitement suppressif oral

IDSA GUIDELINE 2013

Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]

Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin-susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or qid Clindamycin 300 mg PO qid Amoxicillin-clavulanate 500 mg PO tid
Staphylococci, oxacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or doxycycline100 mg PO bid	
β-hemolytic streptococci	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid
Enterococcus spp, penicillin susceptible	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid Minocycline or doxycycline 100 mg PO bid

Antibiotiques et combinaisons contre les OXA-48

Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Cristina Mussini

HALL B

Other β-lactamase inhibitor combinations versus OXA-48 Enterobacteria

Ceftazidime MIC, mg/L	Ceftolozane-tazobactam MIC, mg/L							
	0.25	0.5	1	2	4	8	16	>16
MIC ≤4 mg/L	28	57	42	23	4	1		
MIC >4 mg/L	1	5	10	9	18	27	24	104

Biapenem	No. isolates with MIC, mg/L						
	0.25	0.5	1	2	4	8	16
Alone	4	4	4	3	4	3	3
+ vaborbactam MIC 8 mg/L	5	4	4	3	6	1	2

David Livermore

Gram-negative resistance landscape: is OXA-48 an increasing concern?

ECCMID

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Carbapénémases OXA-48

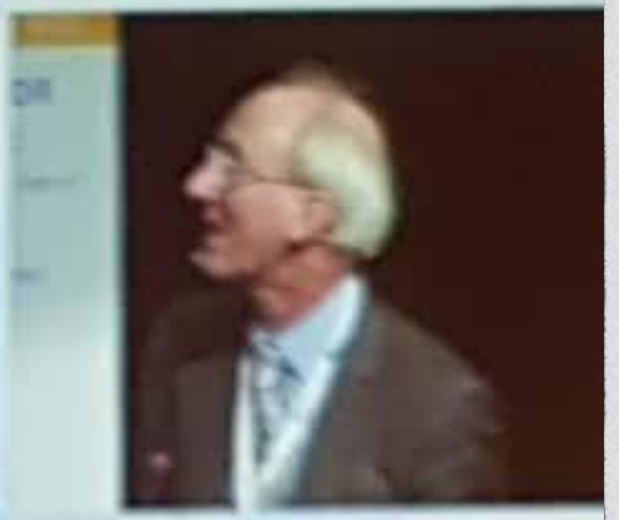
16:00 - 18:00
Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Chairs: Roman Kozlov
Cristina Mussini

HALL

Summary: OXA-48-like carbapenemases

- **OXA = Class D = big diverse β-lactamase family**
- **OXA-48-like = small cluster of carbapenemases (& non-carbapenemases) in one corner**
  - *Major* carbapenemase types are OXA-48 and -181
  - Escaped from *Shewanella*, an aquatic non-fermenter
  - Spread via *Tn1999* and IncL/M plasmids
- **Rare in USA, but predominant carbapenemase in Middle East and much of Europe: France, Spain, Germany, Turkey....**
  - Linked to poor outcomes in severe infection
  - Producers susceptible to CAZ-AVI and positive cases series



David Livermore

Gram-negative resistance landscape: is OXA-48 an increasing concern?

Poirel L, et al. Antimicrob Agents Chemother 2010;54:24-38. Poirel L, et al. Antimicrob Agents Chemother 2012;56:559-62. Tacao M, et al. Int J Antimicrob Agents 2012;40:262-6. Lipman M, et al. Morbid Mortal Weekly Report 2015;64:1313-6. Glasner C, et al. Euro Surveill 2012;17:20203. Poirel L, et al. J Antimicrob Chemother 2012;67:1597-1606. Souza A, et al. J Antimicrob Chemother 2013 doi: 10.1093/jac/dkt295. [Epub ahead of print]. Navarro-San Francisco C, et al. Clin Microbiol Infect 2013;19:E270-4. Balkan II, et al. Int J Infect Dis 2014;25:51-4.

ECCMID

Spectre de l'Avibactam

16:00 - 18:00
Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Chairs: Roman Kozlov
Cristina Mussini

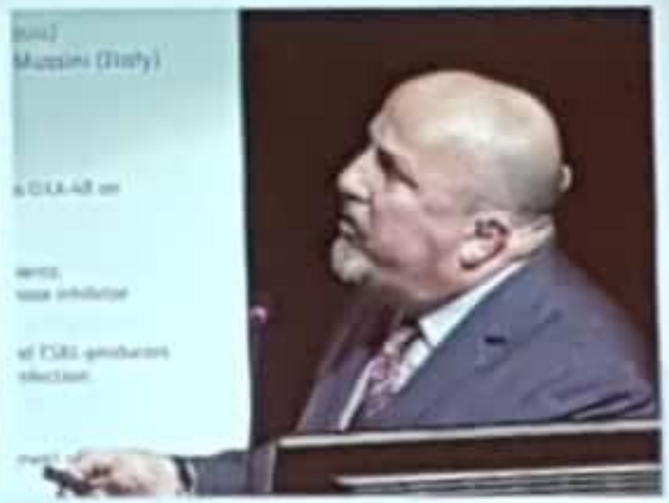
16:29
Saturday, 13 April 2019
HALL B

Avibactam: a broader spectrum of β-lactamase inhibition[1–6]

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM-1	✗	✗	✗
Class C	AmpC	✗	✗	✓
	ACC-1, CMY-1, FOX	✗	✗	✓
Class D	OXA-48	✗	✗	✓

CTX-M, cefotaxime-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; TEM, temoneira; SHV, sulfhydryl variable; VIM, Verona integron-encoded metallo-β-lactamase; OXA, oxacillinase.
Adapted from: 1. Zasloff GD, et al. Drugs 2013;73:159–77; 2. Bradford T, et al. Antimicrob Agents Chemother 2010;54:5132–6; 3. Lagacé-Wiens P, et al. Core Evid 2014;9:13–29; 4. Augmentin® (amoxicillin-clavulanic acid) Summary of Product Characteristics, 2018; 5. Tazocin® (piperacillin-tazobactam) Summary of Product Characteristics, 2017; 6. Zavicefta® (ceftazidime-avibactam) Summary of Product Characteristics, 2018.

PP-ZVA-GLB-0208 April 2019



David Nicolau

Why PK/PD matters in critically ill patients: pharmacology of a β-lactam/β-lactamase inhibitor

29th ECCMID — Amsterdam, Netherlands 13 – 16 April 2019 — ESCMI

Posologie recommandée pour le CAZ-AVI

16:00 - 18:00
Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Chairs: Roman Kozlov
Cristina Mussini

15:44
HALL B

Ceftazidime–avibactam: dosing recommendations

- Dosing regimen – model based and validated across many patient populations[1,2]
  - Based on >90% PTA (>50% $fT_{>MIC}$ (8 mg/L) for CAZ and >50% $fT_{>Cl}$ (1 mg/L) for AVI
  - Validated across the target indications, including critically ill patients with ARC
- Standard dosing is 2.5 g q8h – important to infuse this over 2 h[1]
- Adequate (sufficient) dosing in patients with renal insufficiency is important[3]

ARC, augmented renal clearance; AVI, avibactam; CAZ, ceftazidime; Cl, trough(-ish) concentration; CVVH, continuous venovenous haemofiltration; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration; PTA, probability of target attainment

1. Sime B, et al. Antimicrob Agents Chemother 2018; DOI: 10.1128/AAC.02147-18. Epub ahead of print. 2. Stein GE, et al. Surg Infect 2019;20:59-65.
3. Crass RL, et al. Clin Infect Dis 2019. doi: 10.1093/cid/ciz780. Epub ahead of print.

David Nicolau

Why PK/PD matters in critically ill patients: pharmacology of β-lactam/β-lactamase inhibitors

Quelle ATB probabiliste si *P. aeruginosa* suspecté ?

16:00 - 18:00
Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Chairs: Roman Kozlov
Cristina Mussini

Saturday, 13 A

HAL

Selection of empirical antibiotic treatment when *P. aeruginosa* is suspected

1. Criteria for sepsis or septic shock?
2. High inoculum source?
3. Severe immunosuppression (neutropenia)?
4. Risk for being carrier?
   a) ß-lactam anti-Ps 30–90 prior days
   b) >3–5 days of hospitalisation in a unit with MDR-Ps
   c) Colonisation/prior infection by MDR-Ps

yes (any)	none
CTZ–TZB > CAZ–AVI > MER > CAZ or PTZ–TZB + AMK or COL	MER or CAZ or PTZ–TZB + AMK or CIP

Source control (drainage, implant removal)

Alex Soriano

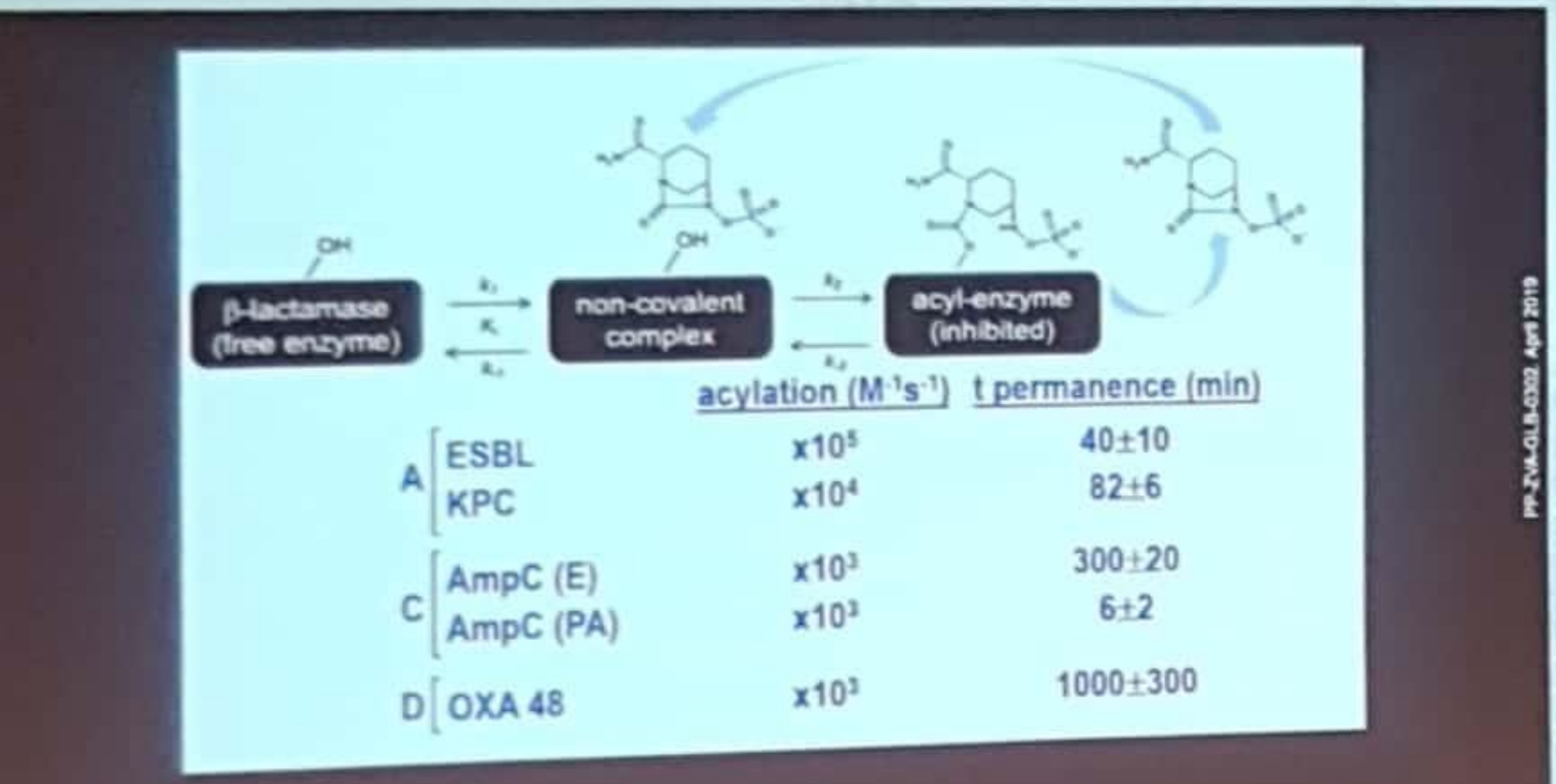
Targeting Pseudomonas aeruginosa and ESBL-producers in an era of resistant Gram-negative infection: what's the evidence?

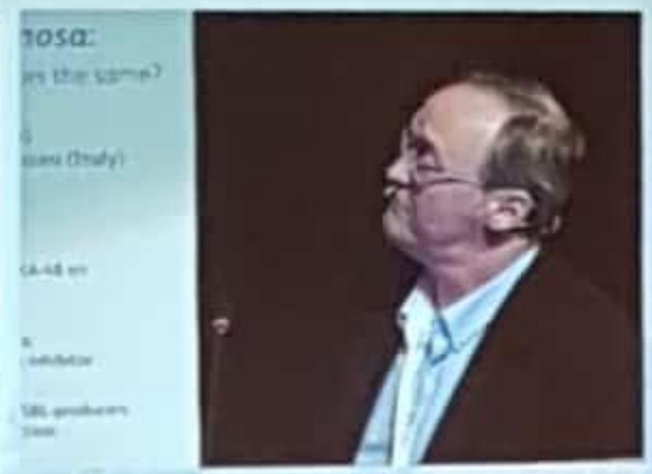
Activité des BLSE/Carbapénémases

16:00 - 18:00
Pfizer - Targeting ESBLs, CRE and MDR Pseudomonas aeruginosa: are all β-lactam/β-lactamase inhibitors the same?

Chairs: Roman Kozlov
Cristina Mussini

17:02
Saturday, 13 April 2019
HALL B





Alex Soriano

Targeting Pseudomonas aeruginosa and ESBL-producers in an era of resistant Gram-negative infection: what's the evidence?

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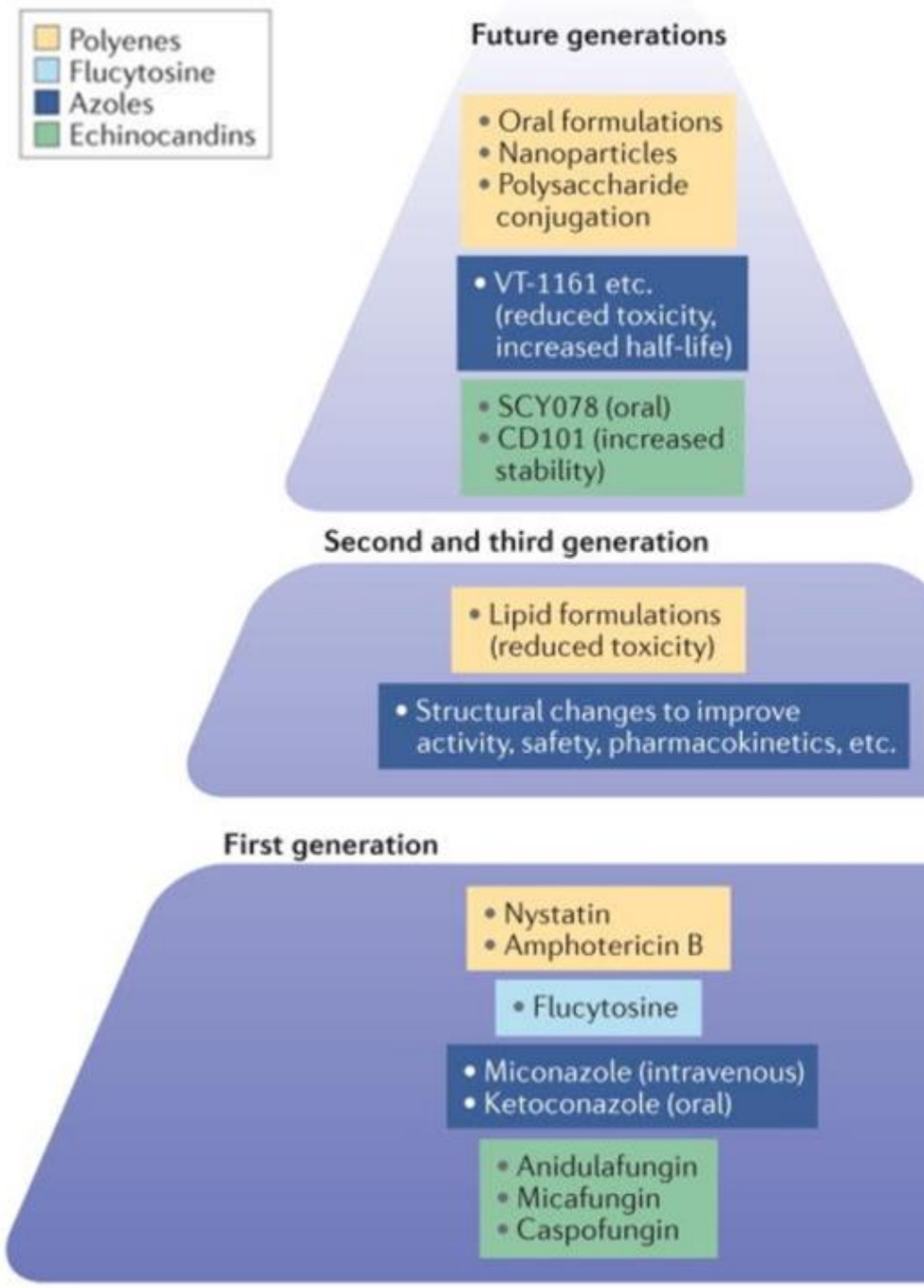
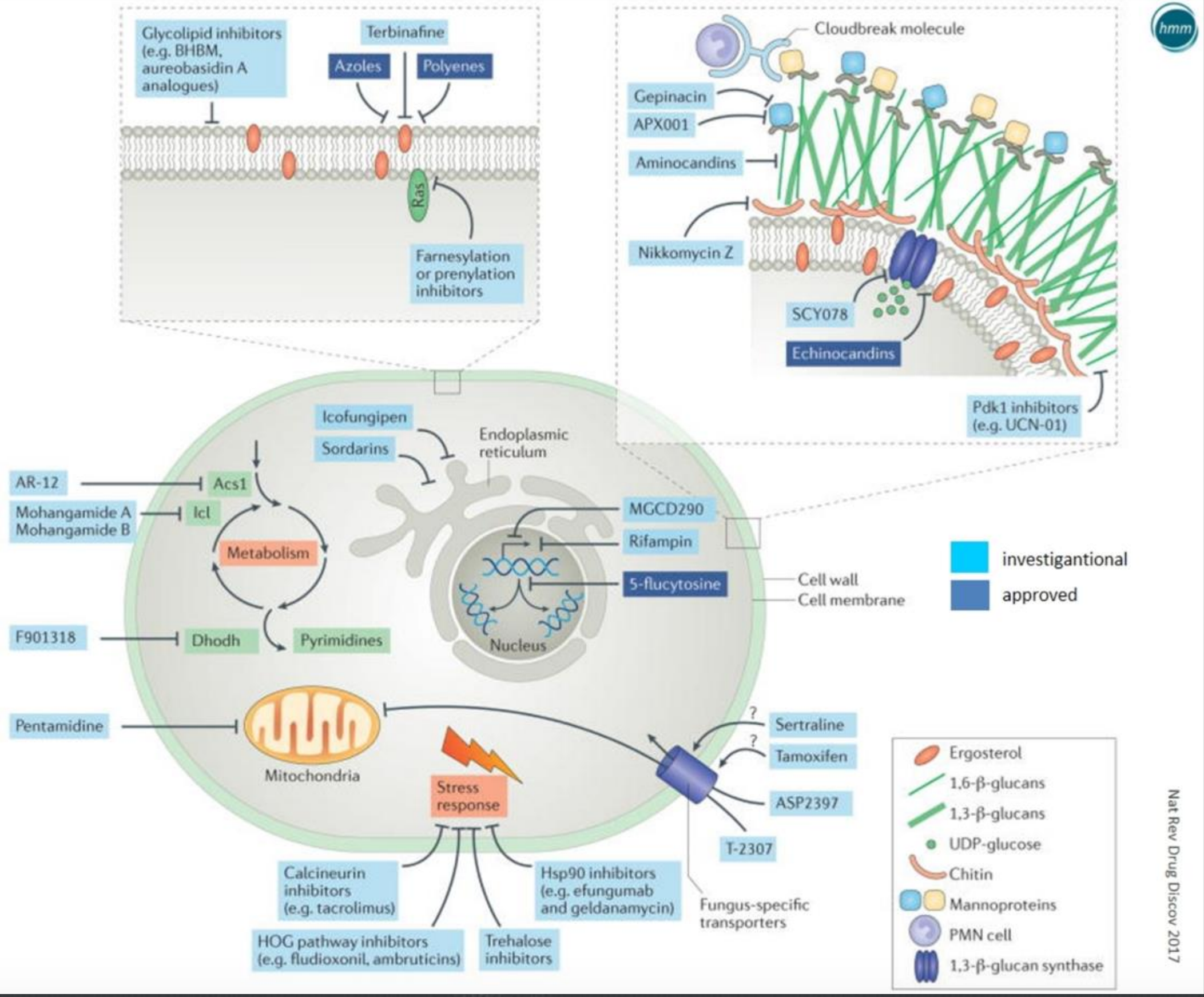


- Improving existing antifungals
- New agents in development
- Novel pathways and targets
- Repurposing old drugs
- Host immune-cell targeted approaches
- Antifungal biological agents

Perfect JR, Nat Rev Drug Discov 2017

Antifungal targets



Nat Rev Drug Discov 2017

New agents – near to or in clinic

SYSTEMIC

- Acrylamide (Toyama; T-2307)
- Inhibitor of fungal glycosylphosphatidylinositol biosynthesis (Amplyx; APX001A)
- Novel and as-yet-unknown targets (Vical; ASP 2397) Discontinue!
- Orotomide (F2G; F901318, olorofim)
- Novel CYP inhibitor (Viamet; VT1129, quilseconazole)
- Novel CYP inhibitor (Mycovia; VT1161)
- New echinocandin (Cidara; CD101, Rezafungin)
- Oral glucan synthase inhibitor (Scynexis, SCY-078, Ibrexafungerp)
- New formulations of amphotericin B (MAT2203, Matinas; cochleate, AMB self-emulsifying drug delivery system iCo)

INHALED

- Itraconazole (Pulmatrix, PUR1900), start phase 2
- Novel triazole antifungal (Pulmocide; PC945, anti-Aspergillus)

Azolés : Algorithme pour les suspicions d'infections fongiques invasives

Practical Algorithm for Azole bIFI

Type d'antifongique antérieur ?

Posa/Vori/Isa/Itra-conazole

Relais empirique d'antifongique + Fibro bronchique

Formulation d'Amphotéricine B

Galactomannane ?

(+) (-)

Taux résiduel ?

Bas

A. fumigatus

A. flavus
A. niger
A. terreus

Adéquat

A. fumigatus

Cryptic "Fumigati" (A. lentulus)
A. viridinutans

Fusarium spp.

Bas

Mucorales

A. fumigatus

Other Aspergilli

Adéquat

Mucorales

Scedosporium spp.

Scopulariopsis spp.
Paecilomyces spp.

Cause ?

Traitement définitif ?

Vori/Isa +/- Echino

Formulation d'Amphotéricine B

Adapté de diapo de Frederic Lamoth

Non-Azolés : Algorithme pour les suspicions d'infections fongiques (IFI) invasives

Practical Algorithm for Non-azole bIFI

Type d'antifongique antérieur ?

Echinocandines

Ampho B

Relais empirique d'antifongique + Fibro bronchique

Azolés à large spectre

Galactomannane ?

(+) (-) (+) (-)

Cause ?

A. fumigatus

Cryptic Fumigati (A. lentulus)
A. udagawae
Other Aspergilli

Fusarium spp.

Mucorales

A. fumigatus

Other Aspergilli
Rare moulds

Aspergillus spp

(A. terreus ?)

Fusarium spp.

Scedosporium spp.

P. Boydii
(Microsporum ?)

Traitement définitif ?

Vori/Isavu-conazole

AmphoB

Vori/Isavu-conazole

Adapté de diapo de Frederic Lamoth

Facteurs de risque de résistance du CMV

Risk Factors for CMV Resistance

Host Factors

Prolonged antiviral CMV drug exposure (>3 months) or Previous antiviral CMV drug exposure

Recurrent CMV infection

Inadequate antiviral CMV drug absorption and bioavailability

Variation in antiviral CMV drug clearance

Subtherapeutic antiviral CMV drug level

Poor compliance

T-cell depletion

Haploidentical and cord blood HCT

Delayed immune reconstitution

CMV-seropositive recipient

Treatment with antithymocyte antibodies

Active graft-versus-host disease

Chemaly RF et al. CID 2018

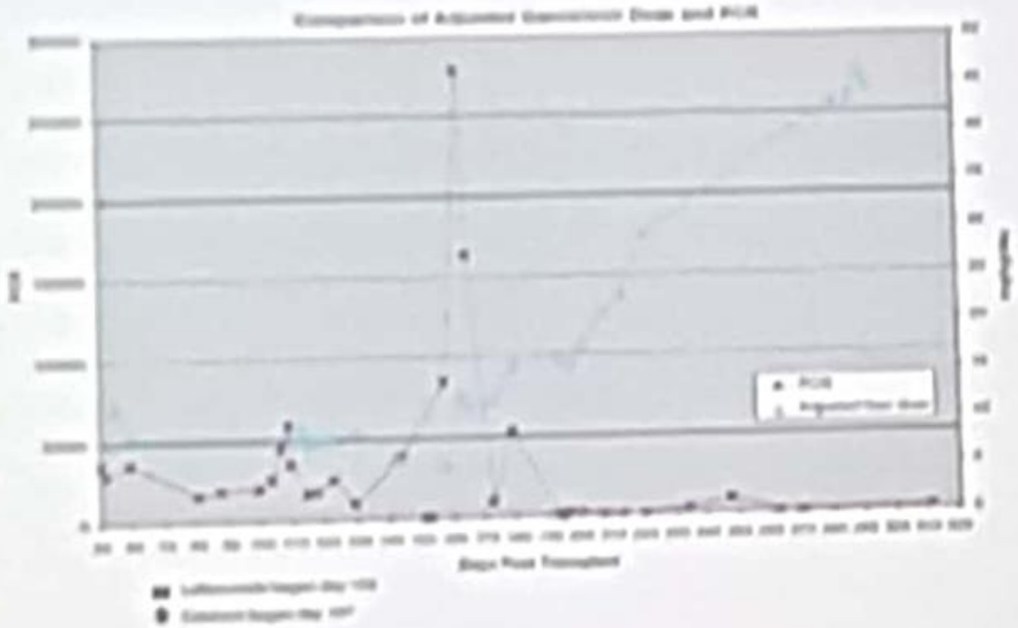
Hautes doses de Ganciclovir chez les CMV résistants ?

High-Dose Ganciclovir

- Emerging experience
  - Adjusted max dose >40 mg/kg/day
- 7.5–10 mg/kg twice daily
  - Adjusted for renal function
  - Testing drug levels
    - Issue: availability
- Valganciclovir
  - Fixed dose
  - Issue drug levels – weight
  - No clinical data on higher doses
- Toxicity
  - G-CSF: preemptive vs. salvage
  - HIV experience

Use of high-dose ganciclovir for a resistant cytomegalovirus infection due to UL97 mutation

P. West[1], M. Schmiedeskamp[2], R. Nowlin[1], J. Oberholzer[3], E. Benedetti[3], B. Kaplan[1]



West P, et al. Transplant Infect Dis. 2008;10:129-32.

Nouveaux-antiviraux versus CMV GCV-résistants

Take Home Messages

- CMV serostatus and reactivation remains an important variable affecting transplant outcomes, including GvHD incidence, graft failure/rejection, NRM and survival

- Novel anti-viral agents with different MOA like letermovir have the potential to render prophylactic therapy more feasible:
  - Though it remains to be determined whether prophylaxis will impact transplant outcomes associated with CMV sero-positivity

- Better treatment options are needed for preemptive therapy and R/R CMV

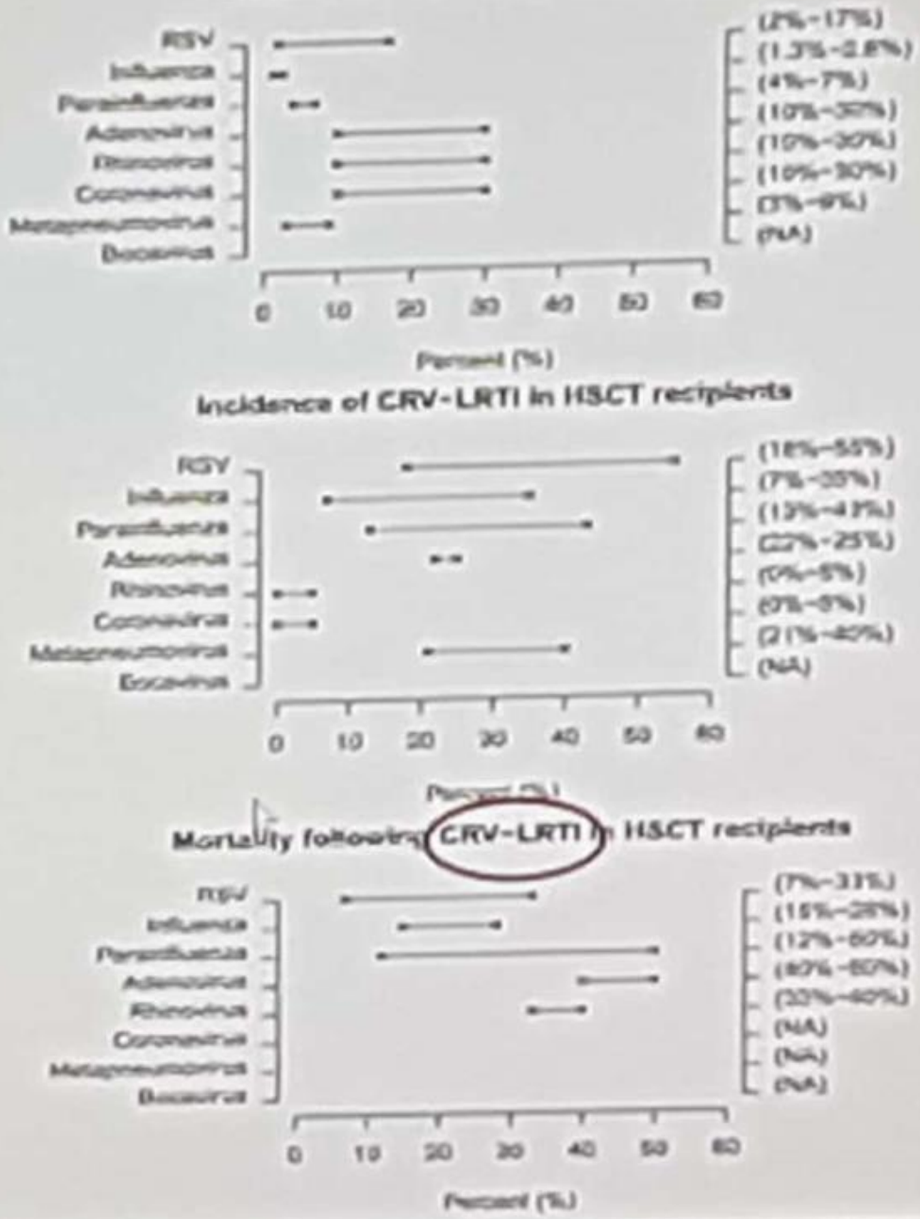
- Maribavir has shown efficacy and safety for preemptive therapy and R/R CMV and phase 3 studies are ongoing for these indications

Impact des pneumonies virales chez les allogreffés de moelle

Burden of Respiratory Viruses in HCT recipients

- High frequency of pneumonia and mortality
- Prolonged viral shedding, despite treatment
- Co-infections

- High potential for nosocomial acquisition
- Outbreaks can occur in absence of community epidemic



Shah DP, Ghosseiji SS, Arora E, Malkoumich V, Chemaly RF. AIDR, 2(4) 201-18, 2013

Pneumonies virales : Traitements possibles

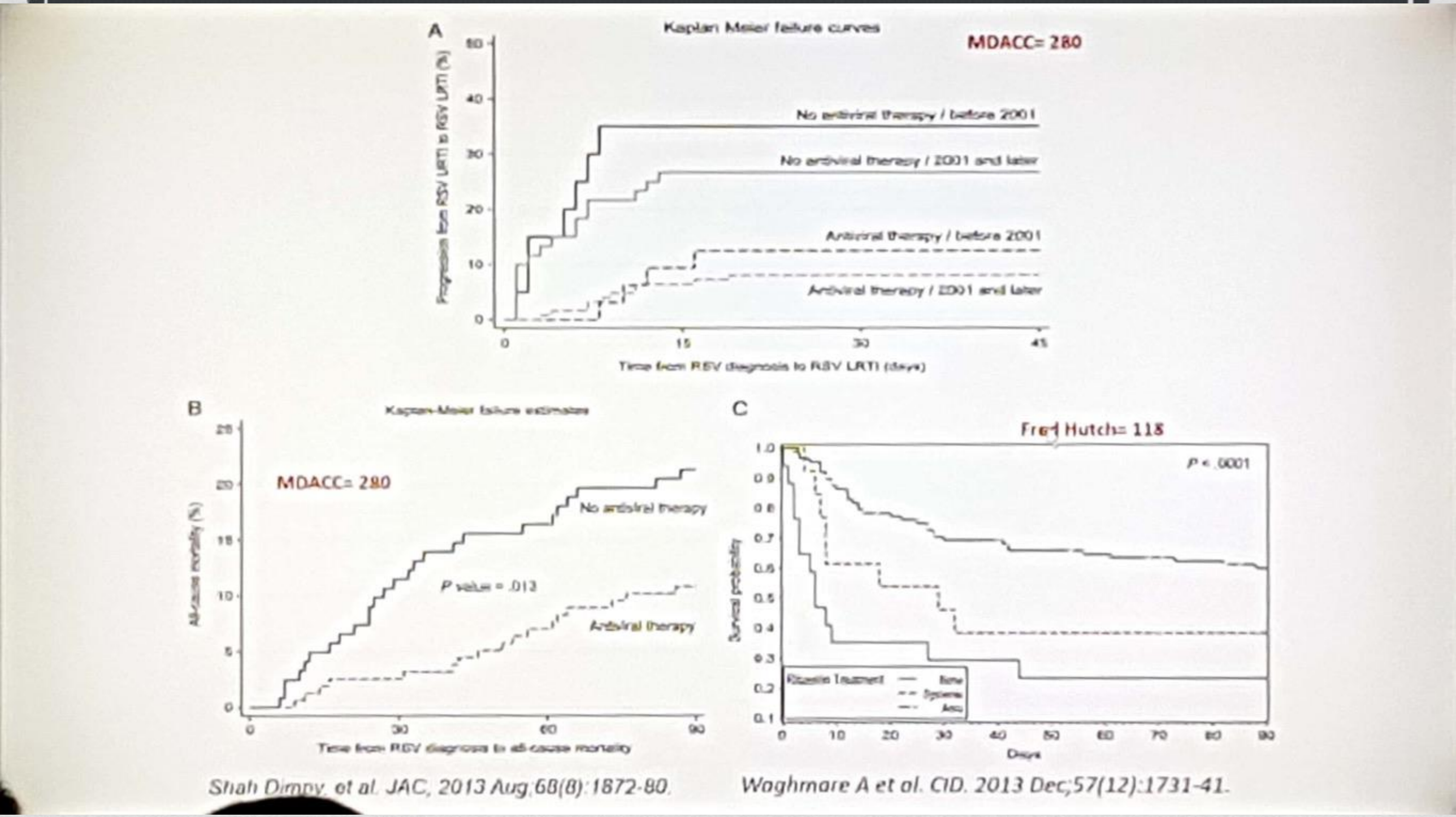
Available Therapy

- Ribavirin
  - Nucleoside analog
  - Aerosolized, Oral, IV formulations

- PVZ
  - RSV-specific monoclonal antibody
  - Target: RSV F glycoprotein

- IVIG / RSV-IVIG

Impact des traitements antiviraux sur les pneumonies virales



Shah Dimpy, et al. JAC, 2013 Aug;68(8):1872-80.

Waghmare A et al. CID. 2013 Dec;57(12):1731-41.

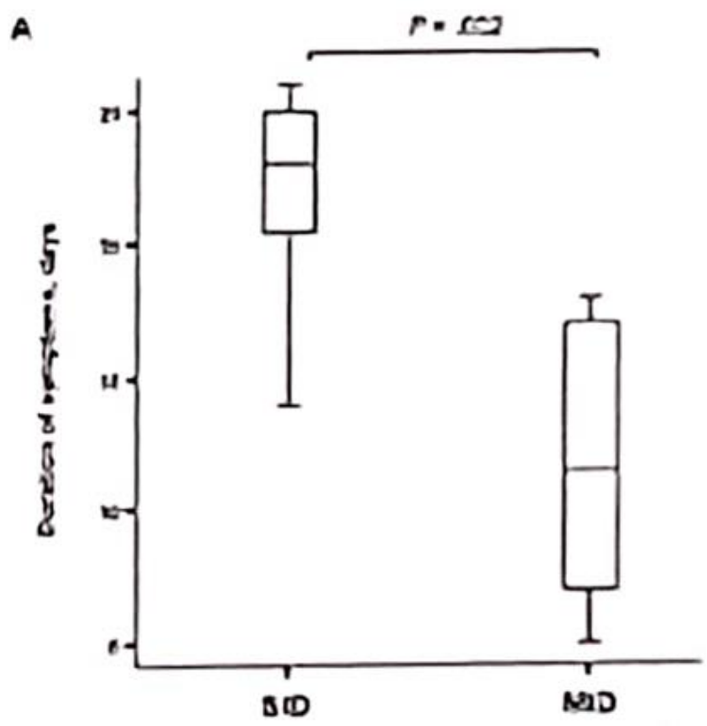
VRS chez les patients atteints d'hémopathies

Respiratory Syncytial Virus Infection in Patients with Hematological Diseases: Single-Center Study and Review of the Literature

Nina Khanna,[1] Andreas F. Widmer,[2] Michael Decker,[2] Ingrid Sudan,[2] Jörg Halter,[2] Diethelm Heim,[2] Maja Weisser,[2] Alois Gratwohl,[2] Ursula Fischiger,[2] and Hans H. Hirsch[1]

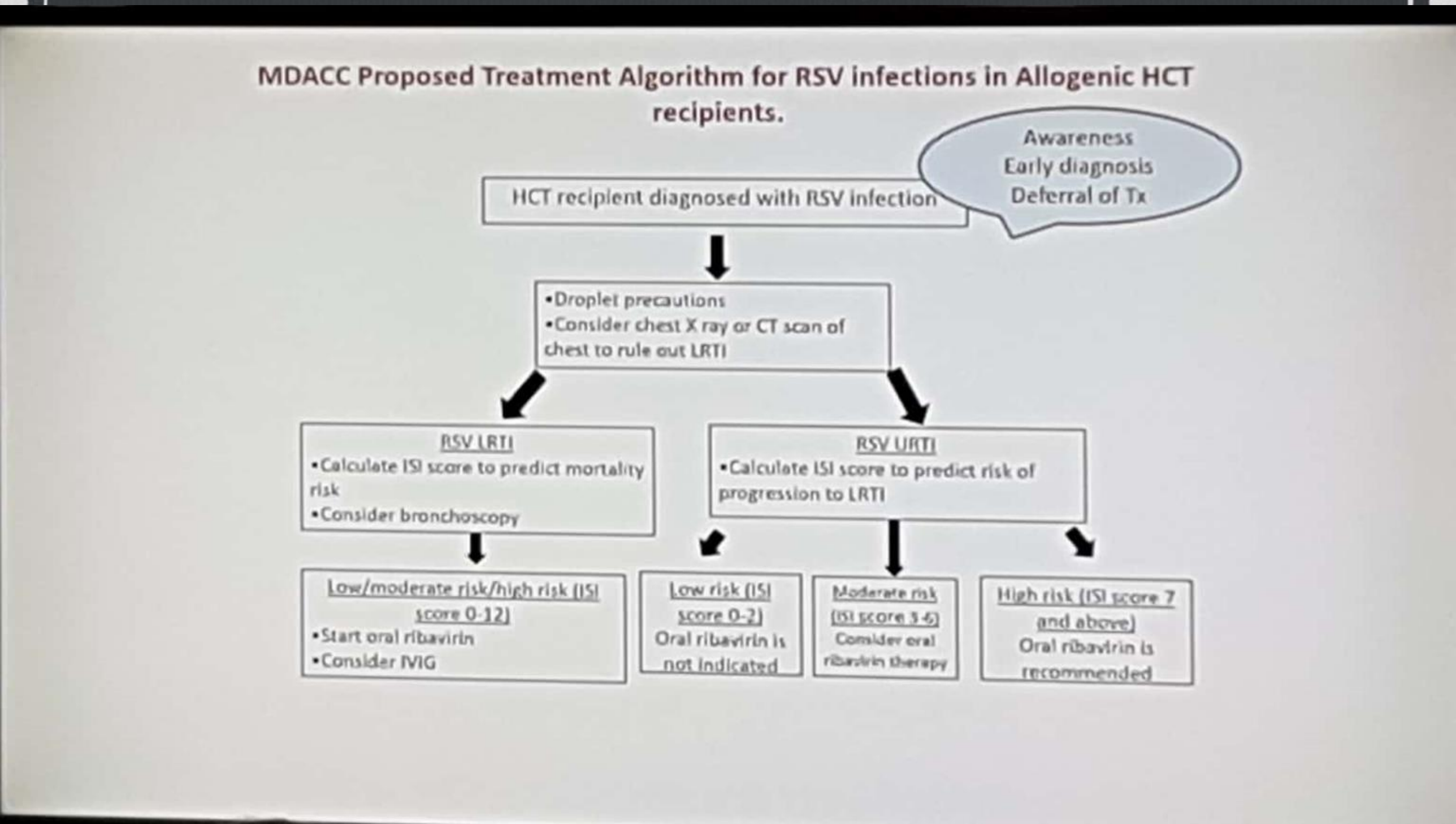
[1]Infectious Diseases and Hospital Epidemiology and [2]Hematology, University Hospital Basel, and [3]Transplantation Virology and Diagnostic Center, Institute for Medical Microbiology, Department of Medicine, University of Basel, Basel, Switzerland

- Severe immunodeficiency (= 1 criteria)
  - Neutropenia < 0.5 x 10^9/l
  - Lymphopenia ≤ 0.1 x 10^9/l
  - < 6 mts after HCT
  - GvHD grade ≥ 2
  - Hypogammaglobulinemia < 4.5 g/l
  - T-cell or B-cell depletion ≤ 3 months ago
- RSV mortality associated with
  - Lower RTI
  - Pre-engraftment
  - 2 criteria for SID (=vSID)



Khanna N et al. Clin Infect Dis. 2008 Feb 1;46(3):402-12

Algorithme de prise en charge VRS chez les patients atteints d'hémopathies



Posologie recommandée de Ribavirine

Dosage

Recommendation at USB (oral RBV implemented in 2005):

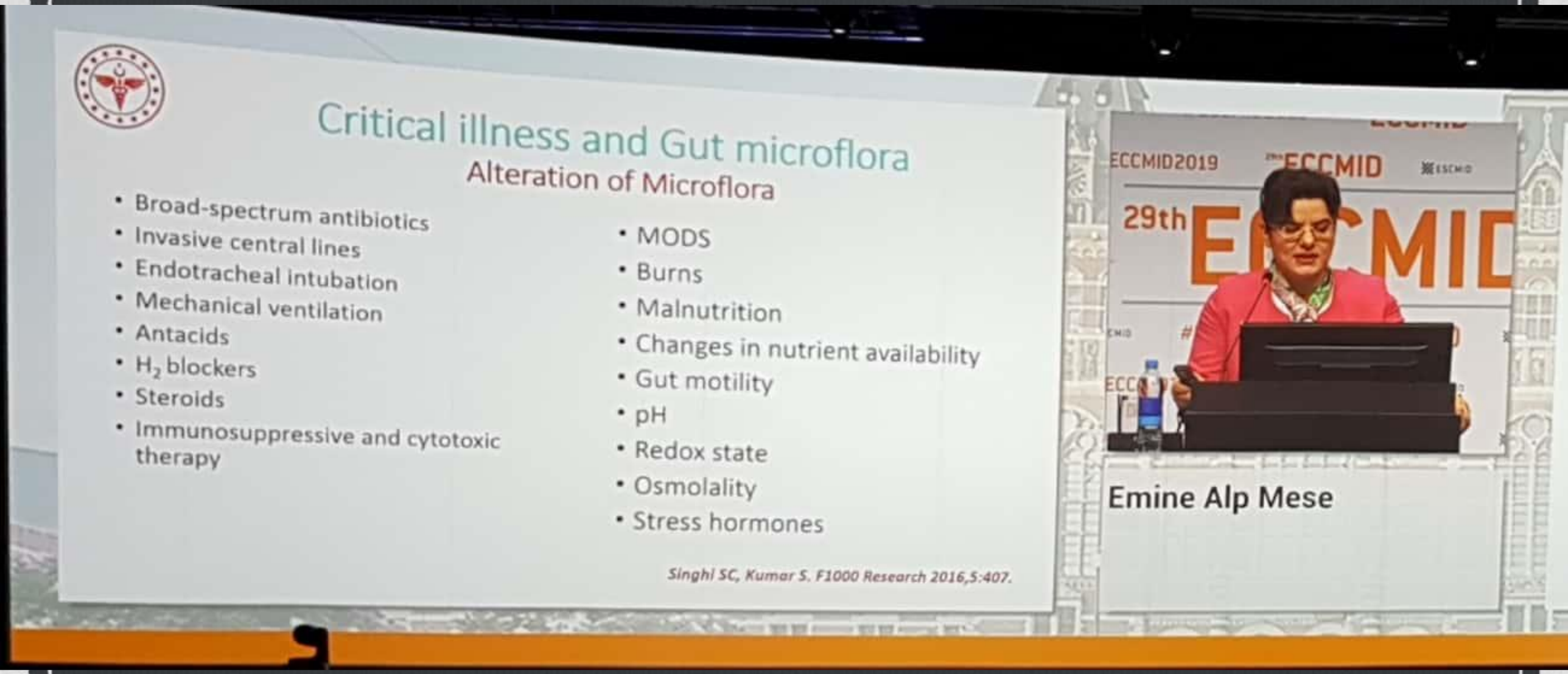
	Ladedosis	Ribavirin-Dosis		
		1. Tag	2. Tag	4. Tag
eGFR >50	600mg	200mg 8-stdl.	400mg 8-stdl.	600mg* 8-stdl.
eGFR 30-50	600mg	200mg 8-stdl.	Keine weitere Dosissteigerung	
eGFR <30	Keine Ribavirin-Gabe möglich			

* falls < 60kg Körpergewicht: Maximale Dosis 10mg/kg 8-stündlich

Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H and Ljungman P, Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of human Respiratory Syncitial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus and Coronavirus. Clin Infect Dis 2014

Khanna N et al. Clin Infect Dis. 2006 Feb 1;40(3):402-12.

Atteinte du microbiome en réanimation



Intérêts des probiotiques ?

Probiotics

Mechanism of beneficial effects

- Activate mucosal immunity
- Stimulate the immune response
  - Cytokine production
  - IgA secretion
  - Phagocytosis
  - Production of substances (such as organic acids, hydrogen peroxide and bacteriocins) that are inhibitory to pathogens
- Compete for nutrients with pathogenic bacteria and inhibit attachment and action of microbial toxin
- Trophic effect on intestinal mucosa (by stimulating the proliferation of normal epithelium that maintains mucosal barrier defenses)
- Modulate innate and adaptive immune defense mechanisms via the normalization of altered gut flora and prevent bacterial translocation

Singhi SC, Kumar S. F1000 Research 2016,5:407.

Intérêts des probiotiques : EBM

Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials*

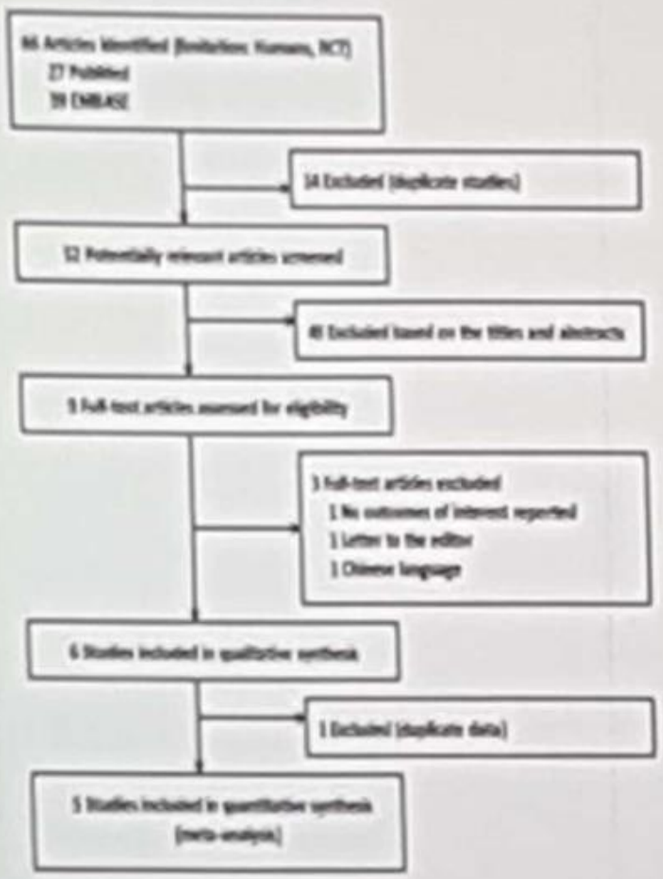
- Meta analysis of randomized controlled trials comparing probiotics and control in patients (689 patients) undergoing mechanical ventilation and reporting on incidence of VAP

- 5 randomized controlled trials were included

Siempos II, et al. Crit Care Med 2010;38:954-62.

Intérêts des probiotiques : EBM (2)

The Effects of Probiotics in Early Enteral Nutrition on the Outcomes of Trauma: A Meta-Analysis of Randomized Controlled Trials



- 5 studies involving **281 patients** met the inclusion criteria

- The use of probiotics was associated a reduction in;
  - the incidence of nosocomial infections
  (5 trials; RR, 0.65;95%, CI, 0.45-0.94,*P*=.02)
  - the incidence of VAP
  (3 trials; RR, 0.59;95%CI, 0.42-0.81, *P*=.001)
  - Length of ICU stay
  (2 trials;SMD, -0.71;95%CI, -1.09 to-0.34, *P*<.001)

- No reduction in mortality
  (4 trials; RR,0.63;95%CI, 0.32-1.26, *P*=.19)

Intérêts des probiotiques : EBM (3)

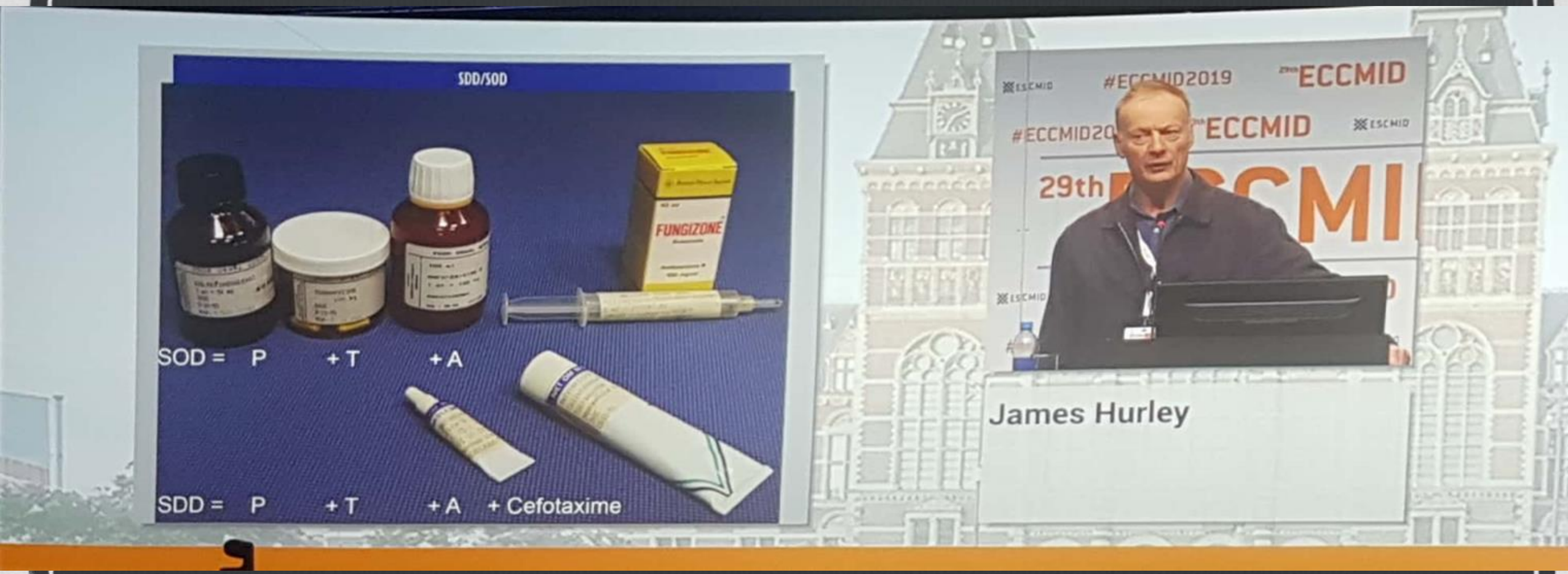
Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial

Conclusion

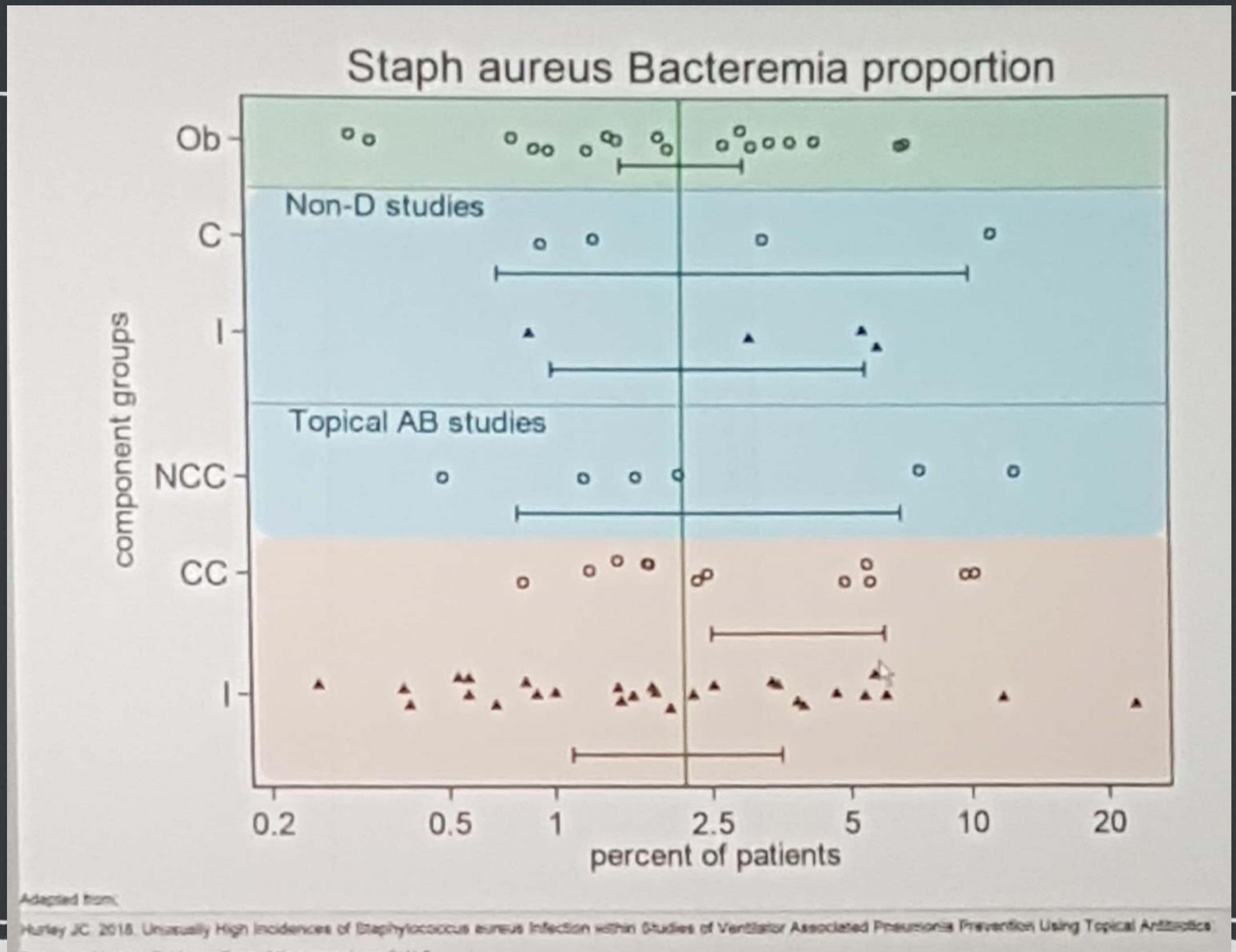
- The administration of probiotics did not result in any improvement in the incidence of clinically suspected VAP, antimicrobial consumption, duration of MV, mortality and length of stay
- Treatment with a combination of live probiotics is effective and safe in preventing VAP in ICU patients with non-prolonged MV
- The underlying mechanism involves prevention of the acquisition of PPMO colonization in the stomach

Zeng J, et al. Intensive Care Med 2016;42:1018-28.

Décontamination digestive sélective (DDS)



DDS et Infection à *Staph. aureus*



Adapted from:

Hurley JC. 2018. Unusually High Incidences of Staphylococcus aureus Infection within Studies of Ventilator Associated Pneumonia Prevention Using Topical Antibiotics: Benchmarking the Evidence Base. Microorganisms 6(1):2

Résistance liée à l'exposition au Cefepime

Cefepime exposure

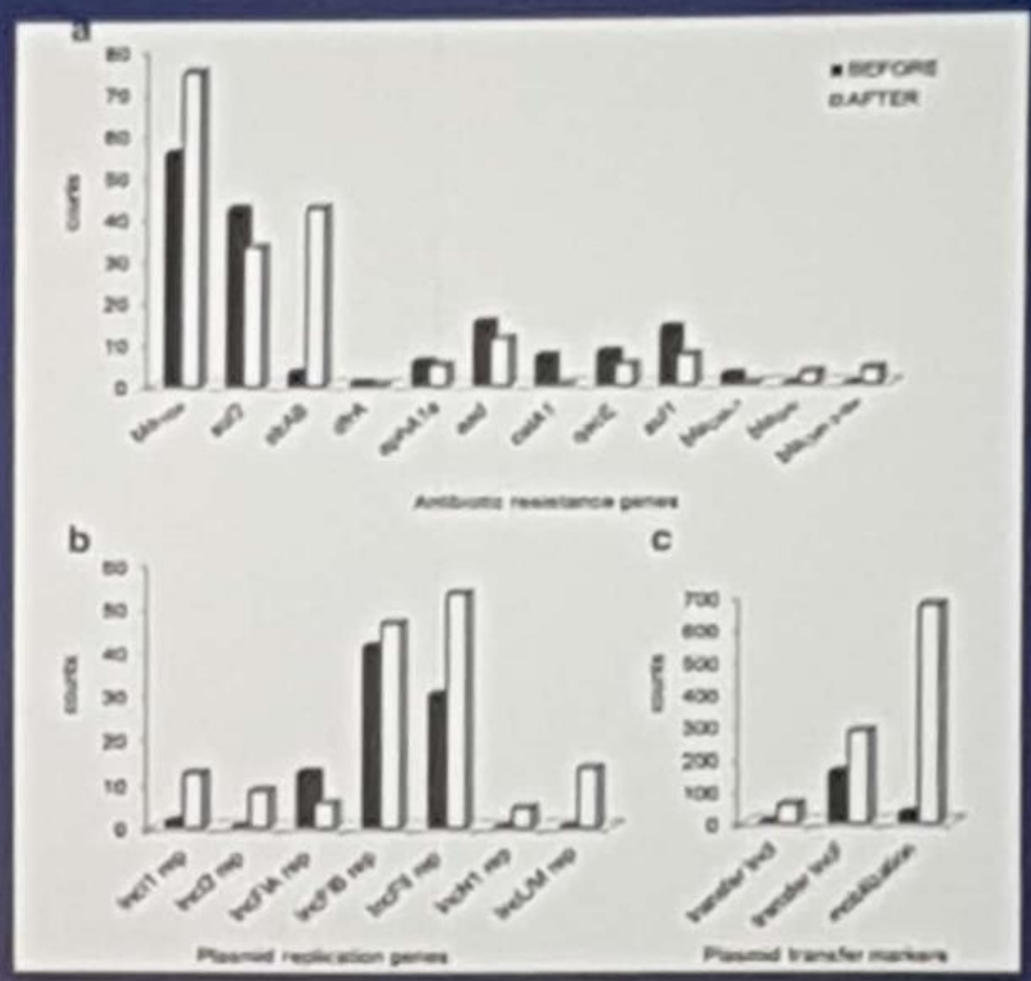
- Antibiotic resistance markers detected before and after cefepime exposure in E. coli isolates from ICU patients

a) Resistance genes

b) Plasmid replication genes

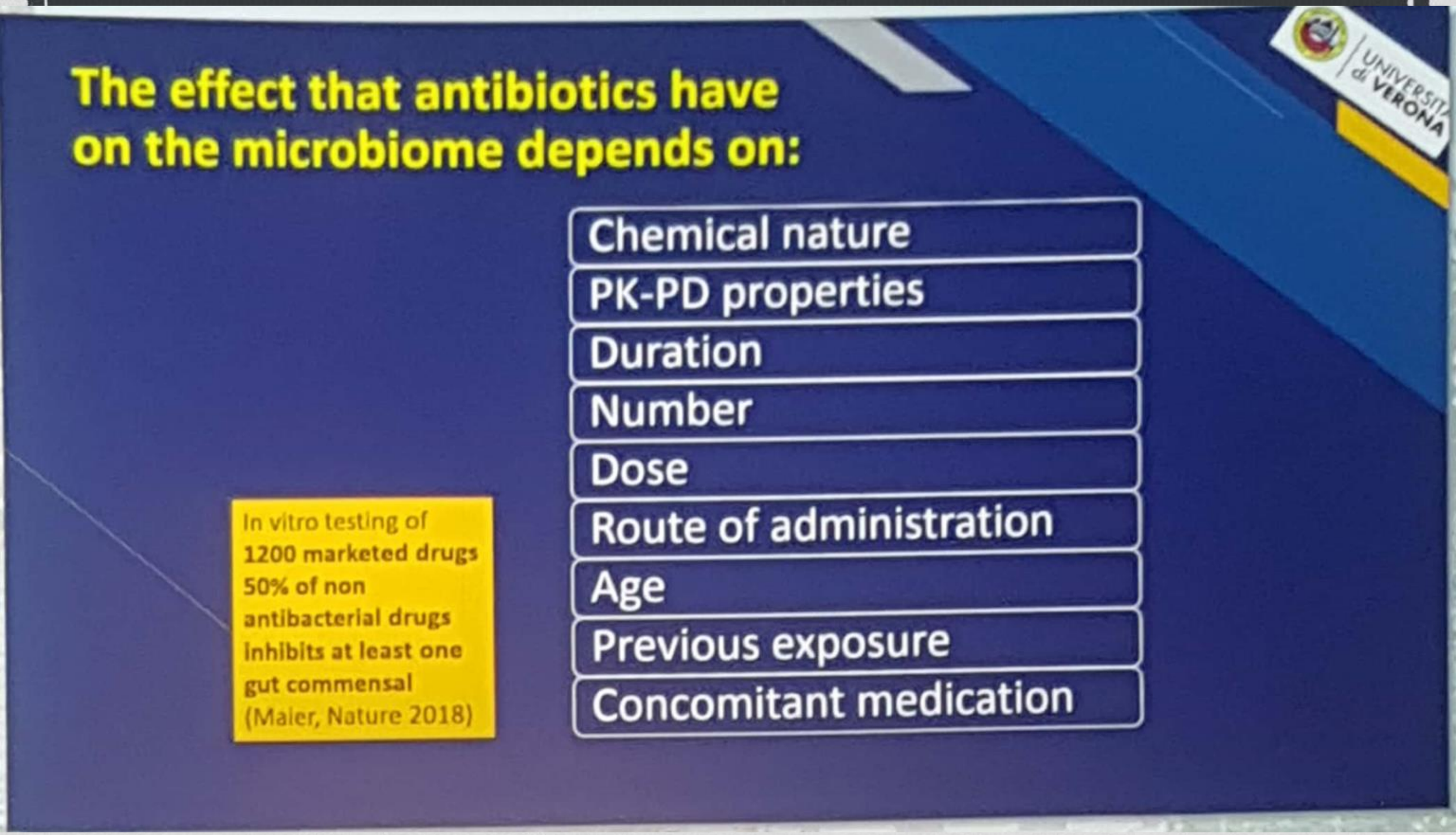
c) Plasmid transfer markers

2–6 colonies per patient of the E. coli population before (black) and after (white) cefepime treatment



Venturini, Intensive Care Medicine Experimental 2018

Effets des antibiotiques sur le microbiote



Effets des antibiotiques sur le microbiote (2)

Antibiotic exposure and microbiome changes

Bhalodi, JAC 2019

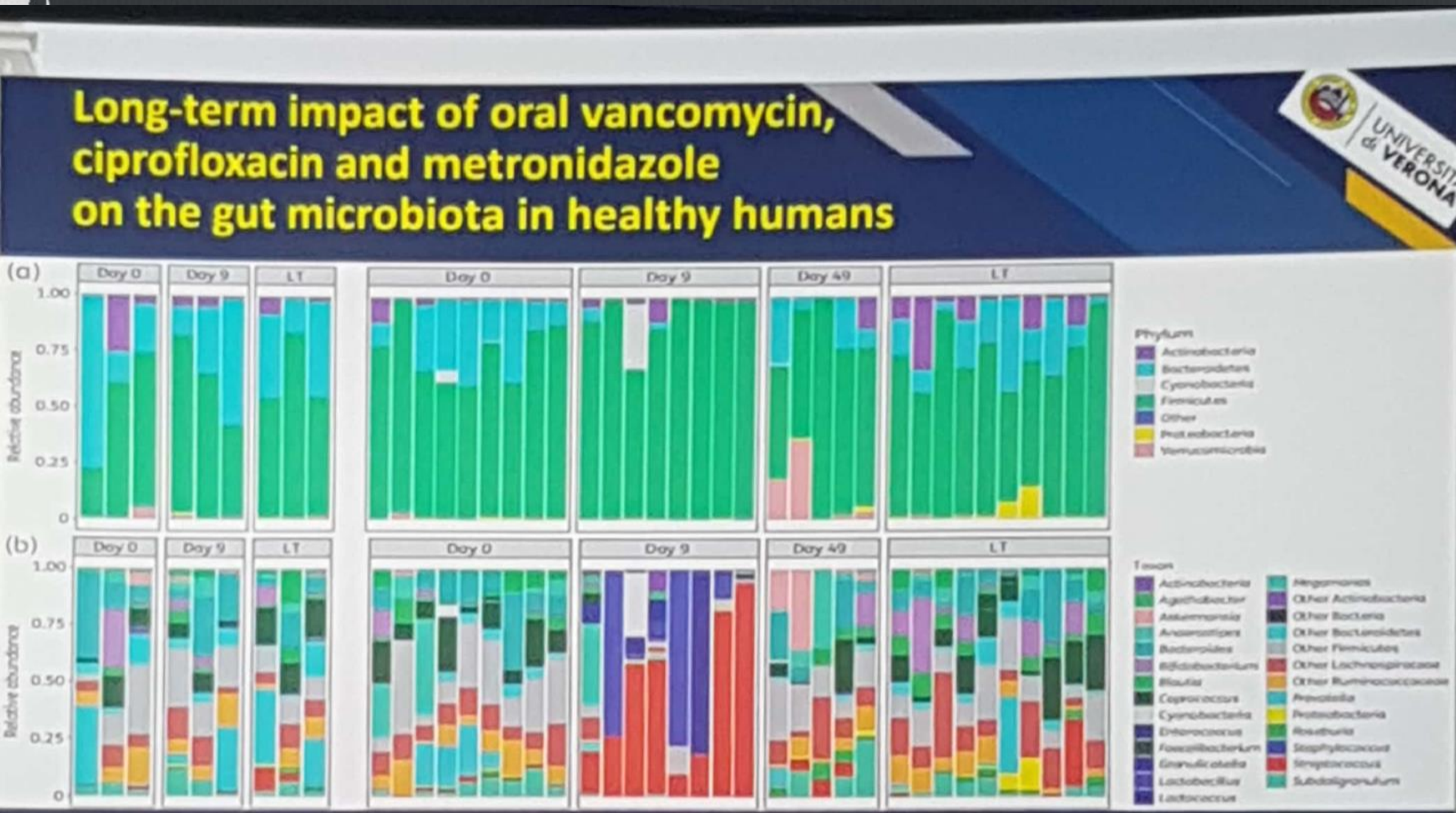
Table 1. Summary of antimicrobials and their effects on the faecal microbiota[a]

Antimicrobial class	Antimicrobial	Effects on faecal microbiota: decrease	increase	stable
Penicillins	piperacillin/tazobactam	Enterobacteriaceae bifidobacteria Eubacteria lactobacilli		*Bacteroides* enterococci clostridia
	Resistant Enterobacter, VRE 30%			
Cephalosporins	cefepime	*E. coli* bifidobacteria		*Bacteroides* clostridia
	ceftazidime **R-Enterobact.**	Enterobacteriaceae lactobacilli		enterococci *Bacteroides*
	ceftriaxone **27%**	Enterobacteriaceae *E. coli* lactobacilli bifidobacteria clostridia	enterococci	*Bacteroides*
	VRE 25%			
Carbapenems	meropenem	Enterobacteriaceae clostridia *Bacteroides*	enterococci	yeast lactobacilli bifidobacteria Eubacteria clostridia
	imipenem	Enterobacteriaceae enterococci bifidobacteria Eubacteria lactobacilli *Bacteroides*		
	ertapenem +++	*E. coli* bifidobacteria *Bacteroides*	enterococci	lactobacilli clostridia
Fluoroquinolones	ciprofloxacin	Enterobacteriaceae	enterococci	anaerobic flora bifidobacteria
	levofloxacin	*E. coli*		bifidobacteria lactobacilli *Bacteroides*
		enterococci clostridia		
	moxifloxacin	*E. coli* enterococci bifidobacteria clostridia		lactobacilli *Bacteroides* fusobacteria
	FQ-Resistant E. coli 20%			

[a]Vancomycin not discussed due to minimal effects of intravenous vancomycin on the gut.[11]

Effets des antibiotiques sur le microbiote (3)

Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans



1-week therapy in 13 healthy volunteers

Haak, JAC 2019

Effets des « Nouveaux » Antibiotiques sur le microbiote

New agents and microbiome effect

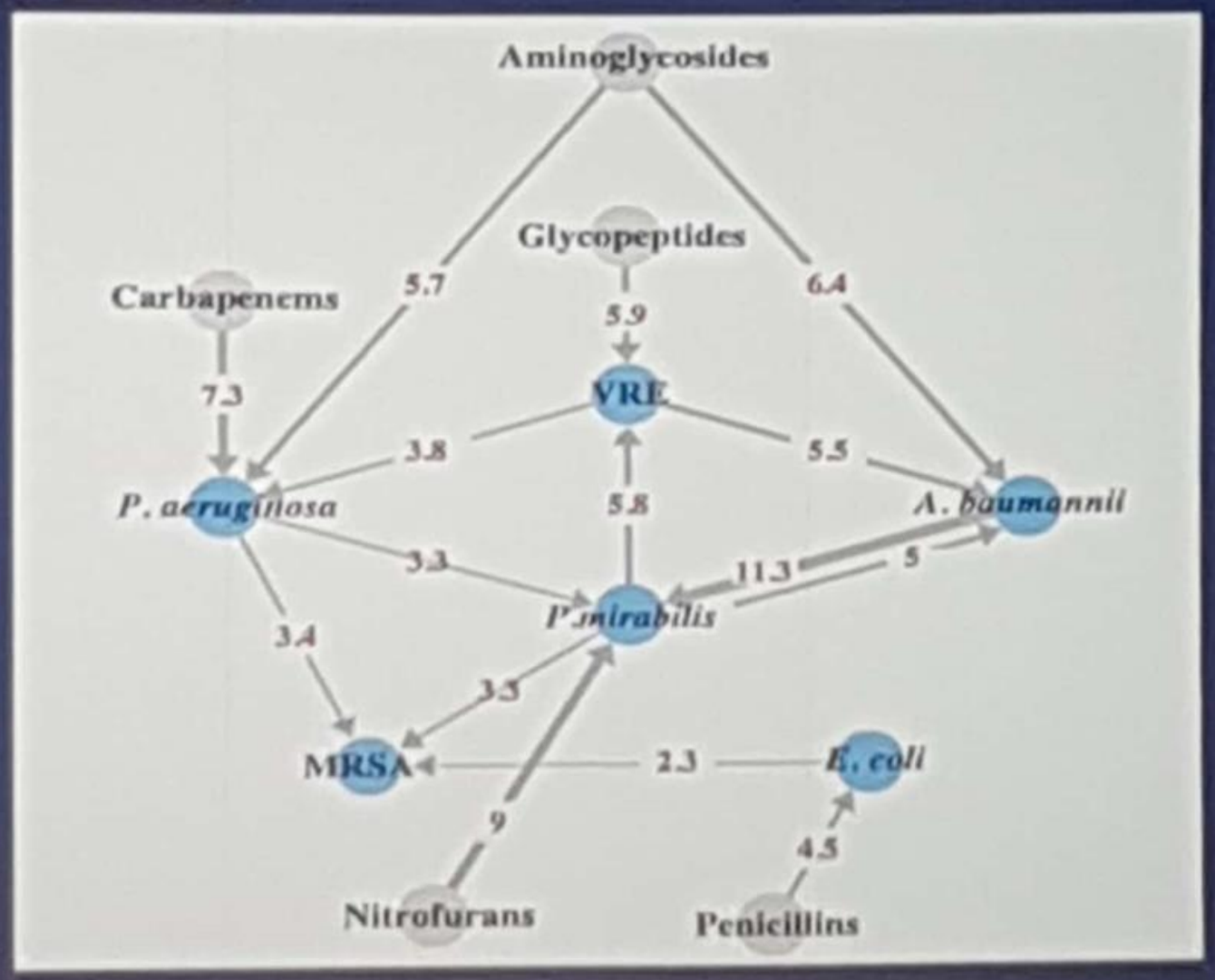
- Ceftaroline, Ceftobiprole, Telavancin
  - Minor ecological effect after 7 days of therapy
- Tigecycline
  - Reduction enterococci, lactobacilli++
  - Selection of tigecycline Enterobacter
- Ceftazidime-avibactam
  - Decrease E. coli and Enterobacteriaceae +++
  - Toxigenic C. difficile strains +++
- Ceftolozane/tazobactam, Meropenem/Varobactam
  - No data

Bhalodi, JAC 2019

Risques croisés liés à l'exposition ?

Complexity of prescriptions

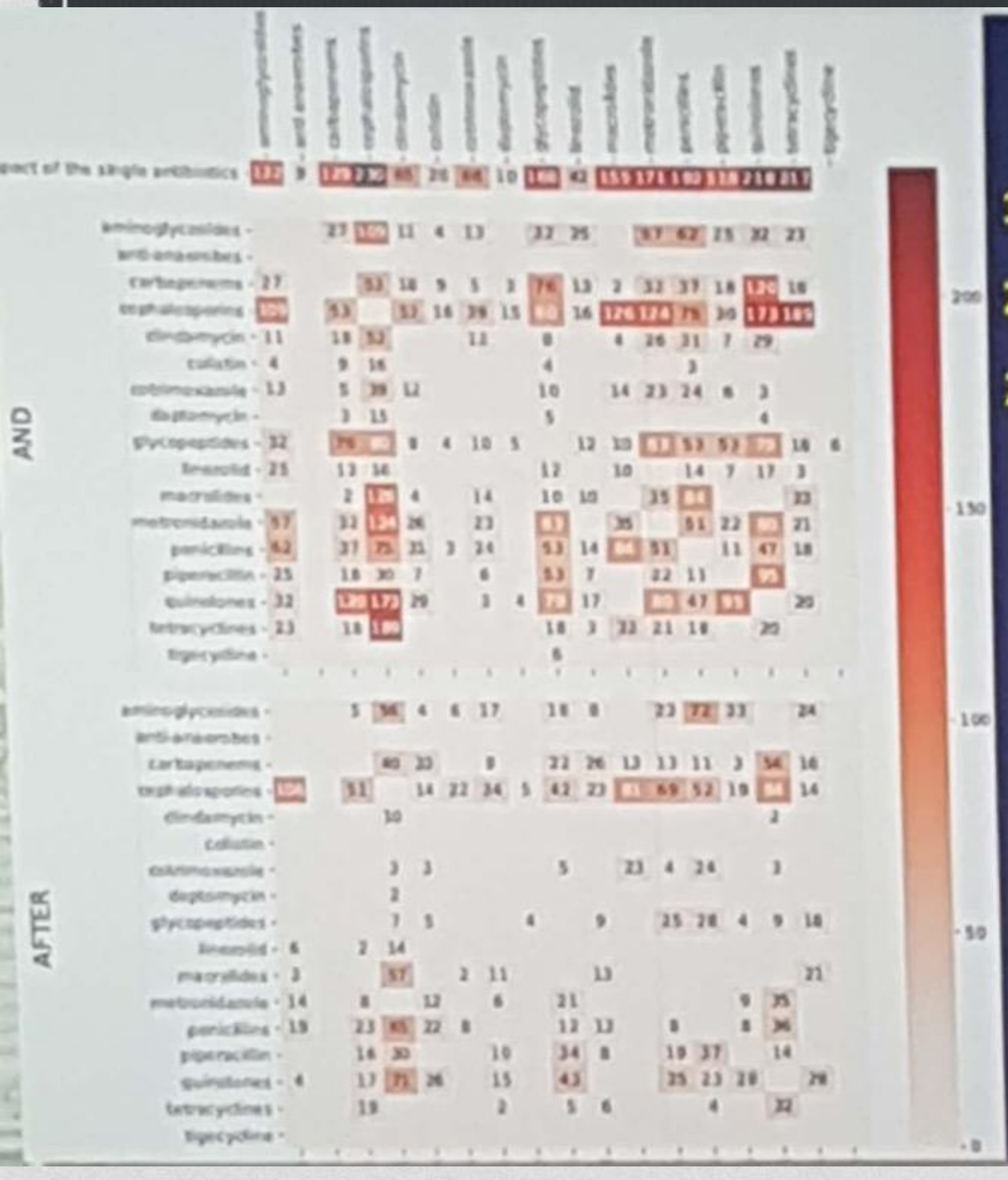
Risk network for MDRO colonization



Antibiotic treatment data for 234 nursing home residents

Wang, PNAS 2017

Machine Learning : étude de l'impact de l'antibiothérapie



Machine learning applied to antibiotic therapy

Tacconelli, under revision

UNIVERSITÀ di VERONA

10,034 patients

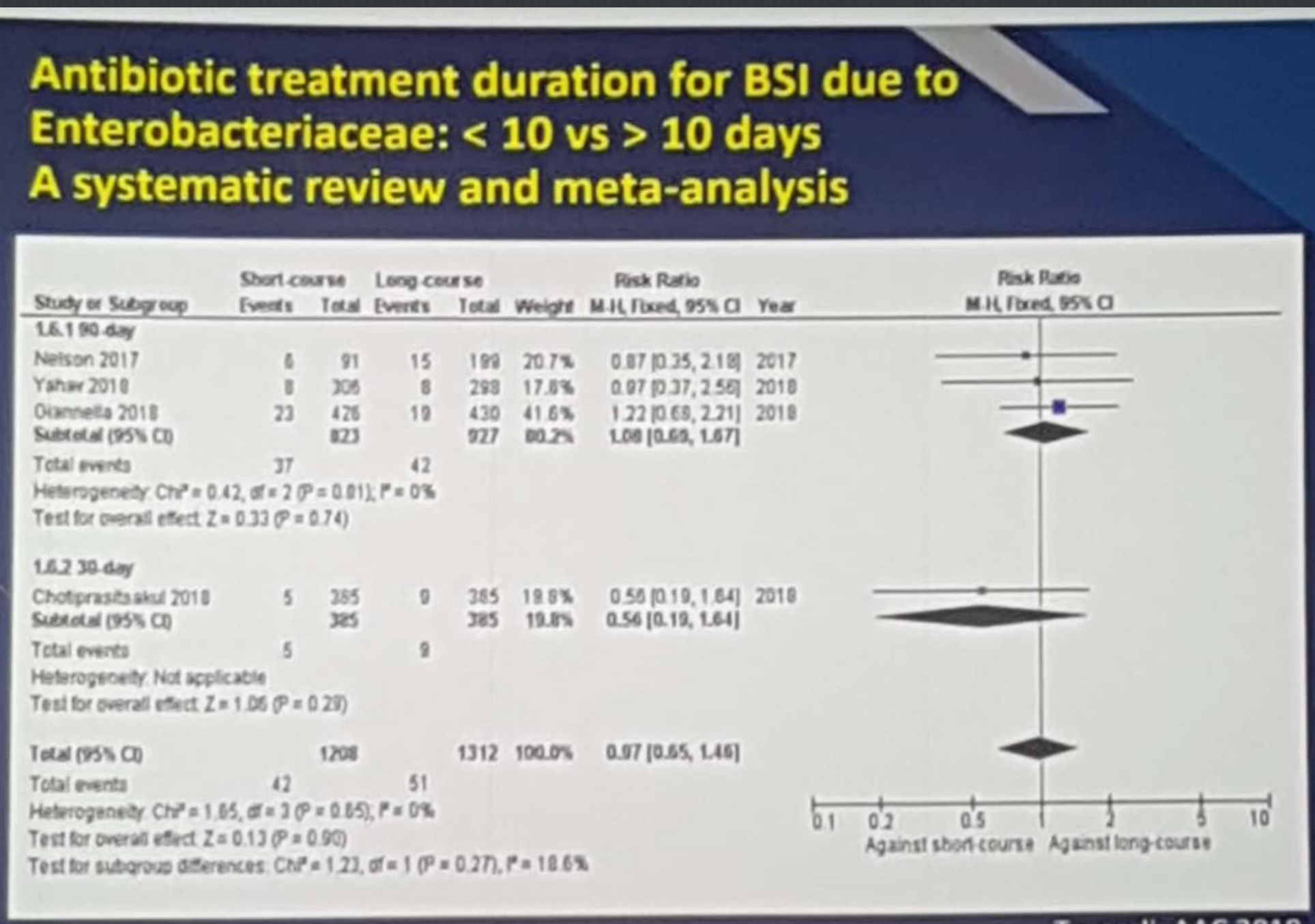
22.345 days antibiotic therapy

28,322 rectal swab samples

- The impact of an antibiotic on new intestinal colonisation with ESBL GN varied depending on whether used as mono or combi and on previous antibiotic exposure
  1. Cephalosporin monotherapy in patients who had not received antibiotics within 72 hours
  2. Tetracycline monotherapy
  3. Penicillins monotherapy
- Cephalosporins in combination therapy had less impact

Durée de traitement des bactériémies à entérobactéries

Antibiotic treatment duration for BSI due to Enterobacteriaceae: < 10 vs > 10 days
A systematic review and meta-analysis



- Pilot RCT
- 11 ICU
- 115 patients enrolled
- Study achievement completed

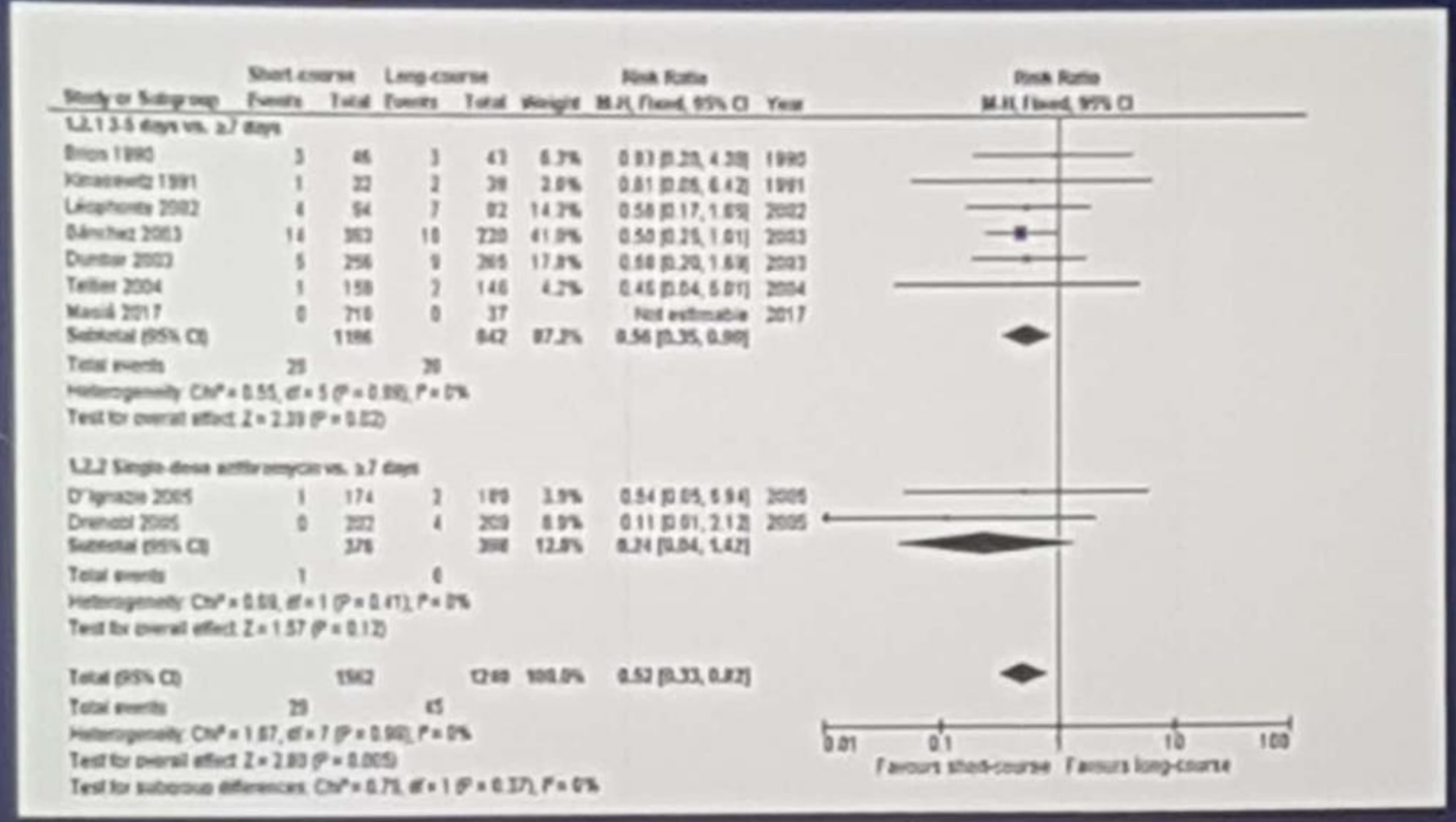
Tansarli, AAC 2019

Daneman, Trials 2018

risk ratios of 90-day mortality

Durée de traitement des PAC

Systematic review and meta-analysis of the efficacy of short-course antibiotic treatments for CAP in adults < 6 and > 7 days



21 CT - 4.861 patients
Clinical cure was similar between groups irrespective of patient setting

risk ratios of mortality

Tansarli, AAC 2019

Durée de traitement des infections urinaires

Duration of antibiotic treatment for acute pyelonephritis and septic UTI — 7 days vs longer treatment: systematic review and meta-analysis of 7 RCT

Study or subgroup	Short Events	Short Total	Long Events	Long Total	Weight	RR M-H, Fixed, 95% CI
Peterson 2008	23	265	21	241	32.8%	1.00 [0.57–1.75]
Sandberg 2012	5	73	6	84	8.3%	0.96 [0.31–3.01]
Talan 2000	10	106	24	106	35.8%	0.42 [0.21–0.83]
Jernelius 1988	3	32	1	29	1.6%	2.72 [0.30–24.70]
Klausner 2007	1	94	1	98	1.5%	1.04 [0.07–16.43]
Mensa 1999	12	123	11	113	17.1%	1.00 [0.46–2.18]
Ode 1980	0	13	2	21	2.9%	0.31 [0.02–6.07]
Total (95% CI)		706		692	100.0%	0.79 [0.56–1.12]
Total events	54		66			

Heterogeneity: $\chi^2 = 6.06$, $df = 6$ ($P = 0.42$); $I^2 = 1\%$

Test for overall effect: $Z = 1.32$ ($P = 0.19$)

RR M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours short Tx Favours long Tx

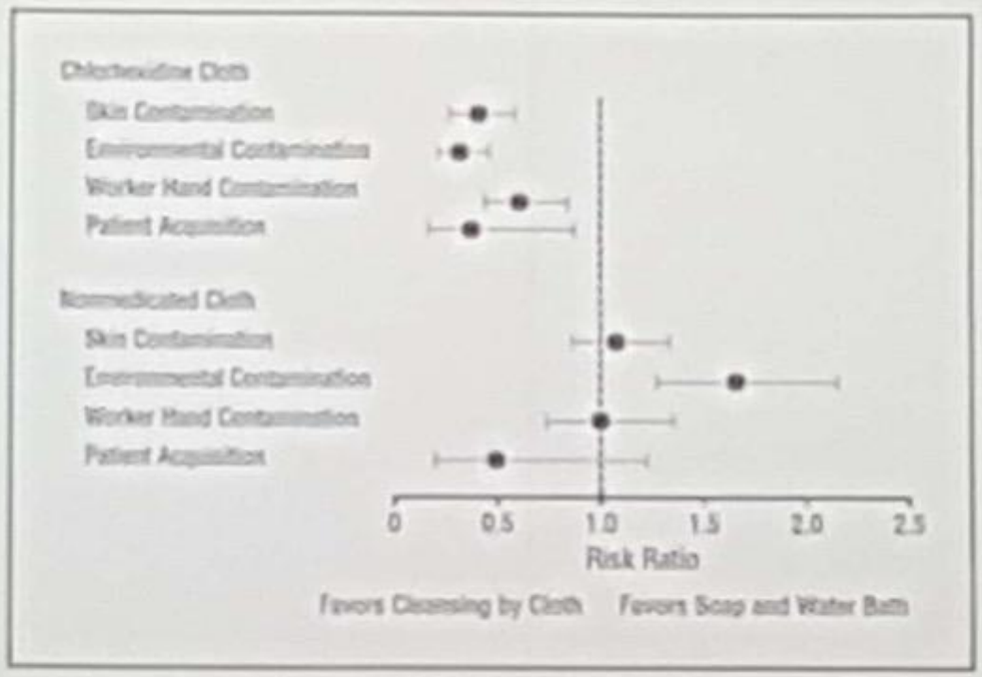
Clinical failure

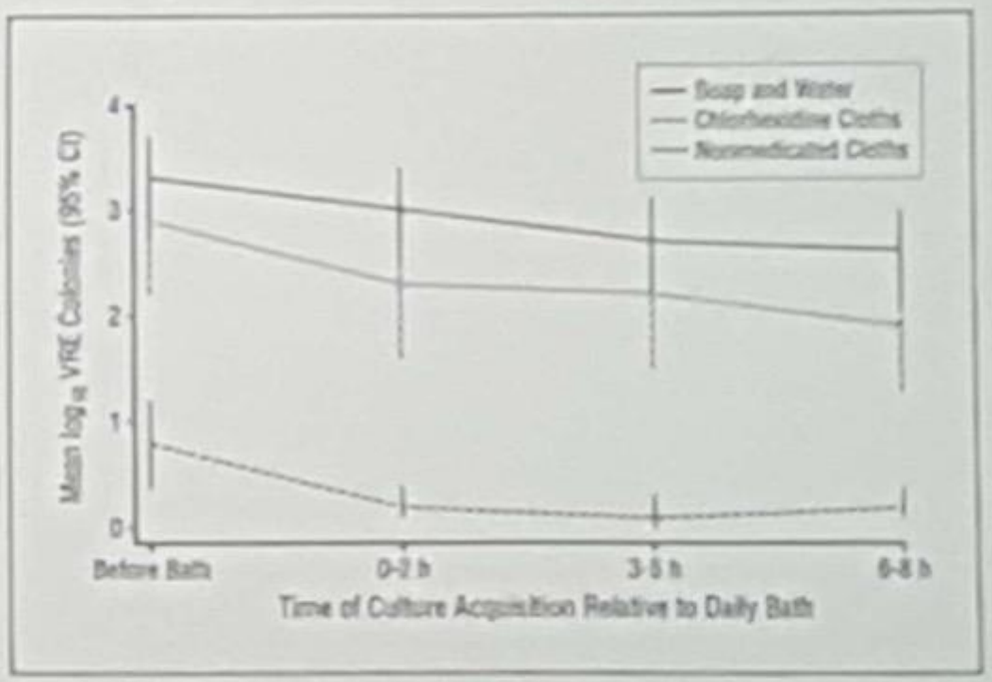
Eliakim-Raz, JAC 2013

Chlorhex vs ERV

CHG and VRE Carriage in ICUs

- 3 Phase Study 21-Bed MICU
  - Routine basin soap → 2% no rinse CHG cloths → non-CHG cloths
  - Sampling: skin, environment, healthcare worker hands





Vernon MO et al. Arch Int Med 2006; 166:306-12

Chlorhex +/- Mupirocine vs SARM

Hospital Trial:
Chlorhexidine With vs Without Mupirocin

	Mup/CHG	Placebo/CHG	p-value
• Nares free	44%	25%	0.06
• MRSA free	25%	18%	0.4
• MRSA Infection	6%	14%	0.32

N = 98

Mean LOS = 24 days

Harbarth et al. AACT 1999:43(6):1412-16

Chlorhex +/- Mupirocine vs SARM (2)

Community Trial: Mupirocin With vs Without Chlorhexidine

4-Month Follow Up	Education N=52	Mupirocin N=51	Mup + CHG N = 49	Mup + Bleach N = 54
Nasal Carriage	50%	**23%**	**24%**	**15%**
Axilla Carriage	21%	27%	14%	9%
Inguinal Carriage	26%	24%	30%	16%
Clearance –1 month	38%	**56%**	**55%**	**63%**
Clearance –All Sites	48%	56%	54%	**71%**

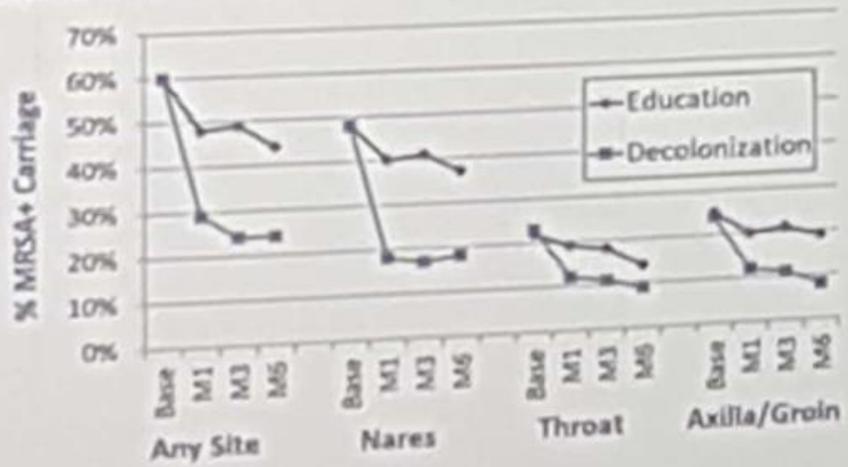
- ✓ Mupirocin appears to be the work horse
- ✓ CHG maybe less effective when rinsed off
- ✓ Bleach effective

Fritz et al. ICHE 2011:32(9):872-80

Chlorhex +/- Mupirocine vs SARM (3)

Multi-Product Post-Discharge Decolonization CLEAR Trial

- 2100+ RCT: Education + Repeated Decolonization vs Education Alone
  - Hospitalized MRSA carriers enrolled in 1 year post-discharge trial
  - Decolonization 5 days twice a month for 6 months
    - 5 days mupirocin plus CHG baths and CHG mouthwash
  - 30% reduction in infection and hospitalization with decolonization



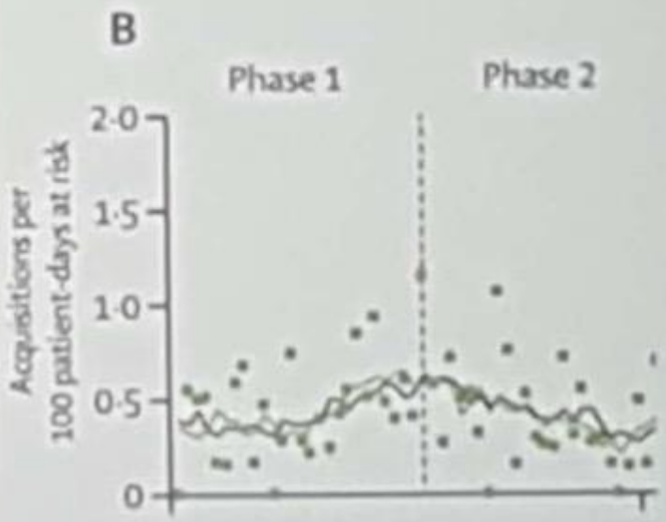
Huang SS et al NEJM 2019; 14:380 (7):638-650

Chlorhex +/- Mupirocine vs SARM = en Réa

CHG Only ICU Decolonization and MRSA

- Does CHG bathing alone reduce MRSA transmission in ICUs?

Variable	Intervention Period	Control Period	P Value
No. of admissions	3970	3842	0.32
Total days of care	24,902	24,983	0.85
MDRO acquisition			
No. of infections	127	165	0.02
Incidence rate (no./1000 patient-days)	5.10	6.60	
VRE acquisition			
No. of infections	89	107	0.05
Incidence rate (no./1000 patient-days)	3.21	4.28	
MRSA acquisition			
No. of infections	47	58	0.29
Incidence rate (no./1000 patient-days)	1.89	2.32	



Viray MA ICHE 2014;35(3):243-250 Climo M NEJM 2013;368 (6):533-542 Derde LPG Lancet ID 2014;14(1):31-39

Chlorhex vs SARM

Chlorhex vs BGN

CHG and Gram Negative Rods

- Chlorhexidine active against Gram Positive and Gram Negative Bacteria
  - MRSA wild type Epidemiologic Cut Off (ECOFF) MIC = 8µg/ml
  - Gram-negative ECOFF MIC 32--128µg/ml
  - 2% leave-on CHG cloths: 20,000µg/ml
  - 4% rinse-off: 40,000µg/ml
  - What remains post-bathing?
  - What replaces post-bathing?
  - From where? [1 2]

Bacterial Species	CHG MIC Epidemiologic Cut-Off (µg/ml)
MRSA	8
E. coli	32
Klebsiella spp.	32
P. aeruginosa	32
S. marcescens	32
Proteus spp.	64
S. maltophilia	64
Burkholderia spp.	64

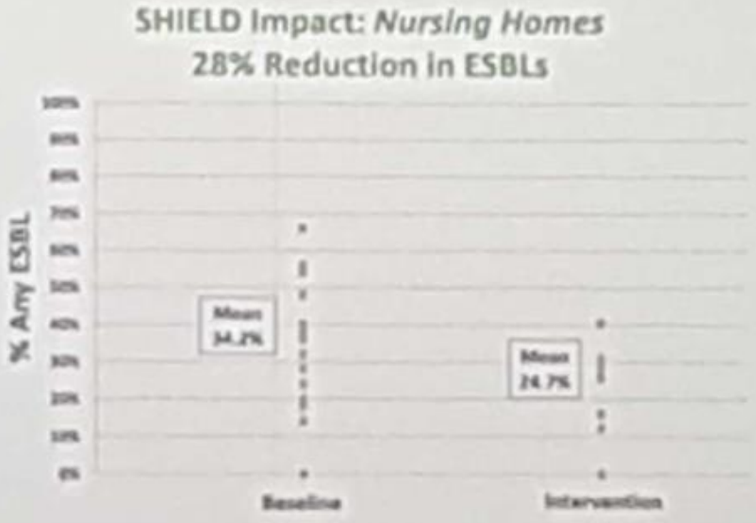
Mengoza-Olazaran S et al. AJIC 2014;42:874-8.
Apisarnthanarak A et al. ICHE 2014;35(1):98-99

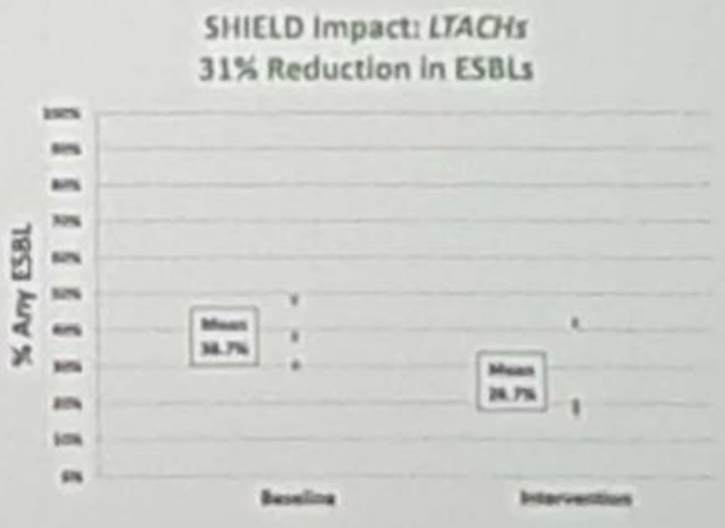
Chlorhex vs portage de BLSE

CHG and ESBL Carriage in Long-Term Care

- Regional decolonization intervention (SHIELD Orange County)
  - 16 nursing homes and 3 long-term acute care hospitals (LTACHs)
  - CHG routine bathing (3x/week in nursing homes) plus twice daily nasal iodophor on admission and Mon-Fri every other week
  - Pre-point point prevalence 15-month assessment of 50 residents

SHIELD OC
Prelim data

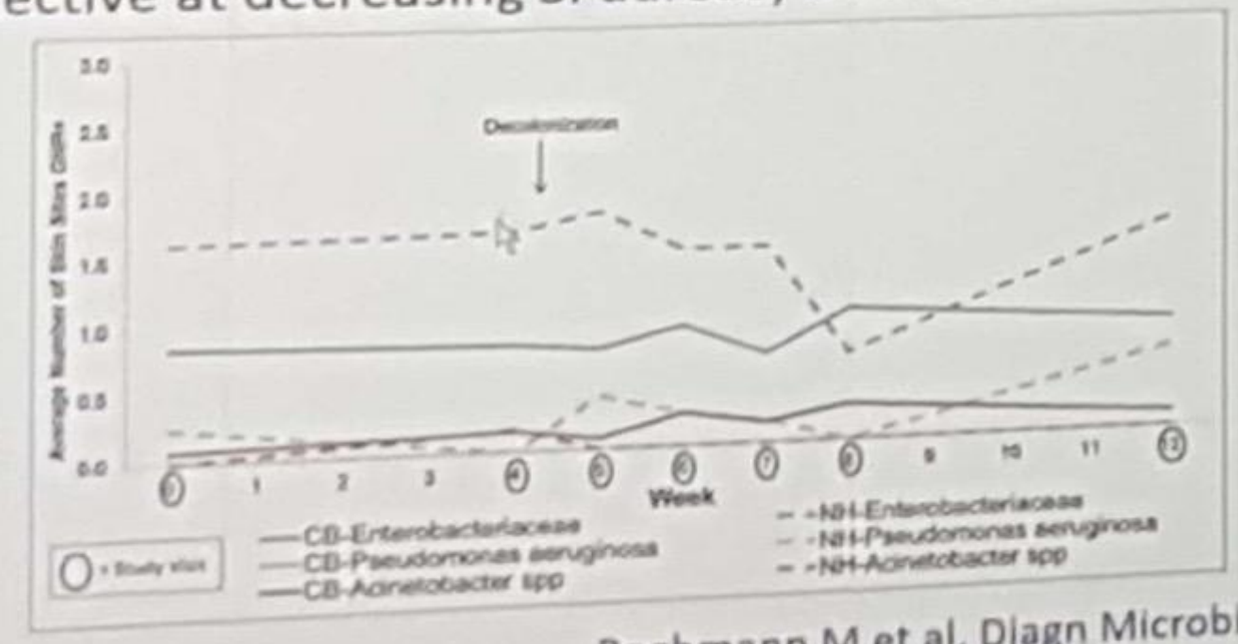




Chlorhex vs entérobactéries

CHG and Enterobacteriaceae

- Community (N=26) and nursing home (N=8) adult *S. aureus* carriers
  - ➢ Sampled before, during and after 5 days of CHG + mupirocin use
  - ➢ NH more MRSA carriers (50%), more GNR on skin (2-fold)
  - ➢ Effective at decreasing *S. aureus*, GNR reduction in NHs appeared "late"



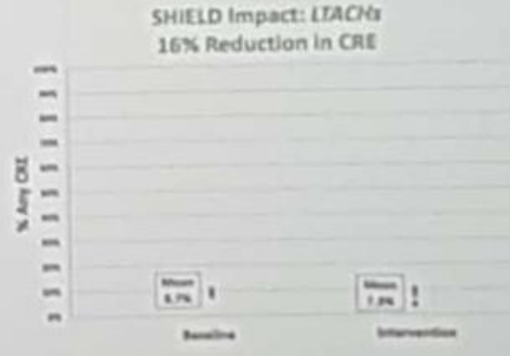
Roghmann M et al. Diagn Microbiol Infect Dis. 2017;88(1):53-57

Chlorhex vs Carbapénémases

CHG and CRE Carriage in Long-Term Care

- Regional decolonization intervention (SHIELD Orange County)
  - 16 nursing homes and 3 long-term acute care hospitals:
  - CHG routine bathing (3x/week in nursing homes) plus twice daily nasal iodophor on admission and Mon-Fri every other week
  - Pre-point point prevalence 15-month assessment of 50 residents

SHIELD OC
Prelim data



Chlorhex vs Levures

CHG and Yeast

- 20 MICU patients, cultured before and after bath up to 8 hours
  - Soap vs CHG cloth vs non-CHG cloth

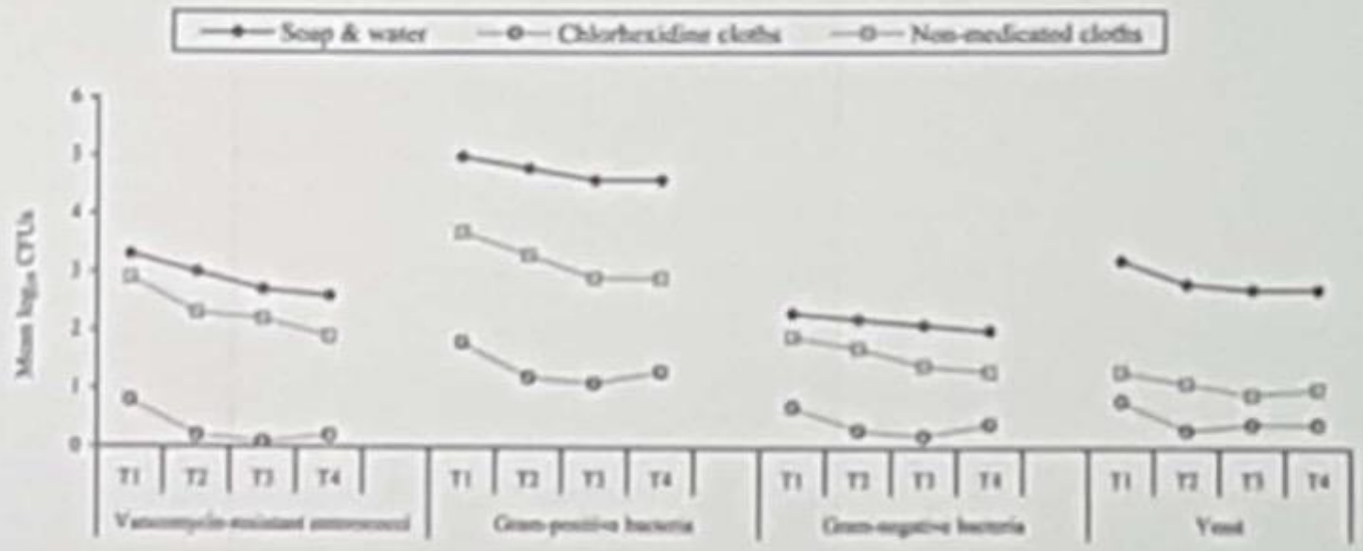


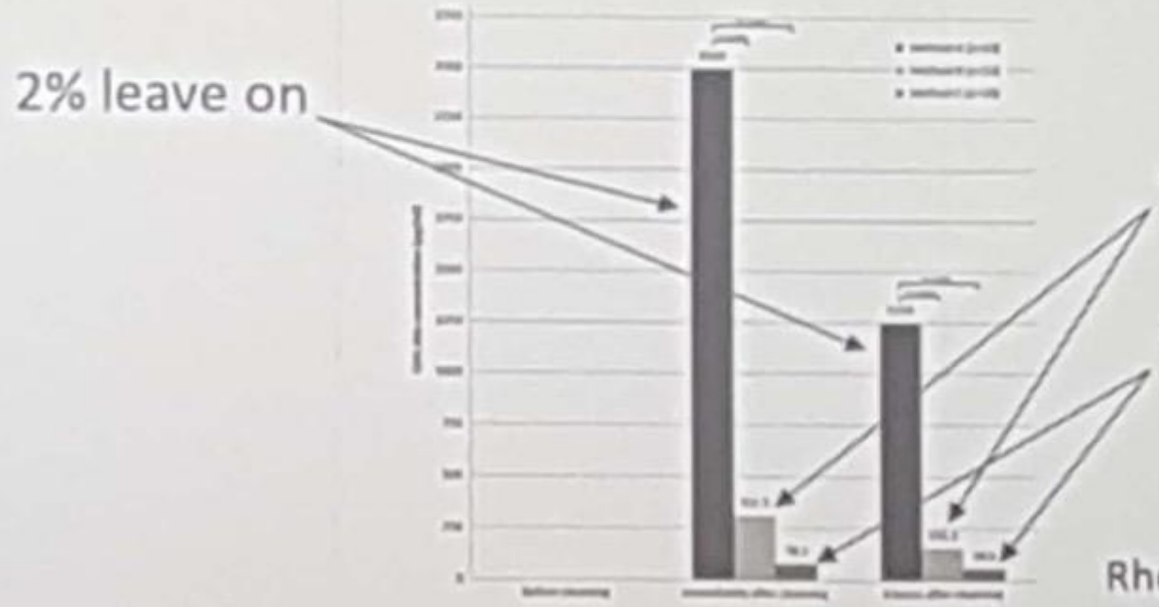
FIGURE 4. Effect of bath procedure on microbial contamination in the inguinal region. Chlorhexidine gluconate (CHG) and nonmedicated baths were performed with no-rinse cloths that contained CHG (and emollients) or only bland cleansing agents (and emollients), respectively.[17] CFU, colony-forming unit; T1, before bath; T2, 0–2 hours after bath; T3, 3–5 hours after bath; T4, 6–8 hours after bath.

Popovich K et al. ICHE 2012;33(9):889-896

Quelle concentration de Chlorhex ?

CHG Skin Concentrations by Bath Type

- Healthy volunteers
  - ➢ One forearm: 2% leave on CHG cloth
  - ➢ Other forearm either 4% wipe off CHG with polyester vs cotton cloth
  - ➢ Skin CHG concentration before, after, and 6 hours after cleansing



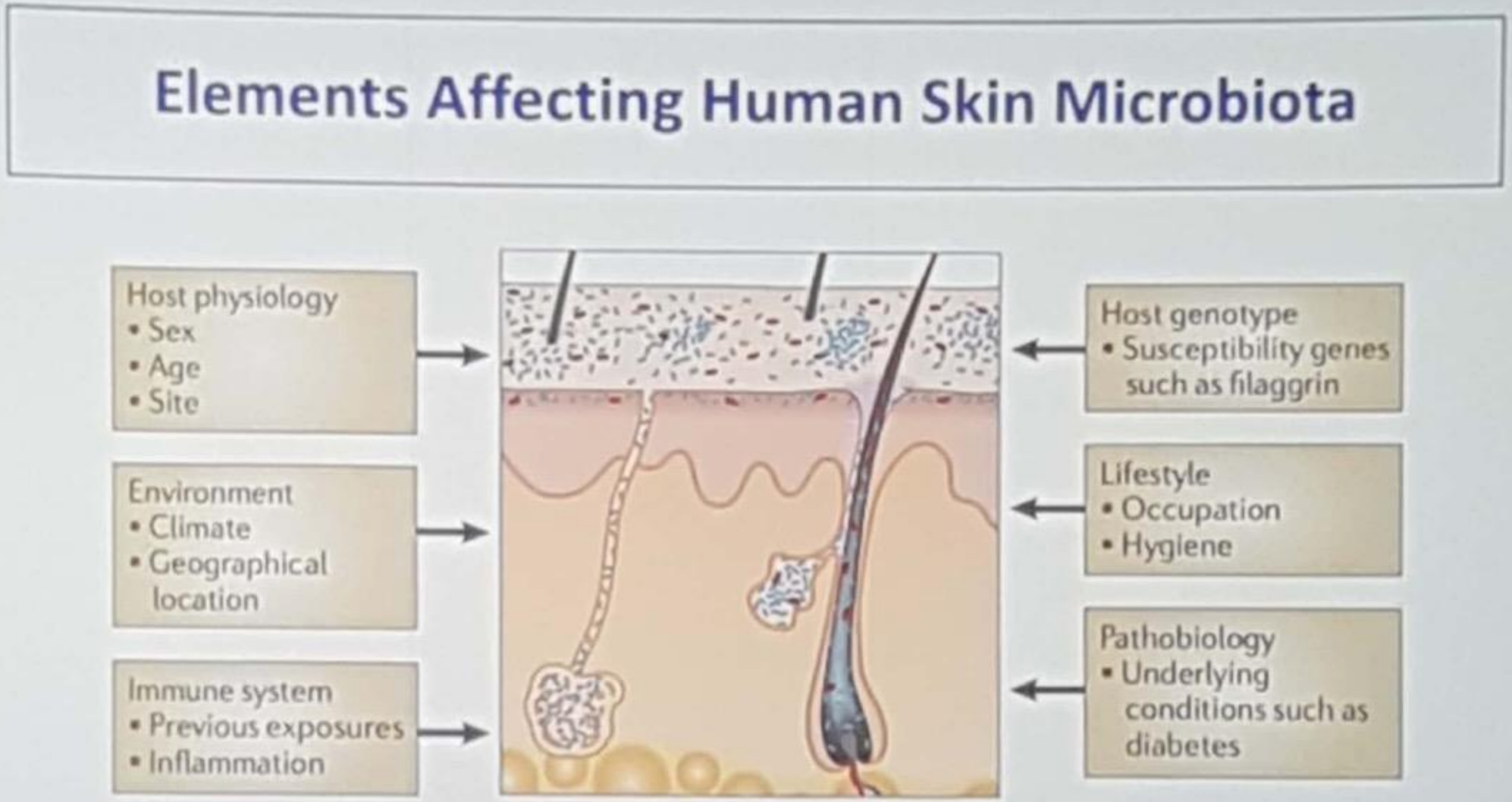
Rhee Y et al. ICHE 2018;39(9):405-411

Microbiote cutané

Skin Microbial Ecosystem

- Largest organ, complex ecosystem
  - Skin discrete distinct areas: pH, sebum, moisture, temperature
  - Site-specific metabolic exchange with symbionts and commensals
  - Sebaceous areas: higher biomass, lower diversity
  - Culturomics: assess viable pathogens, affected by growth in incubation
  - Microbiome analysis: DNA regardless of viability, not affected by differential growth speed

Facteurs de modification du microbiote cutané



Grice EA, Segre JA. Nat Rev Microbiol 2011;9(4):244-53

Impact des antiseptiques sur le microbiote

Impact of Antiseptics on Culturomic Diversity

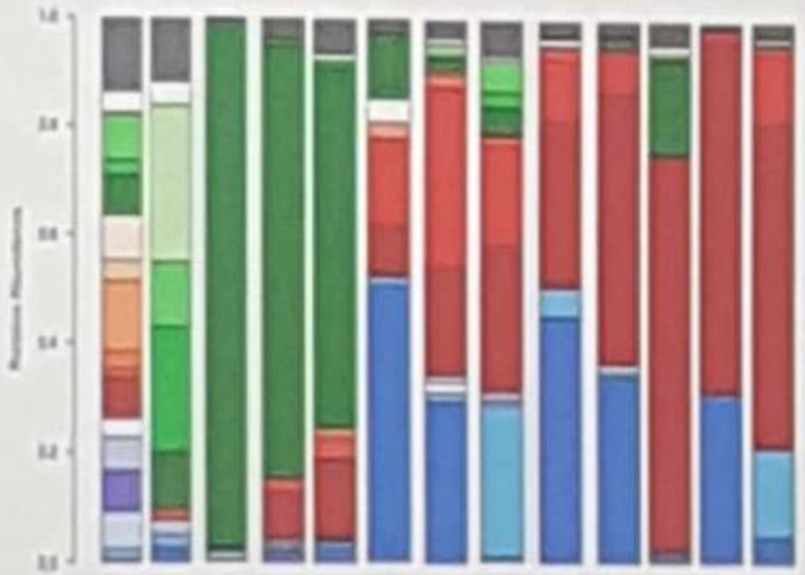
- 8 Community adults receiving bleach baths, sampled before, D5, D30
  - Distinct taxa (richness) shifts before (21), during (18), and after (20) bathing
  - Diversity index shifts before (1.7), during (1.65), and after (1.61) bathing
- 7 ICU adults receiving CHG baths, sampled before, D3-7, at discharge
  - Distinct taxa (richness) shifts before (16), during (12), and after (15) bathing
  - Diversity index decreases before (1.61), during (1.43), and after (1.16) bathing
  - Caveat: all received systemic antibiotics

Burnham C et al. AACT 2016;60(12):7303-12

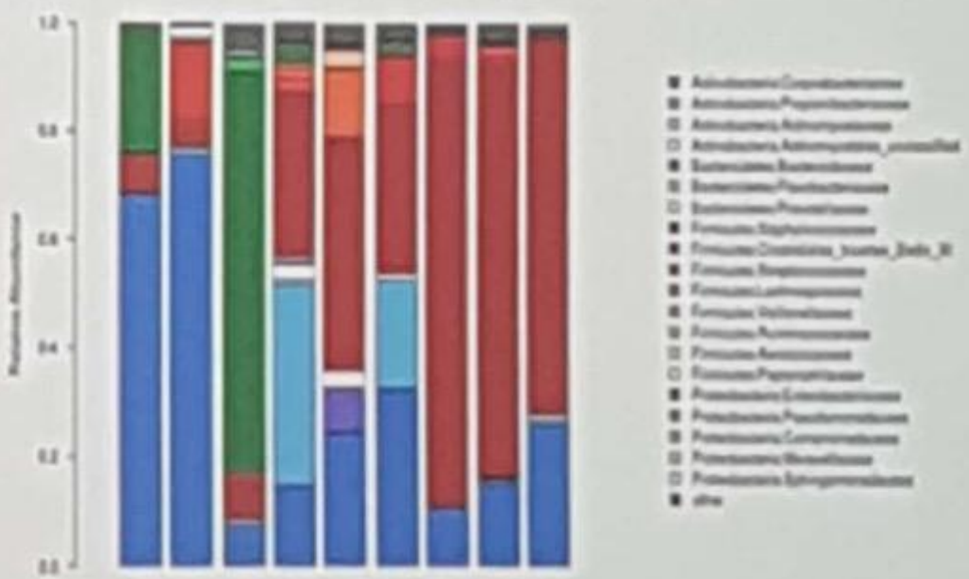
Impact des antiseptiques sur le microbiote

Skin Microbiome Post-CHG Nursing Home Residents

- Ongoing study: nursing home residents in 11 of 28 nursing homes in RCT
- Post bath, CHG vs routine soap: Axillary swabs
  - Amplicon sequencing (16S, ITS1) → Shotgun metagenomics



Post CHG Bath



Post Routine Soap

Unpublished data

Impact des antiseptiques sur le microbiote : conclusion

Summary: CHG and Skin

- **Intended Goals**
  - Protect patients from infection during at risk periods ✓
  - Reduce MDRO prevalence, spread, and infection ✓
  - Avoid vacuum of skin commensals ✓
  - Benefit >> risks
- **Knowledge to Date**
  - Infections reduced (e.g. device, surgical, ICUs, MRSA)
  - MDRO spread and infection reduced (e.g. healthcare, post-discharge settings)
  - Skin commensals remain, emerging from deeper tissues
  - Future: better understand reconstitution post-bathing
  - Future: watch and quantify risk of resistance vs averted infections
  - Future: disentangle patient factors, antibiotics

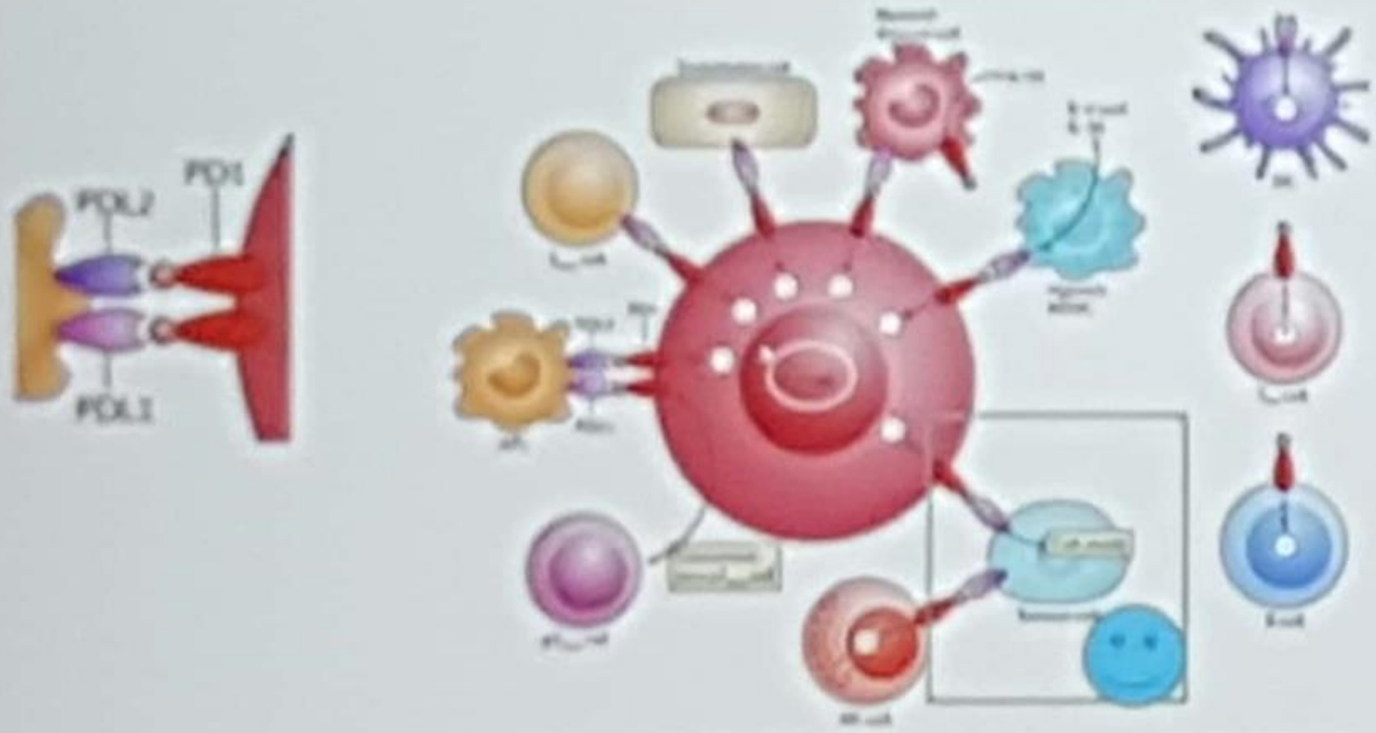
Mécanisme des PD-1/PD-L1

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Campo
David van Duin

11:03
HALL B

The tumor cell and its microenvironnement exploit the PD-1 / PD-L1 axis to avoid the killing of cancer cells by cancer-specific T cells

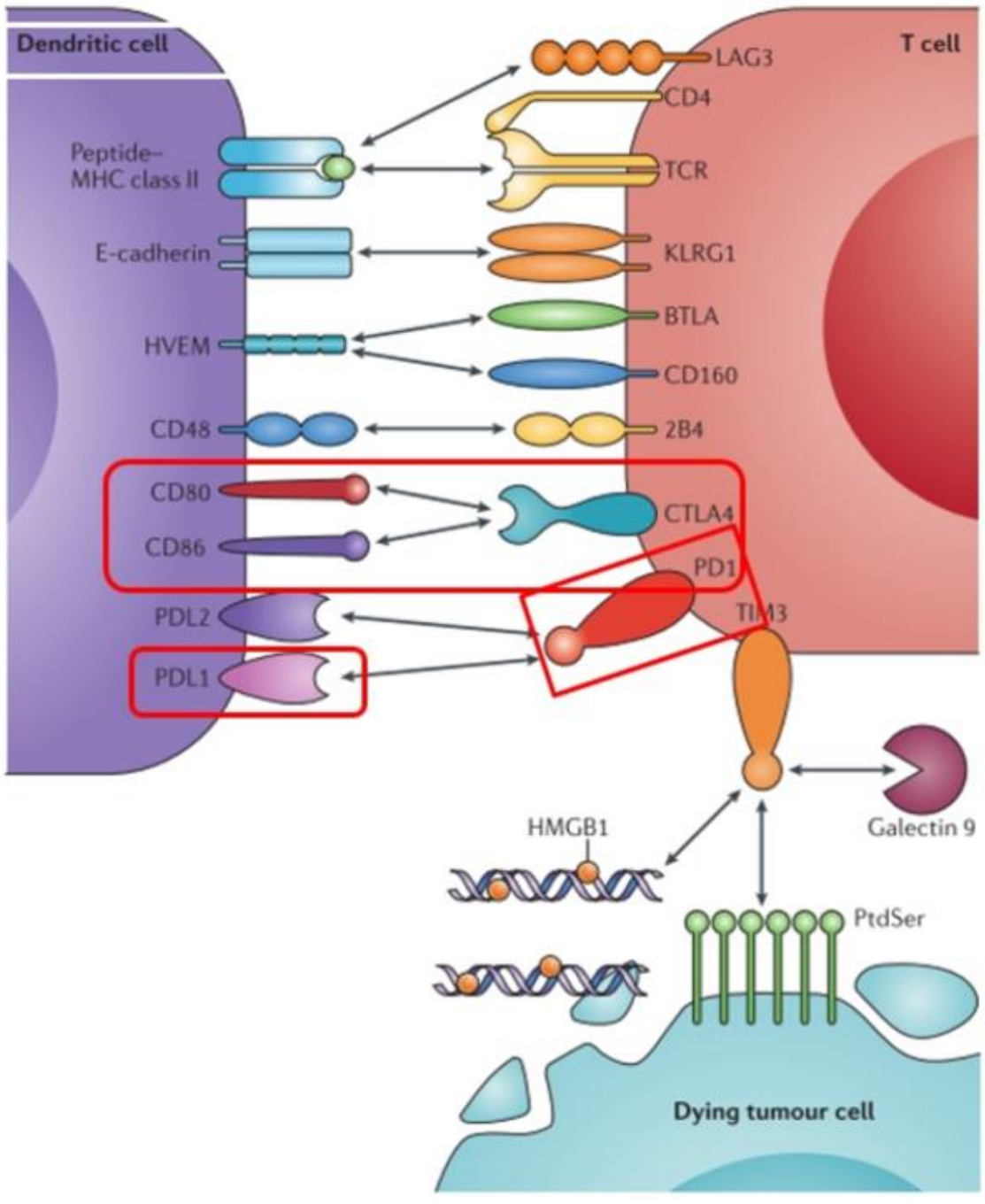


Nguyen et al. Nature Rev Immunol 2013

Olivier Lambotte

Immune checkpoint inhibitors and infections

Immunothérapie



The world of the checkpoint inhibitors blocking activation of T lymphocytes

- Expression on T lymphocytes
- Activation induced
- Described for most of them in humans on tumor-specific and virus-specific T cells

- Ligands expressed on numerous cells of the immune system but also on cells from various organs
- Pathways PD-1 and CTLA4 the most studied

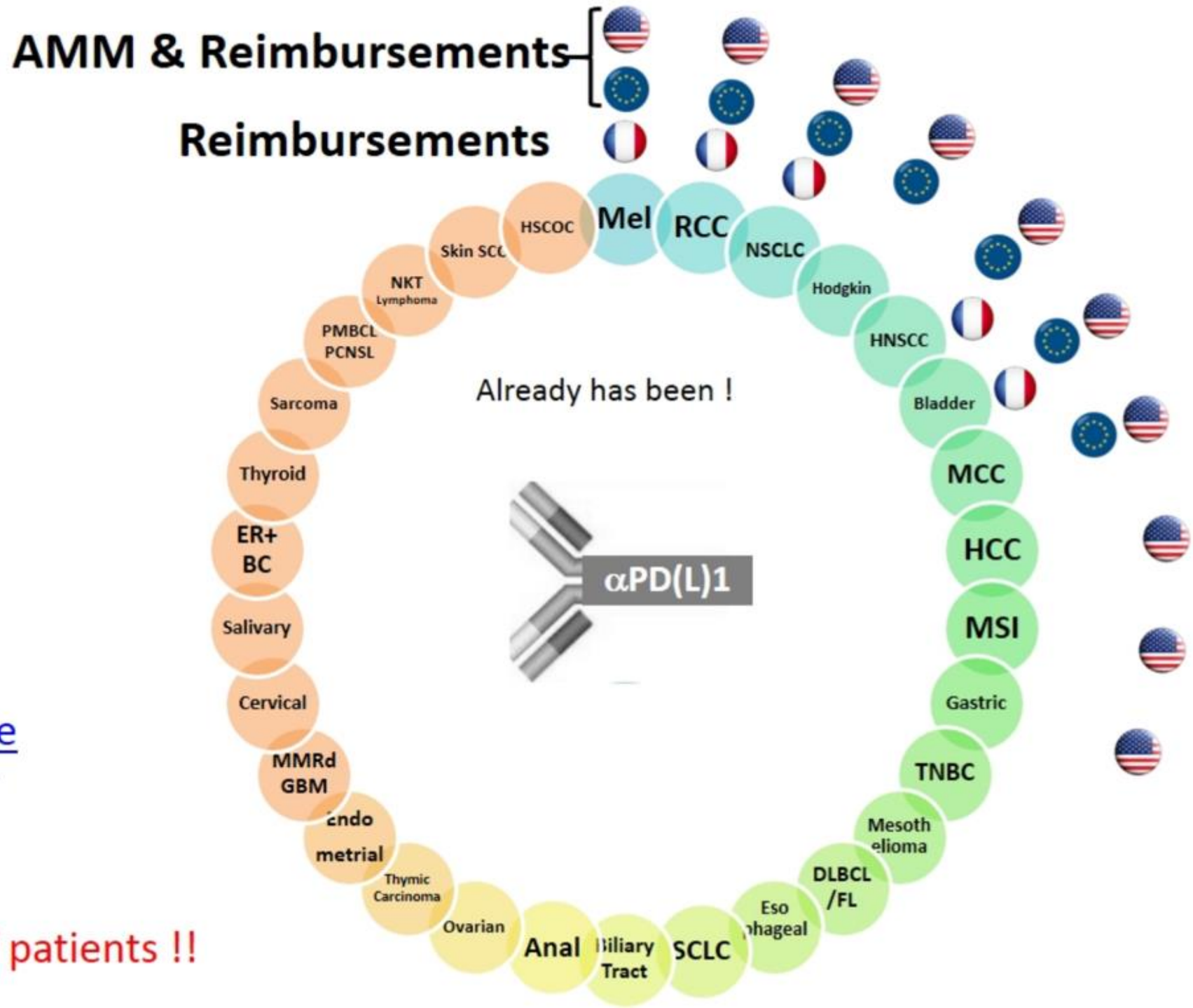
Nguyen et al. Nature Rev Immunol 2015

Anti-CTLA4
Ipilimumab

Anti-PD-1
Nivolumab
Pembrolizumab

Anti-PD-L1
Atezolizumab
Durvalumab
Avelumab

Major indications in France
Non small cell lung cancer
Urothelial tumors
Head and neck cancer
= an increasing number of patients !!



Impact de l'Ipilimumab

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:09
Sunday, 14 April 2019
HALL B

COLITIS
Steroids +/- anti-TNFα
irAEs grades 3-5 possible

Steroids +/- MMF

Rash, pruritus >> Lyell Sd, Stevens Johnson Sd
1-4% grades III-IV

Topical steroids

IMMUNE-MEDIATED ADVERSE REACTIONS

Ipilimumab

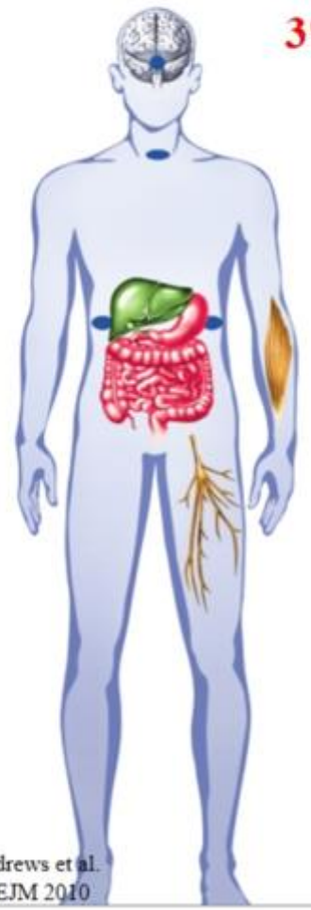
Yervoy™, package insert, BMS 2011

GASTROINTESTINAL 30%
GO TO PAGE 6
Signs and symptoms such as
- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER
GO TO PAGE 8
Signs such as
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

5%

SKIN 40% 50%
GO TO PAGE 10
Symptoms such as
- Pruritus
- Rash



3%

Peripheral neuropathies
Guillain Barré Sd
Myasthenia
Meningitis
NEUROLOGIC
Steroids and specific treatment (IgIV…)

ENDOCRINE
8%
Hypophysitis
Thyroïditis with hypo/hyperT
Surrenal insufficiency
Type 1 diabetes
Hypophysite
Tt= opotherapy
- Abnormal thyroid function tests and/or serum chemistries

irAEs grade 3-4 ≈ 20%

Please see each organ system section

Prieto et al. Clin Cancer Res, 2013, Andrews et al. Cancer Manag Res 2012; Hodi et al. NEJM 2010

Olivier Lambotte

Immune checkpoint inhibitors and infections

29th ECCMID
Amsterdam, Netherlands
13 – 16 April 2019
ESCMID

Impact des anti-PD-1/PD-L1

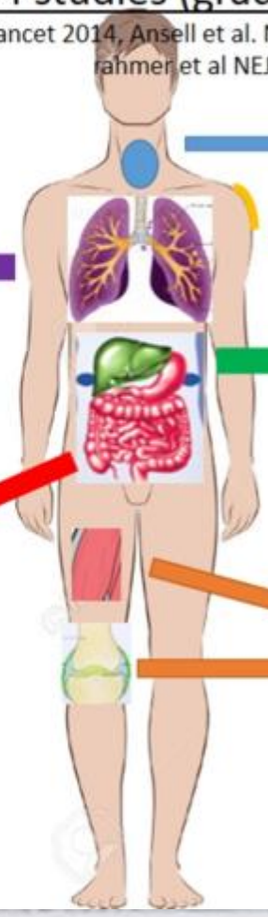
11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:09
Sunday, 14 April 2019
HALL B

Immune related adverse events with anti-PD1 and anti-PDL1

Mean Frequencies (range) in 13+4 studies (grade 1 to 5) (Brahmer et al. JCO 2010-2013, Topalian et al. Nejm 2012, JCO 2014, Weber et al. JCO 2013, Robert et al, NEJM 2014, Lancet 2014, Ansell et al. NEJM 2014, Hamid et al. NEJM 2013, Westin et al. Lancet Oncol 2014, Motzer et al. NEJM 2015, Garon et al. NEJM 2015, Brahmer et al NEJM 2015) Brahmer et al. NEJM 2012, Powles et al. Nature 2014, Herbst et al. Nature 2014)



ENDOCRINOPATHIES
10% -15%
Thyroïditis with hypo/hyper
Adrenal insufficiency, Hypophysitis
Tt= hormonal replacement
Follow TSH

LUNGS
3% (0 – 8%)
Interstitial Pneumonia (with grade 5)
Check for other diagnosis
CT scan and spirometry for grade >=2
Bronchoscopy with BAL
Treatment with steroids + ATB

SKIN
30%
Vitiligo, rash, sicca sd

LIVER
5% (0 – 10%)
Cytolysis > cholestase
Steroids

Rare: Guillain Barre
myasthenia

GUT
13% (2,5 – 27%)
Diarrhea and abdominal pain
CT scan and rectoscopy Collins et al. Ann Oncol 2017
Treatment with steroids +/- anti-TNFα
Pancreatitis

ARTHRALGIA MYALGIA
8% - 2,5% (0 - 16%)
Polyarthritis, PMR, myositis (check for myocarditis)
Treatment with steroids +/- MTX anti-TNFa

irAEs grade 3-4 ≈ 10%

Olivier Lambotte

Immune checkpoint inhibitors and infections

Impact des combinaisons d'immunothérapie

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

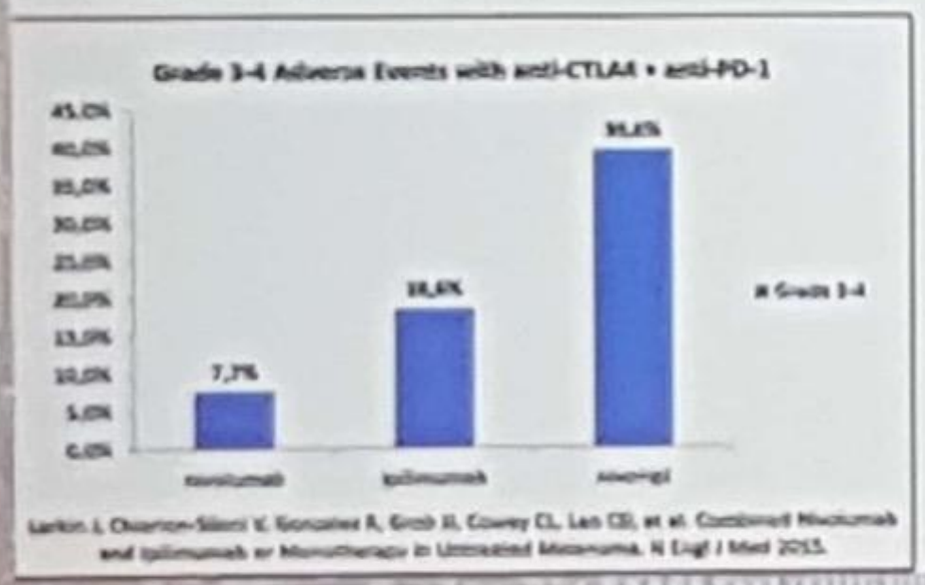
11:10
Sunday, 14 April 2019
HALL B

IrAEs and combinations...

- Majoration of toxicities
  - Nivolumab + ipilimumab (Wolchok et al. NEJM 2013)

  53% of IrAEs grade 3-4

  38% treated with steroids and 3 with immunosuppressants



Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015.

- Majoration of toxicities
  - Carboplatine – paclitaxel +/- pembrolizumab (Pen-Ares NEJM 2018)

  Combo : 30% irAEs with 11% grade 3-5

Olivier Lambotte

Immune checkpoint inhibitors and infections

Immunothérapie et tuberculose

Tuberculosis

Involvement of the PD-1/PD-L1 pathway to limit inflammation in tuberculosis primary infection but…

The PD-1/PD-L1 pathway favors Koch bacilli persistance (Sakais et al. PLoS Pathogen 2016)

Proc Natl Acad Sci U S A. 2010 Jul 27;107(30):13402-7. doi: 10.1073/pnas.1007394107. Epub 2010 Jul 12.

Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis.

Lázár-Molnár E[1], Chen B, Sweeney KA, Wang EJ, Liu W, Lin J, Porcelli SA, Almo SC, Nathenson SG, Jacobs WR Jr.

- Several observations of TB reactivation in patients treated with anti-PD-1 (without steroids!)

Clin Microbiol Infect. 2018 Mar;24(3):216-218. doi: 10.1016/j.cmi.2017.12.003. Epub 2017 Dec 18.

Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment.

Picchi H[1], Mateus C[2], Chouaid C[3], Besse B[4], Marabelle A[5], Michot JM[6], Champiat S[5], Voisin AL[7], Lambotte O[8].

Sci Transl Med. 2019 Jan 16;11(475). pii: eaat2702. doi: 10.1126/scitranslmed.aat2702.

Tuberculosis following PD-1 blockade for cancer immunotherapy.

Barber DL[1], Sakai S[2], Kudchadkar RR[3], Fling SP[4,5], Day TA[6], Vergara JA[6], Ashkin D[7], Cheng JH[8], Lundgren LM[5], Raabe VN[9], Kraft CS[10], Nieva JJ[8], Cheever MA[4,5], Nghiem PT[11], Sharon E[12].

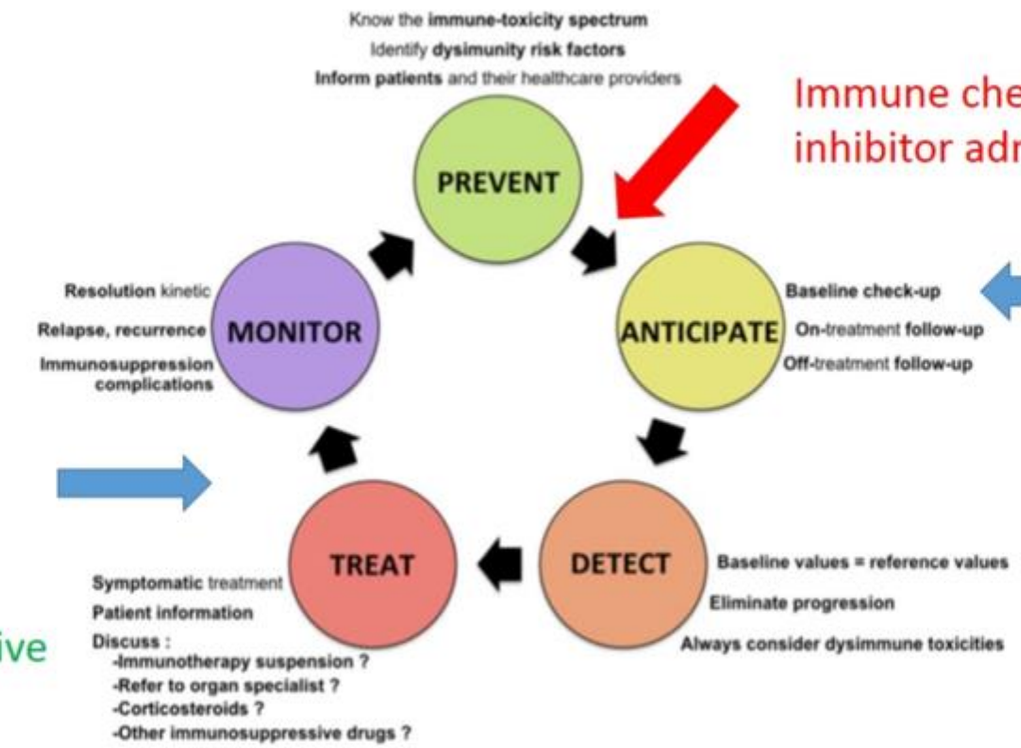
Risque infectieux lié à l'immunothérapie

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:17
HALL B

Infections in patients receiving immunotherapy in oncology



Immune checkpoint inhibitor administration

Infectious risks related to chronic infection? Minimal++

Infectious risks
YES related to steroids and immunosuppressive drugs

Champiat et al. Annals Oncol. 2015

Olivier Lambotte

Immune checkpoint inhibitors and infections

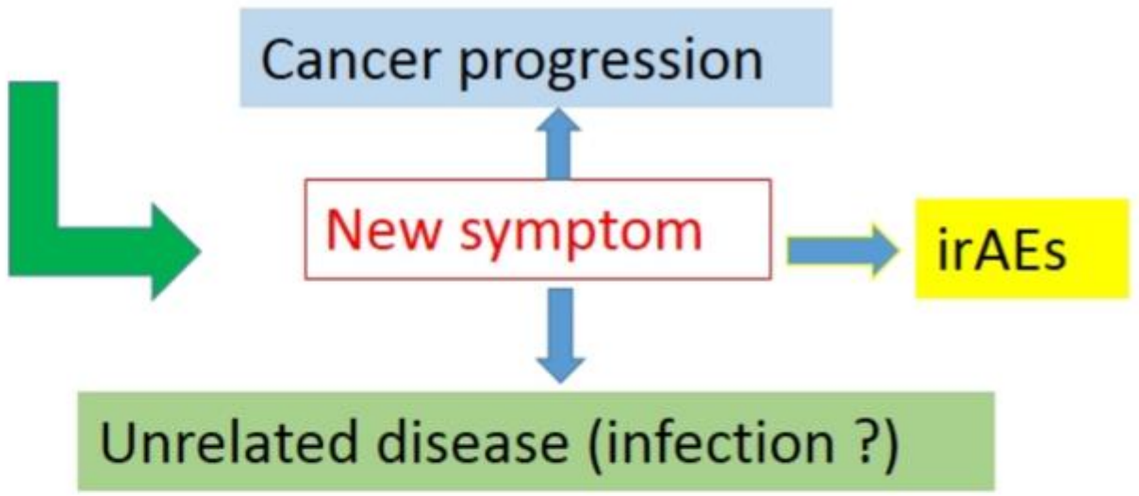
ECCMID

Amsterdam, Netherlands

ESCM

Be careful ! A new symptom in a patient treated with immune checkpoint inhibitor could be an infection rather than an irAE !

- Infections are differential diagnosis of irAEs (Kyi et al. J Immunother Cancer 2014, Pradere et al. Eur J Cancer 2017…)
  - CMV colitis or *Clostridium difficile* infection
  - Pulmonary aspergillosis, pneumocystosis, flu…
  - Hepatitis E
- A symptom = systematic investigations



Some recommendations:

Pneumocystis prophylaxis if prednisone ≥ 20mg/d ≥ 3 weeks

Look for an opportunistic infection if the patient's status worsens after the start of immunosuppressive treatment

What are the infectious risks for cancer patients treated with ICIs?

1. No intrinsic infectious risk related to the molecules (Redelman-Sidi G et al. Clin Microbiol Infect 2018)
2. The main risk is related to the use of steroids and immunosuppressants in immunocompromised patients with metastatic cancer
3. Is there a risk of Immune Reconstitution Syndrome in patients with chronic infection?

   = Exclusion in clinical trials of
   - Chronic viral hepatitis
   - HIV infection

Is a chronic viral infection is a contraindication for the use of immune checkpoint inhibitors?

- Hepatitis B and C: NO, but monitoring of liver enzymes, and better to have negative HBV DNA
- HIV : ? IRIS? NO!

J Thorac Oncol. 2018 Jul;13(7):1037-1042. doi: 10.1016/j.jtho.2018.03.031. Epub 2018 Apr 6.

Safety and Efficacy of PD-1 Inhibitors Among HIV-Positive Patients With Non-Small Cell Lung Cancer.

Ostios-Garcia L[1], Faig J[2], Leonardi GC[1], Adeni AE[1], Subegdjo SJ[1], Lydon CA[1], Rangachari D[2], Huberman MS[2], Sehgal K[2], Shea M[2], VanderLaan PA[3], Cheng MP[4], Marty FM[4], Hammond SP[4], Costa DB[2], Awad MM[5].

Ann Oncol. 2018 Apr 1;29(4):1065-1066. doi: 10.1093/annonc/mdx817.

PD-1 blockade in HIV-infected patients with lung cancer: a new challenge or already a strategy?

Lavolé A[1,2], Guihot A[3,4,5], Veyri M[6], Lambotte O[7,8,9,10], Autran B[3,4,5], Cloarec N[11], Le Garff G[12], Flament T[13], Cadranel J[1,2], Spano JP[6,14,15].

Optimisation pré-immunothérapie

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:18
HALL B

How to optimize the management of infections in patients who <u>will be treated / are treated</u> with immune checkpoint inhibitors ?

1. Perform HIV, HBV, HCV serologic testing for ALL cancer patients…

Ramsey et al. JAMA Oncol 2019

1. Get an IGRA for patients at risk for tuberculosis ? For all ?

2. Vaccinations allowed !!

- <u>Wijn DH et al. Eur J Cancer.</u> 2018 : a cohort study during two years

Influenza vaccination in patients with lung cancer receiving anti-programmed death receptor 1 immunotherapy <u>does not induce immune-related adverse events.</u>

Anti-PD-1 in vaccination optimization : a perspective ? … (<u>Pan E et al. Front Immunol.</u> 2018)

Olivier Lambotte

Immune checkpoint inhibitors and infections

ECCMID

Amsterdam, Netherlands
13 – 16 April 2019

ESCM

Optimisation des patients sous immunothérapie

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:19
Sunday, 14 April 2019
HALL B

How to optimize the management of infections in patients treated with immune checkpoint inhibitors ?

1. Set up a network of organ specialists and internists in Paris Sud University
2. Set up a dedicated meeting for discussion and management of difficult situations (national meeting iTOX, twice / month, conf call.)
3. Creation at G Roussy of a prospective registry of the irAEs: REISAMIC (2014)
4. Identification of a reference center at Paris Sud University
centre.immunotox.hups@aphp.fr

Olivier Lambotte

Immune checkpoint inhibitors and infections

Ann Oncol. 2016 Apr;27(4):559-74. doi: 10.1093/annonc/mdv623. Epub 2015 Dec 28.

Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper.

Champiat S[1], Lambotte O[2], Barreau E[3], Belkhir R[4], Berdelou A[5], Carbonnel F[6], Cauquil C[7], Chanson P[8], Collins M[9], Dercharch A[9], Edeline S[10], Faivre S[11], François H[9], Lazarovici J[12], Le Pavec J[13], De Martin E[14], Mateus C[15], Michot JM[16], Samuel D[14], Soria JC[1], Robert C[17], Eggermont A[18], Marabelle A[19].

Pembrolizumab & JC virus

Some exemples ?

JC Virus

2019

8 patients including to 2 HIV-infected
2 improvements
4 stable diseases
2 worsenings and deaths
1-3 infusions
Boost of JC-specific immune responses
2 irAEs (rash / flare of psoriasis)

ORIGINAL ARTICLE

Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy

Irene Cortese, M.D., Pawel Muranski, M.D., Yoshimi Enose-Akahata, Ph.D., Seung-Kwon Ha, D.V.M., Ph.D., Bryan Smith, M.D., MariaChiara Monaco, Ph.D., Caroline Ryschkewitsch, B.S., Eugene O. Major, Ph.D., Joan Ohayon, M.S.N., Matthew K. Schindler, M.D., Ph.D., Erin Beck, M.D., Ph.D., Lauren B. Reoma, M.D., Steve Jacobson, Ph.D., Daniel S. Reich, M.D., Ph.D., and Avindra Nath, M.D.

Risque d'IFI sous immunothérapie

Immune Checkpoint Inhibitors
IFI treatment

- CTLA-4
  - Aspergillosis: higher CTLA-4 expression in CD4+ in mice infected with *A. fumigatus*
  - Cryptococcosis: CTLA-4 blockade improved survival in mice with cryptococcosis
- PD-1
  - Histoplasmosis
    - PD-1 deficient mice resistant to histoplasmosis
    - PD-1 blockade increased survival of lethally infected mice
  - Candidiasis
    - Anti-PD-1 or anti-CTLA-4 treatment improved survival in mice with candidiasis
    - Higher PD-1 levels on CD4+ and CD8+ in patients with *C. albicans* sepsis

Anti-PD1/PD-L1 pour le sepsis ?

Some exemples ?

Sepsis

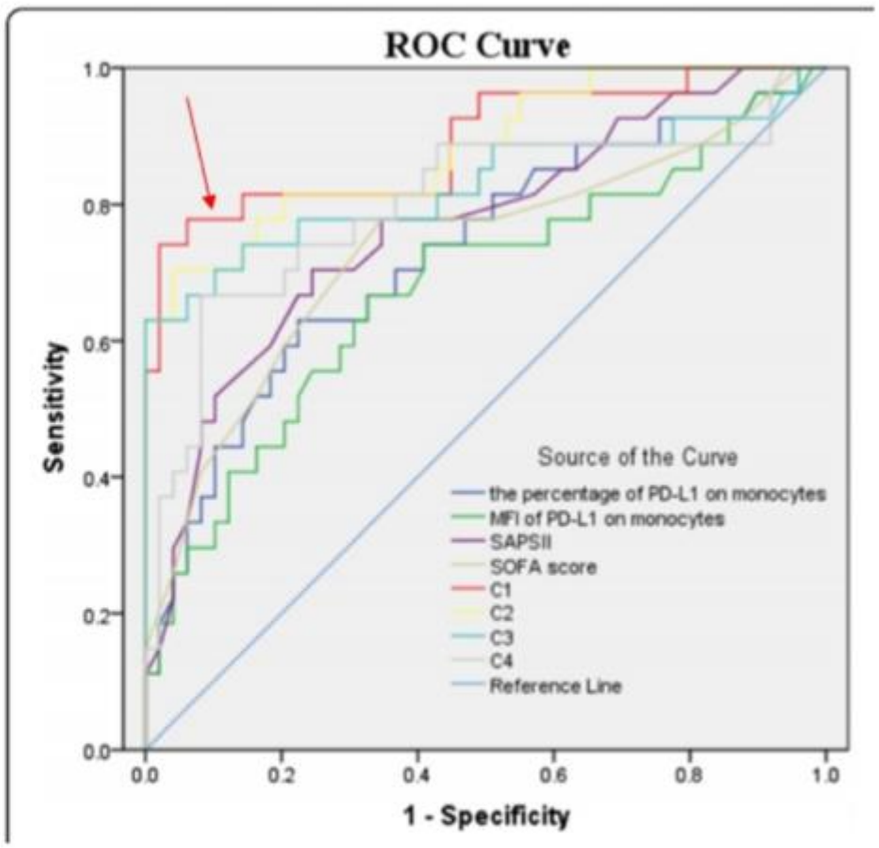
Involvement of the PD-1/PD-L1 pathway to limit the inflammation but could favor a secondary phase of immunodepression

Shao *et al. Critical Care* (2016) 20:124
DOI 10.1186/s13054-016-1301-x

Critical Care

RESEARCH Open Access

Monocyte programmed death ligand-1 expression after 3–4 days of sepsis is associated with risk stratification and mortality in septic patients: a prospective cohort study



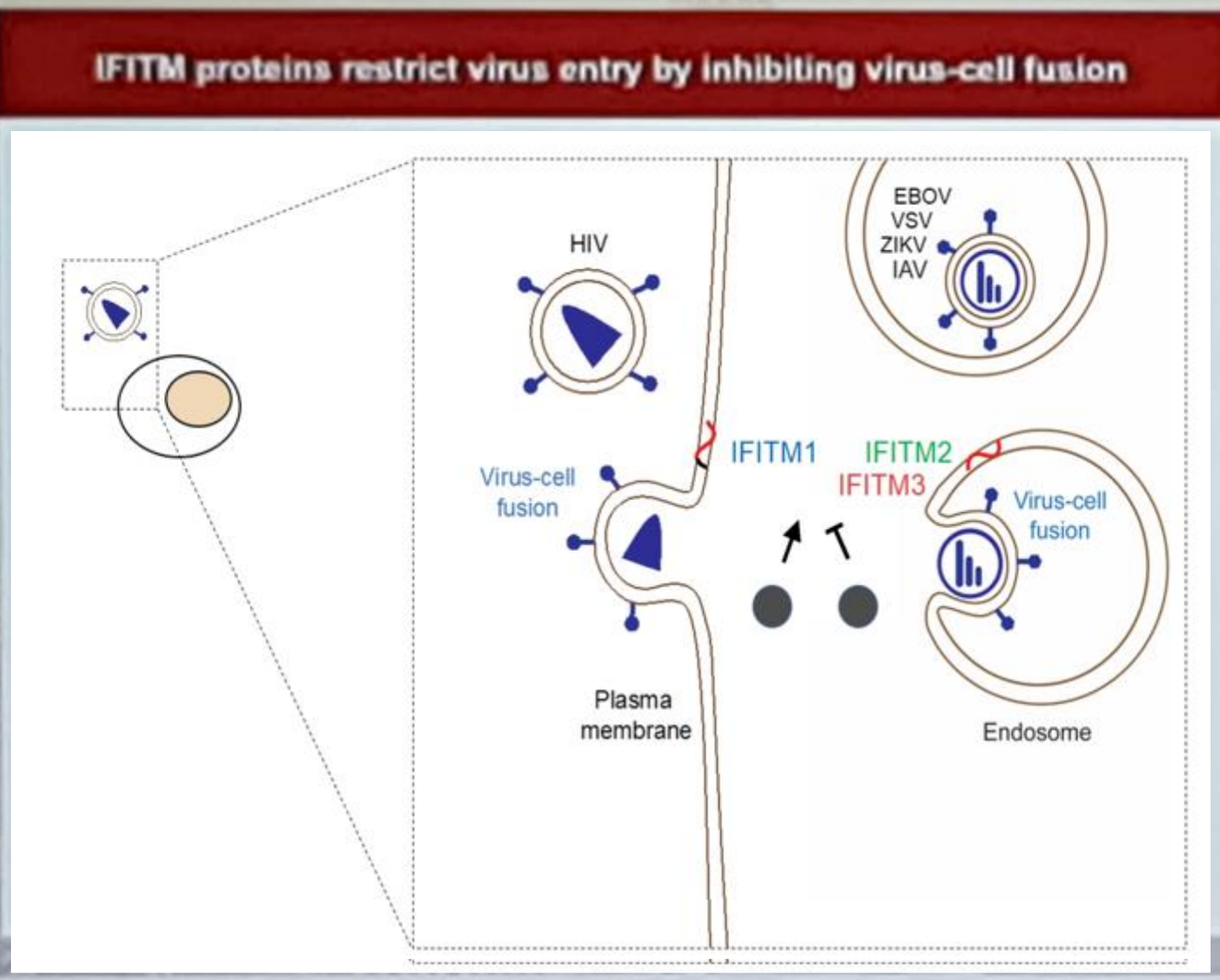
C1= % PD-L1 monocytes + SAPSII

Inhibiteurs de mTOR versus infections virales : mécanisme

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

11:36
HALL B



Alex Compton

mTOR inhibitors as broad-spectrum therapeutics: relevance for infection

Inhibiteurs de mTOR versus infections virales

11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

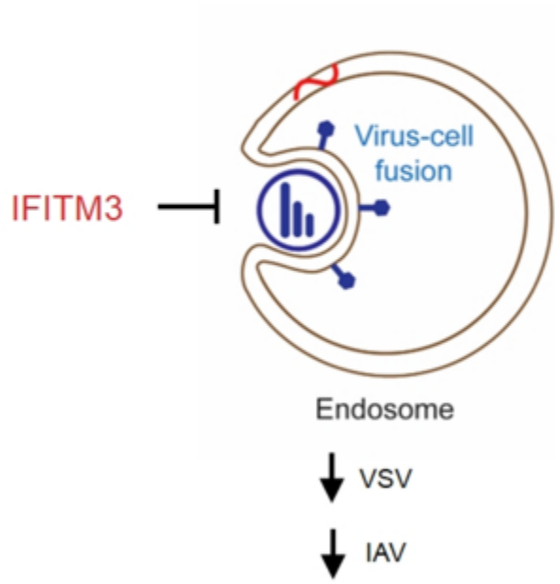
Chairs: Isabel Ruiz-Camps
David van Duin

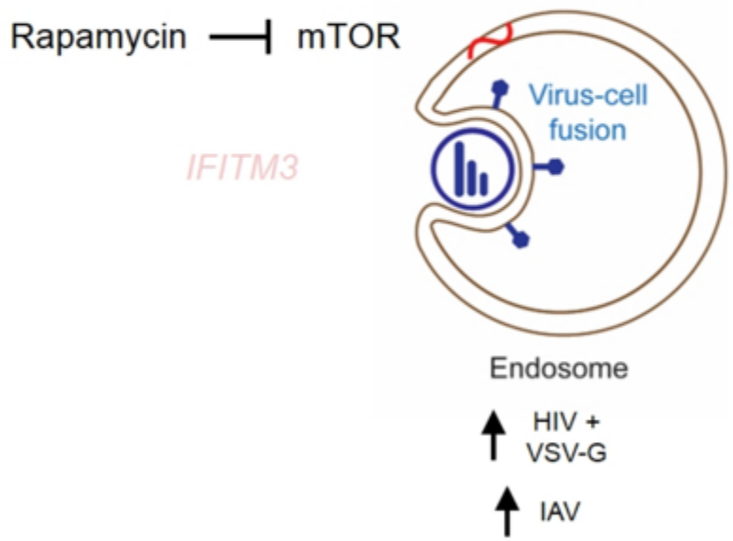
11:41
Sunday, 14 April 2019
HALL B

The mTOR pathway as novel regulator of IFITM3

mTOR inhibitors lower an intrinsic barrier to virus infection mediated by IFITM3

Guoli Shi[a], Stosh Ozog[b], Bruce E. Torbett[b], and Alex A. Compton[a,1]



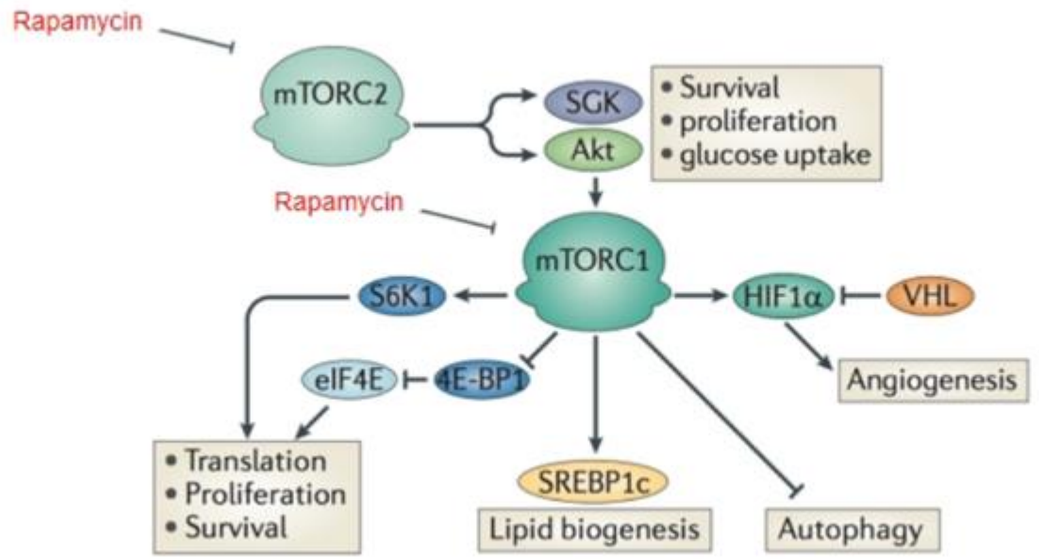


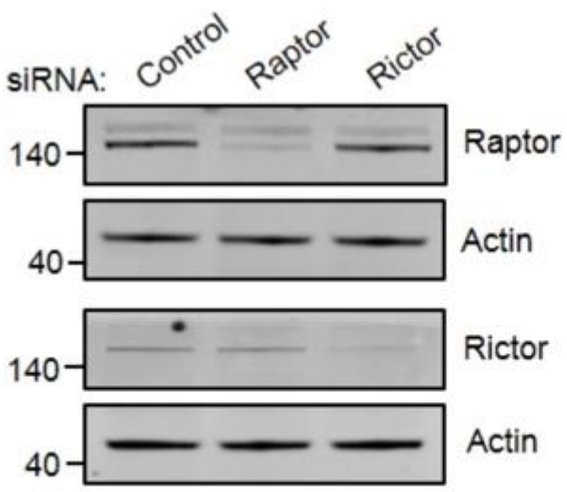
Shi, Ozog, Torbett, and Compton. *PNAS*, 2018

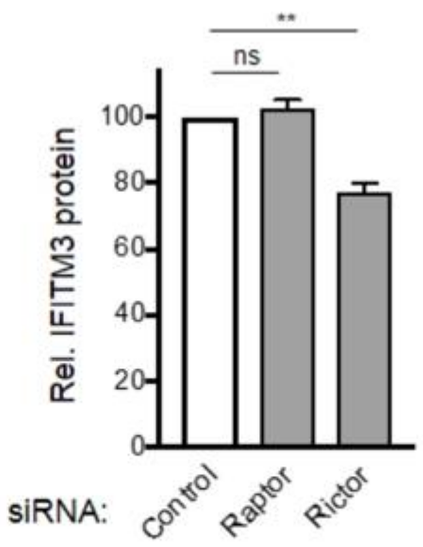
Alex Compton

mTOR inhibitors as broad-spectrum therapeutics: relevance for infection

mTORC2 inhibition results in IFITM3 degradation



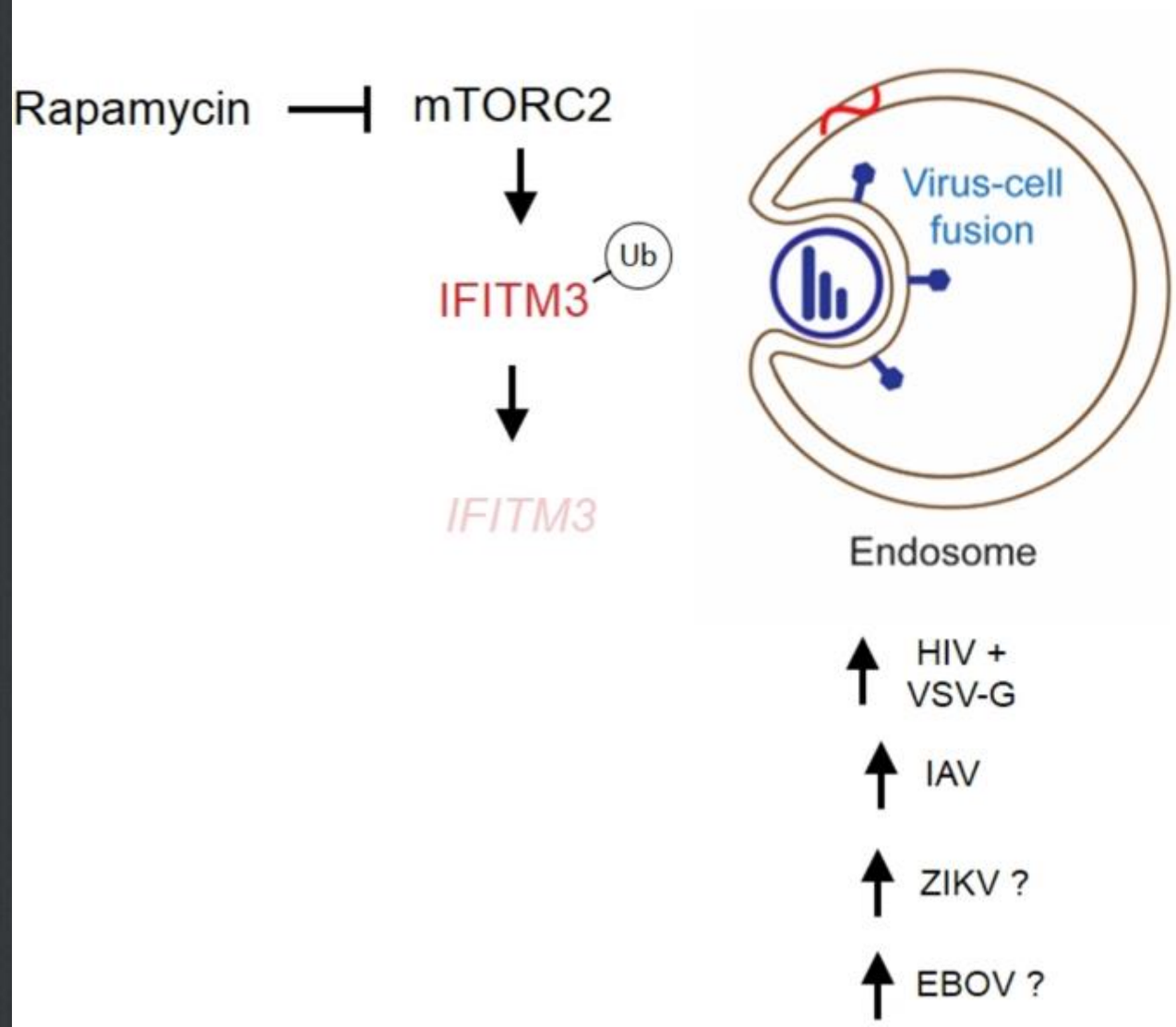




11:00 - 12:00
Possible impact of new immunomodulators on infection and infection management

Chairs: Isabel Ruiz-Camps
David van Duin

The mTOR pathway as novel regulator of virus entry



Shi, Ozog, Torbett, and Compton. *PNAS*, 2018

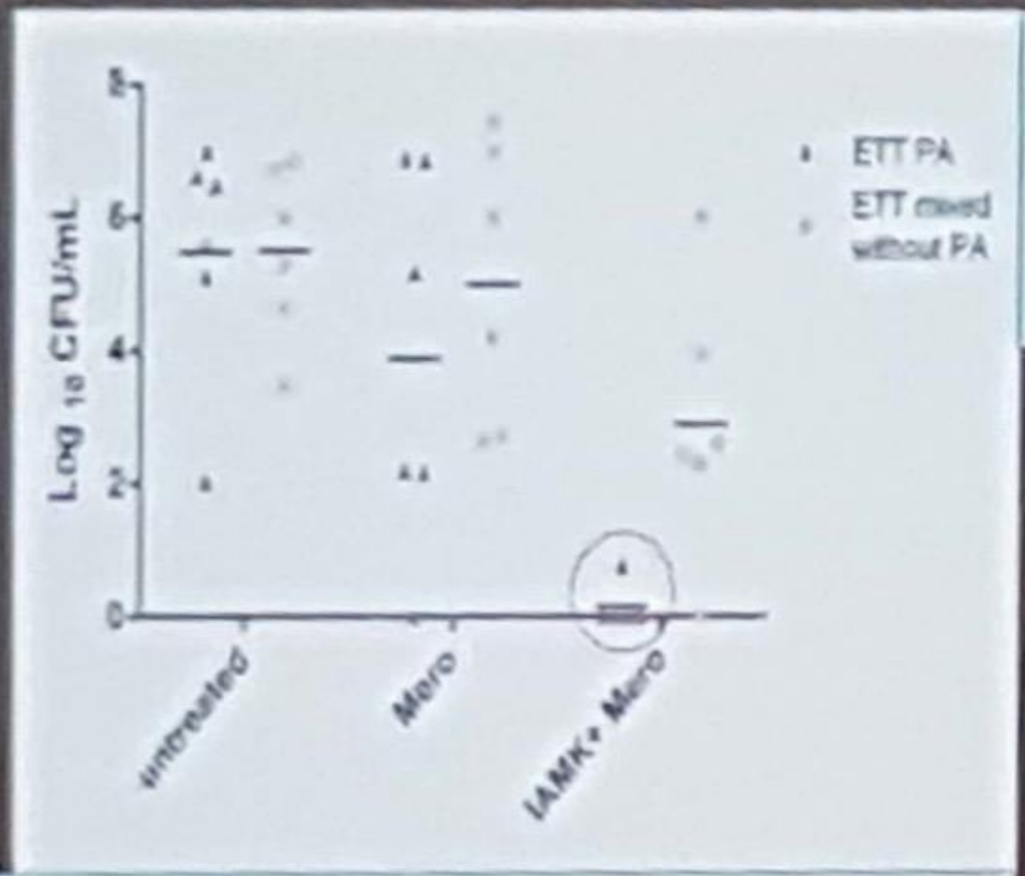
Impact des ATB sur le biofilm de la sonde d'IOT

16:00 - 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Dilenta Pezzani

16:40
HALL N

What about Biofilm?



L Fernandez et al. Poster ECCMID 2019

ETT PA: Pseudomonas aeruginosa endotracheal tube growth

Antoni Torres

When pharmacokinetics and pharmacodynamics should be used for the antibiotic management of hospital-acquired pneumonias?

Intérêt des ATB inhalés ?

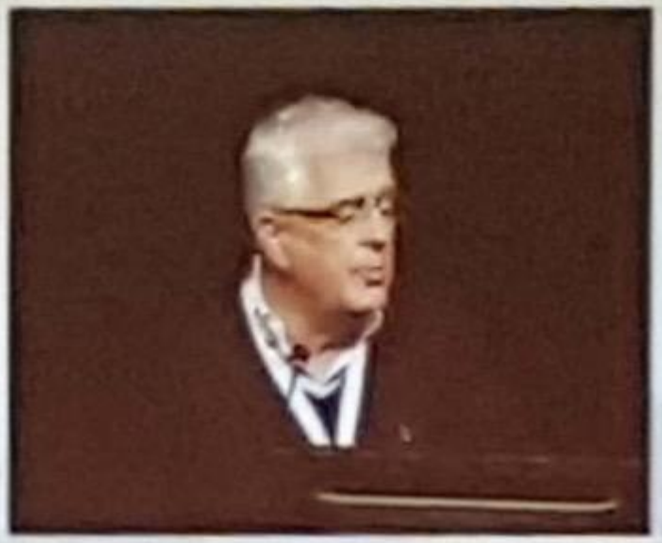
16:00 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Diletta Pezzani

16:41
HALL N

Conclusions

- Nebulized antibiotics are frequently administered in mechanically ventilated patients
- However:
  - The two RCT in Gram Negative VAP have resulted negative
  - They seem to decrease upper but not distal airway bacterial burden. Consequently they can b effective to treat VAT
- The role in MDR/XDR VAP needs to be further explored for eficacy and for prevention of relapses



Antoni Torres

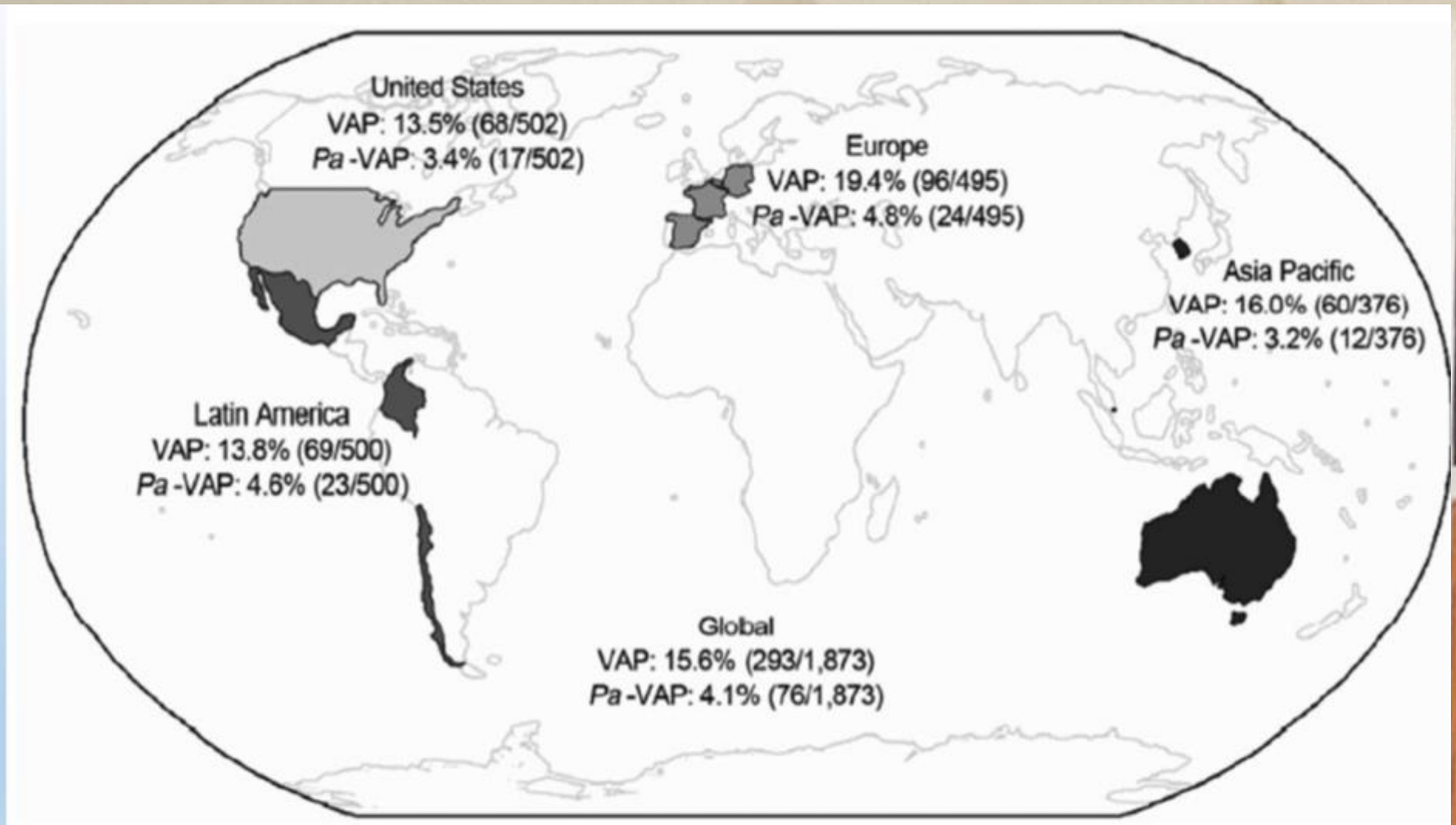
When pharmacokinetics and pharmacodynamics should be used for the antibiotic management of hospital-acquired pneumonias?

PAVM à *P. aeruginosa* : épidémiologie

16:00 - 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Diletta Pezzani

17:04
HALL N



Mark L. Metersky

Can Pseudomonas ventilator-associated pneumonia be treated with 7 days of antibiotic therapy?

Kollef M, Crit Care Med, 2014

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PAVM à *P. aeruginosa*

16:00 - 18:30
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Dilerto Pezzani

17:04
HALL N

Pseudomonas VAP

- Mortality common
  - Attributable mortality recently estimated at 20%
  - Seems to be due to prolongation of ICU stay, not direct cause of death

    Von Cube, M, Intensive Care Medicine, 2018
  - Worse than estimated 13% attributable mortality due to VAP overall

    Melsen W, Lancet Infect Dis 2013
- Recurrence common
  - 19.7% of 314 had at least one recurrence

    Planquette B, AJRCCM, 2013

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Mark L. Metersky

Can Pseudomonas ventilator-associated pneumonia be treated with 7 days of antibiotic therapy?

16:00 - 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Diletta Pezzani

17:19
HALL N

What about Acinetobacter?

- One retrospective cohort study, multivariate analysis
  - Included VAP, VAT, colonization

Table 3
Variables associated with ICU mortality – multivariate analysis.

Variable	ICU non-survivors	ICU survivors	Multivariate analysis: OR (95% CI)	P
VAP	53 (52.5%)	17 (32.7%)	0.9 (0.91–1.55)	0.151
Monotherapy treatment	31 (30.7%)	19 (36.5%)	0.97 (0.74–1.23)	0.824
Bacteremia at diagnosis	11 (10.9%)	1 (1.9%)	1.0 (0.71–1.37)	0.836
Adequate empirical therapy	29/86 (33.7%)	7/43 (16.3%)	1.0 (0.80–1.32)	0.468
SOFA score at diagnosis	8.6 (3.7)	5.7 (2.6)	1.06 (1.03–1.09)	0.001
Time of treatment			0.98 (0.96–1.01)	0.160

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da Silveira F, J Crit Care, 2019

Comment améliorer le pronostic des PAVM à pyo ?

16:00 - 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Grietta Rezzani

17:20
HALL N

How can outcomes be improved?

- Treatment failure does not appear to be due to delay in appropriate therapy in most cases
- Not associated with dual therapy (except XDR-PA)

Planquette B, AJRCCM, 2013
Deconinck L, Infectious Diseases, 2017

- Not improved by aerosolized antibiotics
- Not improved by prolonged course of antibiotics

- **Removes targets for improving outcome**

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Mark L. Metersky

Can Pseudomonas ventilator-associated pneumonia be treated with 7 days of antibiotic therapy?

Pas d'intérêt à une bithérapie ou un ttt plus long

16:00 18:00
Controversies in the management of hospital-acquired pneumonia

Chairs: Ignacio Martin-Loeches
Maria Diletta Pezzani

17:23
HALL N

Summary

- Pseudomonas VAP common, associated with poor outcomes
- Dual antibiotic therapy not associated with improved outcomes
- **Longer courses of therapy not associated with improved outcomes**
- Adjunctive treatment with aerosolized antibiotics, vaccines have not improved outcomes

- Currently, VAP prevention strategies are the most important interventions

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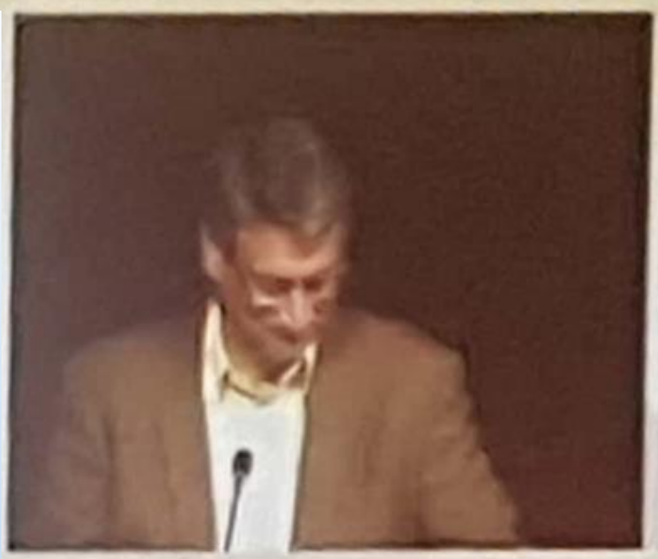


Mark L. Metersky

Can Pseudomonas ventilator-associated pneumonia be treated with 7 days of antibiotic therapy?

Maladie émergente :
Variole du singe

11:00 - 12:00
Monkeypox: management issues of an emerging viral infection

Chairs: Francesco Castelli
Marc Van Ranst

11:06
Monday, 15 April 2019
HALL E

What is Monkeypox?

Viral zoonotic disease similar but milder than small pox

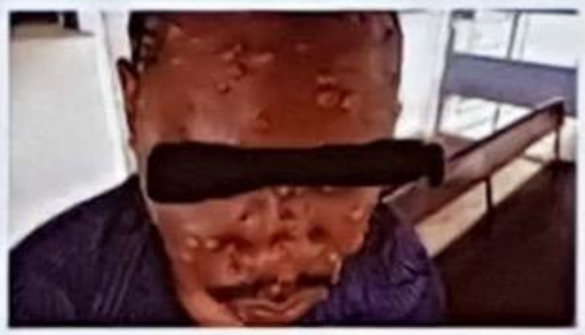
Primary infection from animals with secondary human to human transmission

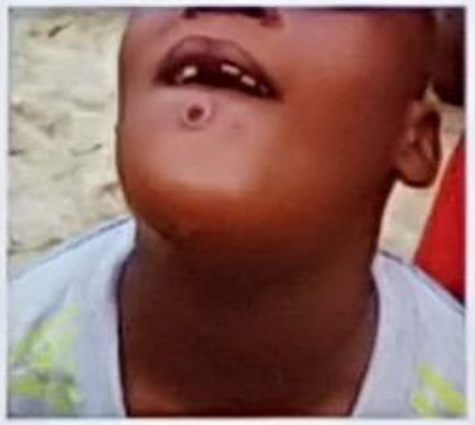
Two genetic clades of the monkeypox virus have been characterized: West African and Central African

Typical lesions - centrifugal distribution; on palms of the hands/ soles of feet

Lymphadenopathy is common

Appears more severe than it actually is





Chikwe Ihekweazu

Lessons from African monkeypox outbreaks

15/04/2019 | NIGERIA CENTRE FOR DISEASE CONTROL | 6

High Consequence Infectious Diseases (HCID)

00 - 12:00
nkeypox: management issues of an emerging viral infection

Chairs: Francesco Castelli
Marc Van Ranst

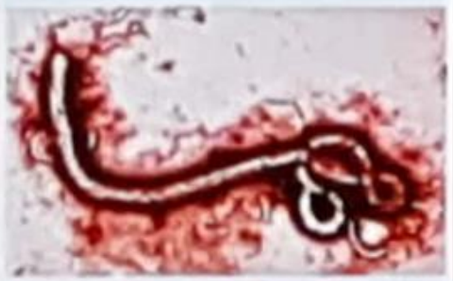
11:30
Monday, 15 April 2019
HALL E

Examples: Contact HCIDs

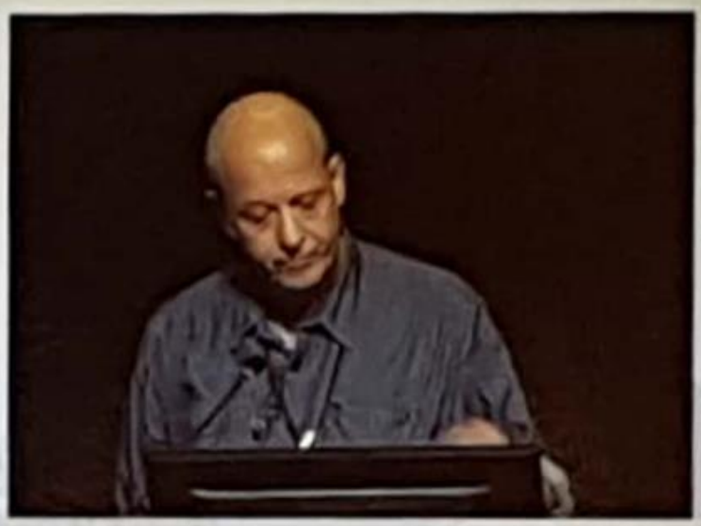
Also known as viral haemorrhagic fever (VHF):

- **Crimean-Congo haemorrhagic fever (CCHF)**
- **Ebola virus disease**
- **Lassa fever**
- **Marburg virus disease**

- Lujo virus disease
- Argentinian and Bolivian haemorrhagic fever
- Severe fever with thrombocytopaenic syndrome



Where we all make a difference



Mike Beadsworth

Imported monkeypox

Traitement de la variole du singe

11:00 - 12:00
Monkeypox: management issues of an emerging viral infection

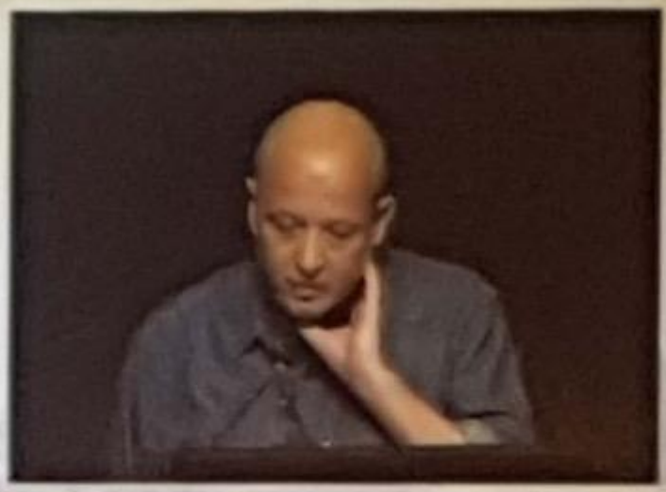
Chairs: Francesco Castelli
Marc Van Ranst

11:46
Monday, 15 April 2019
HALL E

Experimental treatments

- **Tecovirimat (TPoxx)**
  - Pan-orthopox p37 inhibitor - prevents virus from leaving an infected cell
  - Prevents death in lethal challenge monkeypox and rabbitpox animal models
  - Phase I trial – well tolerated, no SAEs - FDA approved for smallpox
- **Brincidofivir**
  - Lipid conjugate prodrug of cidofivir – oral; less renal toxicity
  - Active *in vitro* against orthopox viruses, CMV, adenovirus, BK virus, HSV
  - Survival advantage in lethal rabbitpox model, even with delayed treatment
  - Phase I trials >1000 subjects; Phase III trials for CMV in STC patients (failed)
  - Ongoing trials for adenovirus
  - Increased ALT/AST common; diarrhoea with cumulative exposure

Where we all make a difference



Mike Beadsworth

Imported monkeypox

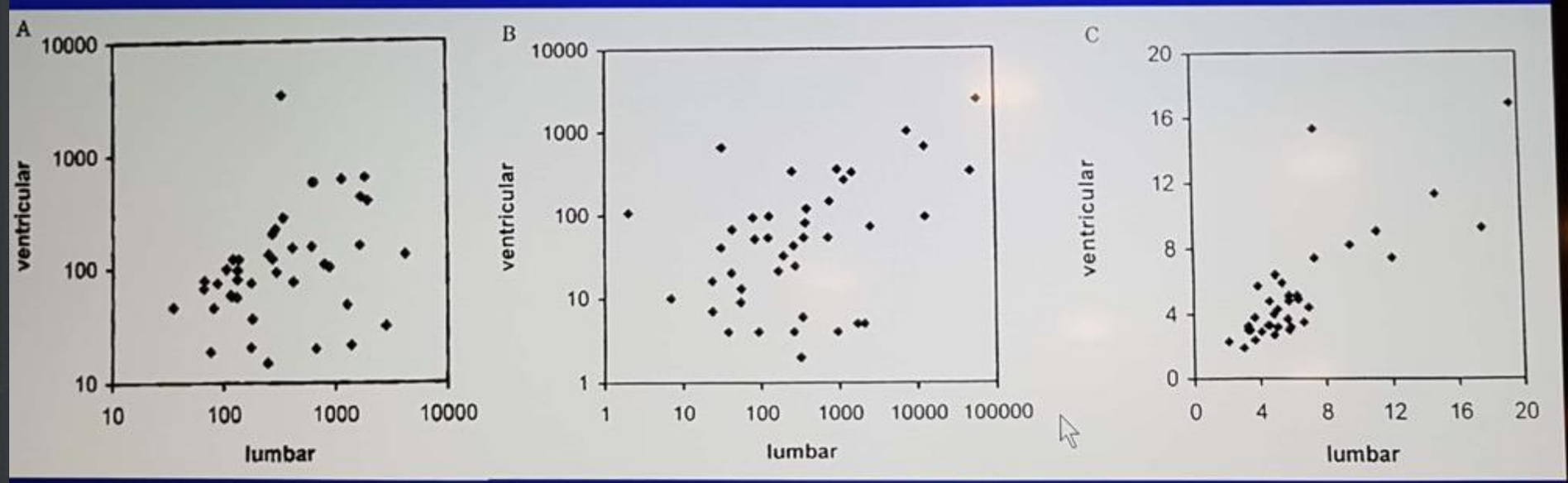
29th ECCMID ESCMID

Paramètres du LCR

CSF space - neither in health nor during infections a homogeneous compartment

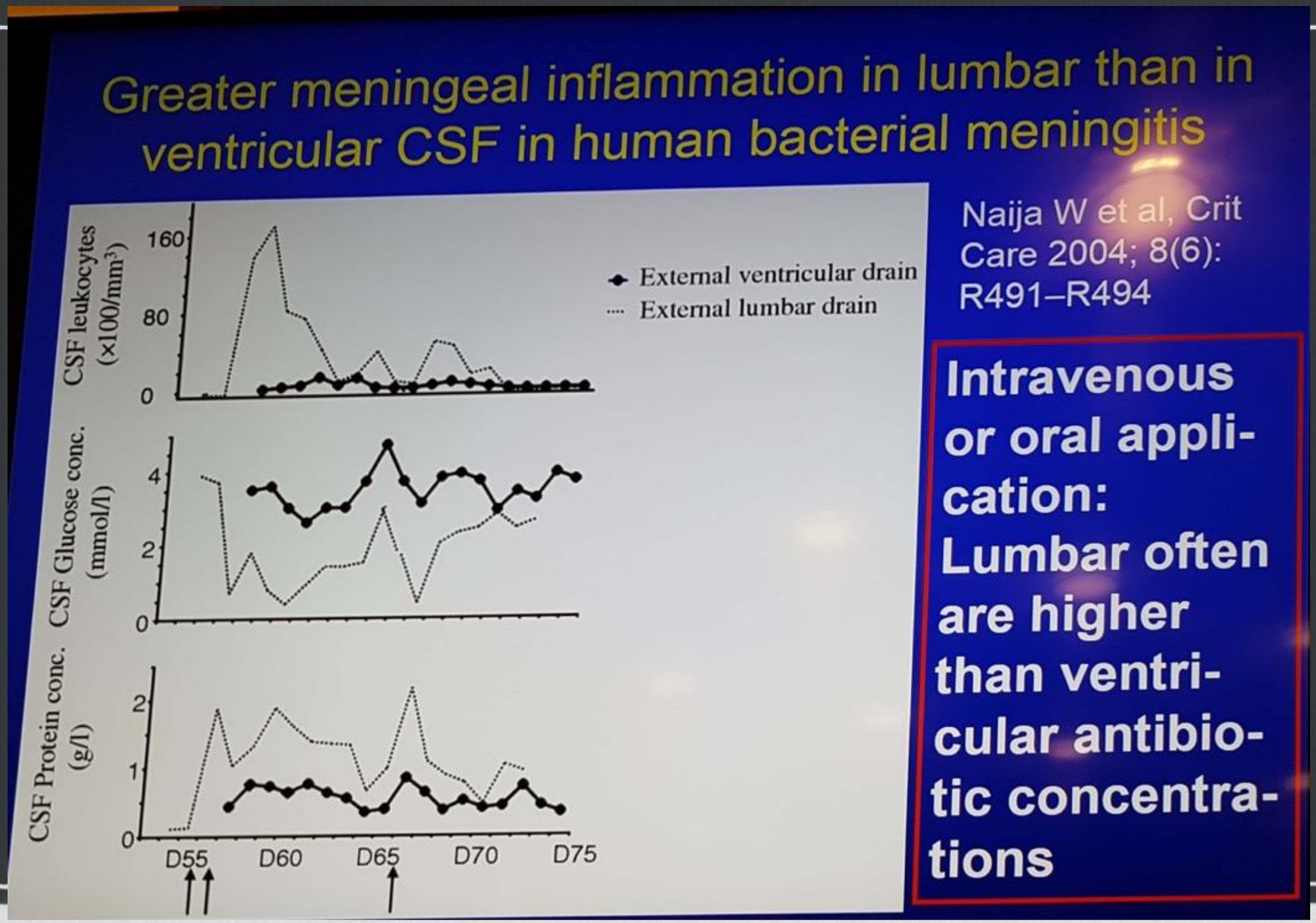
Gerber J et al, Neurology 51 (1998) 1710-1714

Parameters in ventricular and lumbar CSF during CNS infections



Protein (mg/l) Leukocytes (μl^{-1}) Lactate (mmol/l)

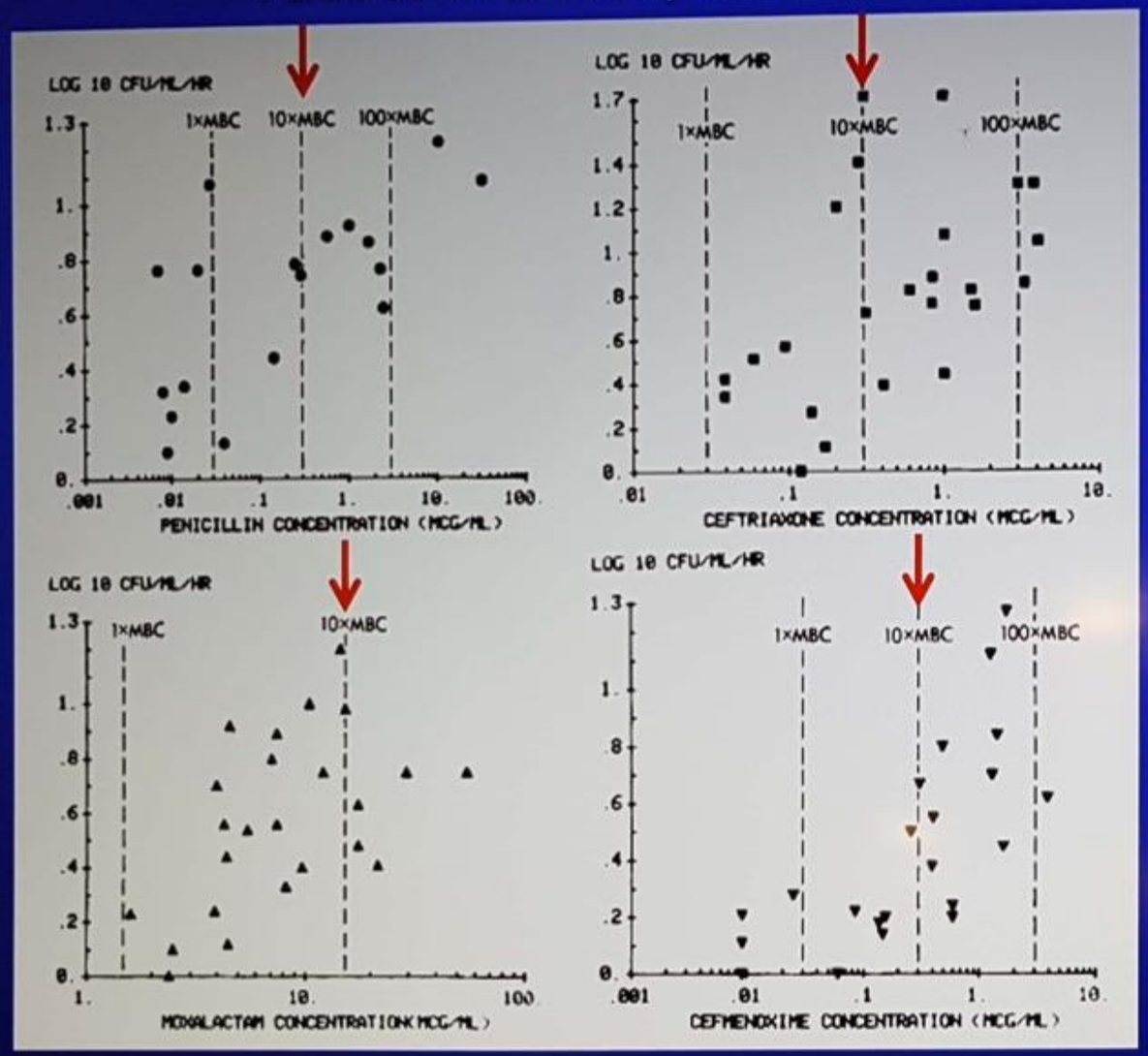
PK/PD LCR


Greater meningeal inflammation in lumbar than in ventricular CSF in human bacterial meningitis
CSF leukocytes (×100/mm³)
160
80
0
External ventricular drain
External lumbar drain
CSF Glucose conc. (mmol/l)
4
2
0
CSF Protein conc. (g/l)
2
1
0
D55
D60
D65
D70
D75
Naija W et al, Crit Care 2004; 8(6): R491–R494
Intravenous or oral application: Lumbar often are higher than ventricular antibiotic concentrations

PK/PD LCR (2)

„Classical“ concept

Täuber MG et al, J Infect Dis 1984; 149:568-74



Antibacterials in CSF less active than in broth or plasma

-lower pH

-poorer nutritional supply

-reduced replication

“CSF drug concentrations of greater than or equal to 30 times the MBC against the infecting organism”

MIC = minimal inhibitory concentration; MBC = minimal bactericidal concentration

PK/PD LCR (3)

At steady state, plasma (or free plasma) and CSF concentrations often are not equal: ceftazidime and ceftriaxone distribution in cerebrospinal fluid and cerebral extracellular space in rats by microdialysis (no meningitis)

Granero L et al., Antimicrob Agents Chemother 1995;39:2728-31

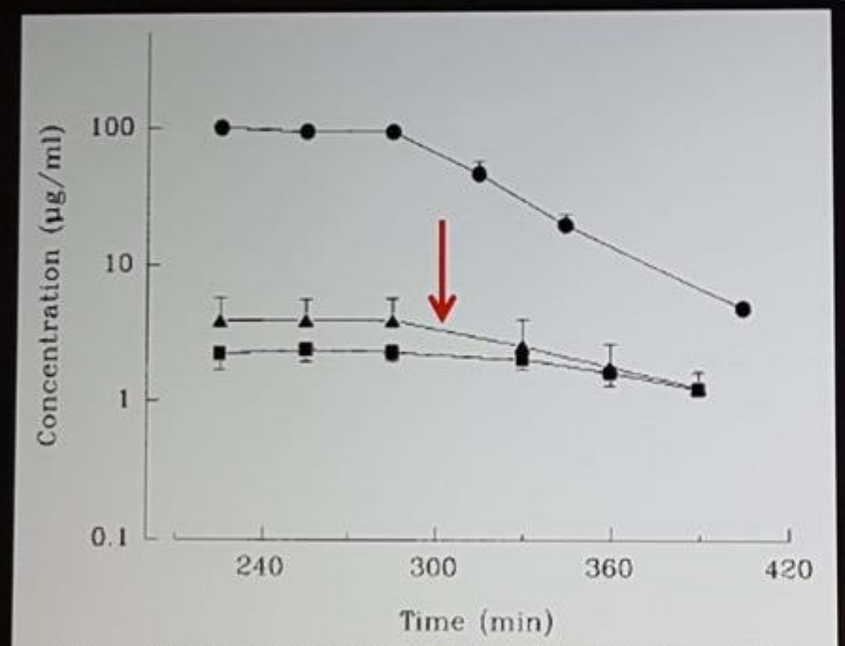


FIG. 1. Mean levels and standard deviations of CFZ in plasma (●), the extracellular space of the striatum (■), and the CSF of the lateral ventricle (▲) after administration of a constant-rate intravenous infusion of 18 mg/h to rats.

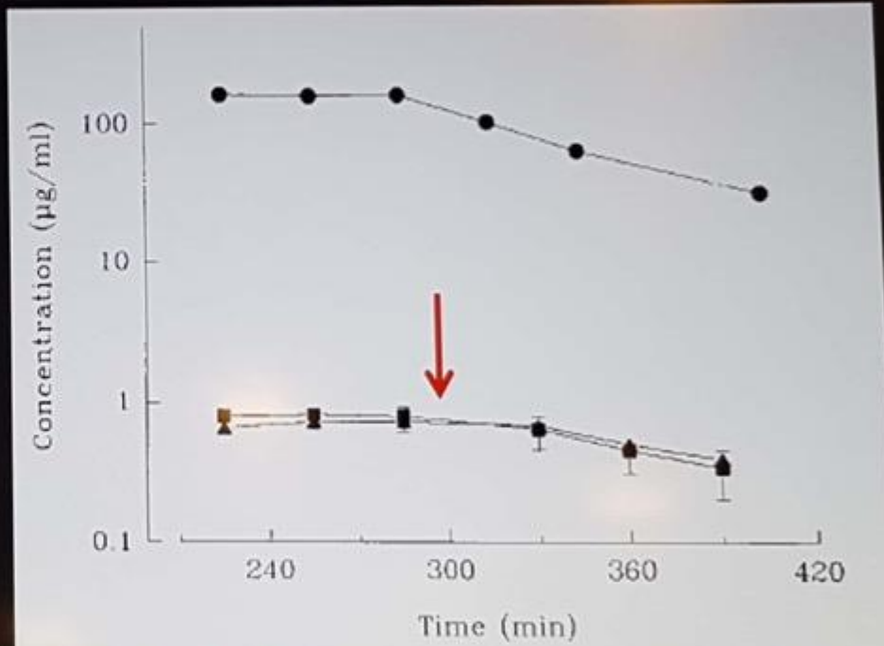


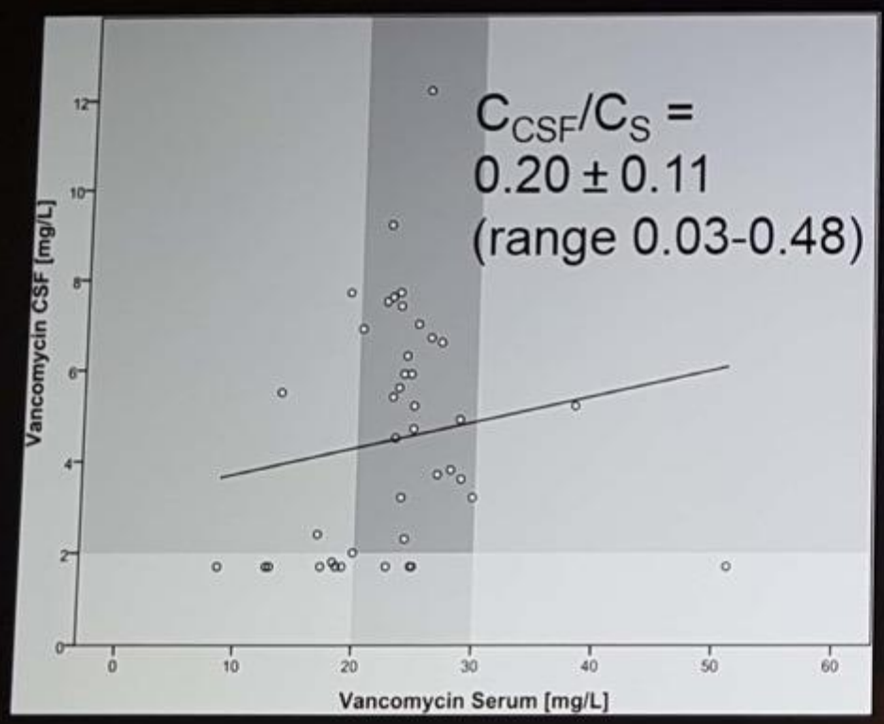
FIG. 2. Mean levels and standard deviations of CFX in plasma (●), the extracellular space of the striatum (■), and the CSF of the lateral ventricle (▲) after administration of a constant-rate intravenous infusion of 18 mg/h to rats.

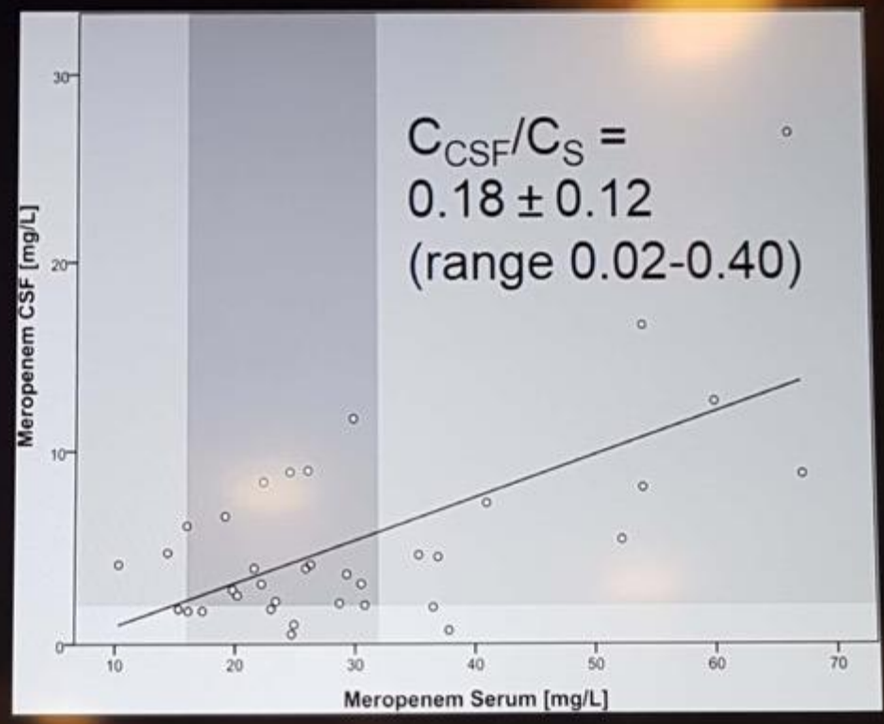
Steady state after 210min, i.v.-infusion stopped at 300min

PK/PD LCR (4)

Intrathecal penetration of meropenem and vancomycin administered by continuous infusion in 22 patients suffering from ventriculitis

Mader MM et al, Acta Neurochir 2018;160(11):2099-2105





Repeated sampling, retrospective analysis

Vancomycin started with a dose of 30 mg/kg/day (initial bolus of 30 mg/kg), target serum concentrations 20 to 30 mg/L.

Meropenem started at a dose of 6 g/day after an initial bolus of 1 g over 30 min, target serum concentrations 16 - 32 mg/L.

PK/PD LCR : physiologie

Why are the concentrations of many drugs lower in CSF than in serum?

- $CL_{in} = CL_{diff}$
- $CL_{out} = CL_{diff} + CL_{bulk}$

$\longrightarrow$ $CL_{out} = CL_{in} + CL_{bulk}$

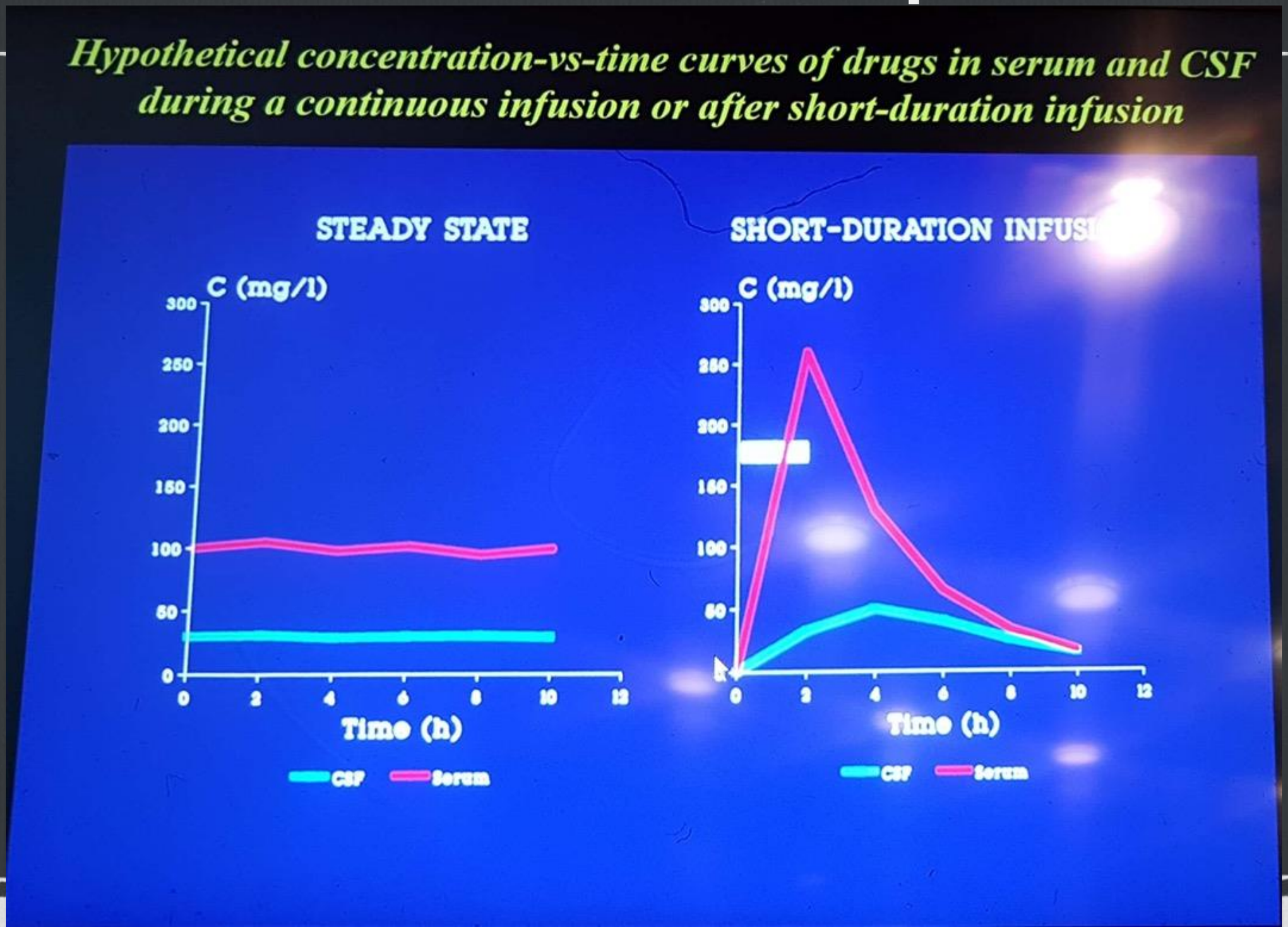
Hydrophilic and/or high molecular mass:

$CL_{bulk} >> CL_{diff}$ $\longrightarrow$ $C_{CSF}/C_{Serum,\ free} << 1$

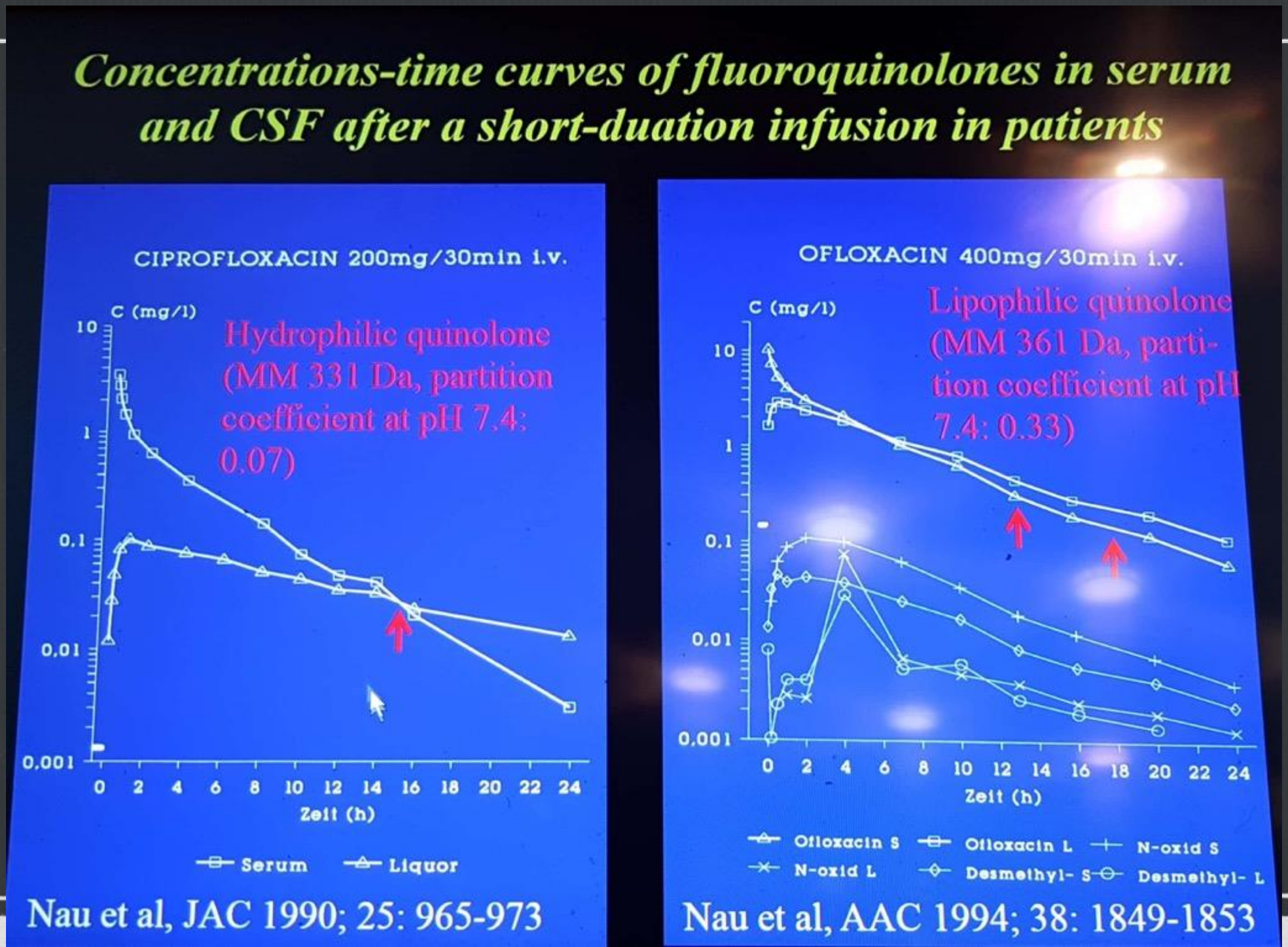
Lipophilic and/or low molecular mass:

$CL_{bulk} << CL_{diff}$ $\longrightarrow$ $C_{CSF}/C_{Serum,free} = 1$

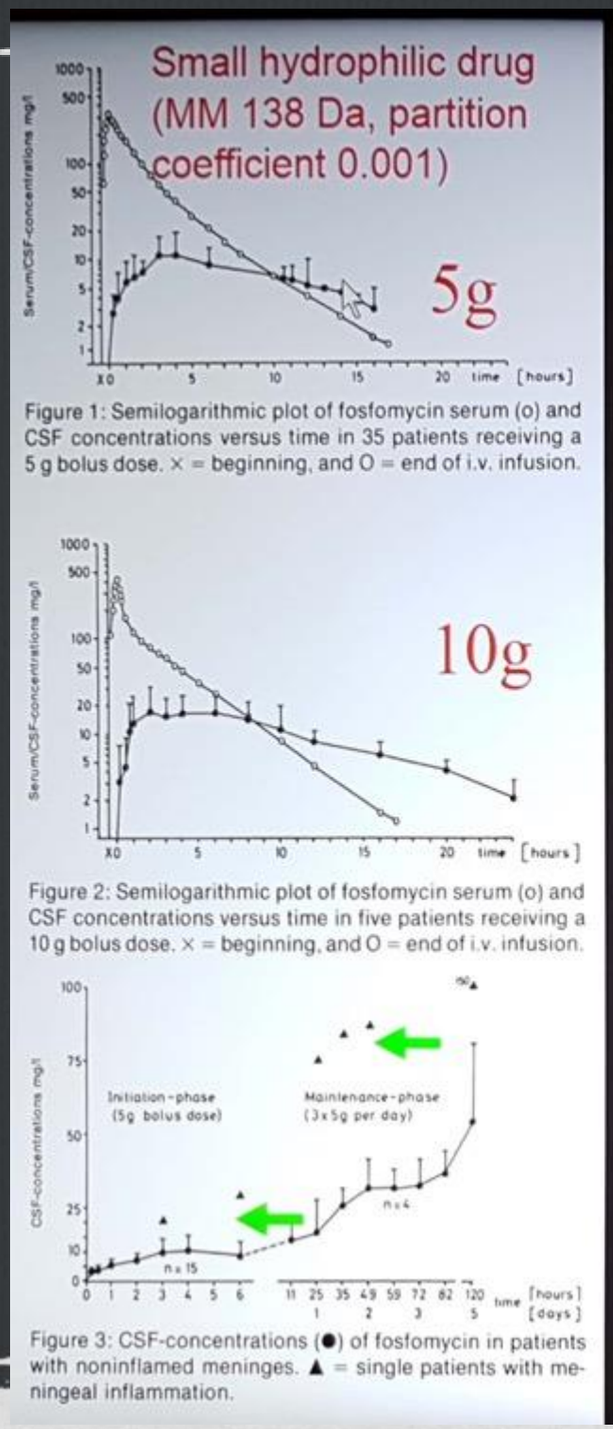
PK/PD LCR (5) : selon les antibiotiques



PK/PD LCR des fluoroquinolones



PK/PD LCR de la Fosfomycine



Hydrophilic small molecule: concentration-time curves of fosfomycin (MM 138.1 Da) in serum and CSF after a short-duration infusion in patients without meningitis

	C_{maxCSF}	AUC_{CSF}/AUC_S
5g	11.6mg/l	**0.092**
10g	17.7mg/l	**0.138**

← Single patients with meningitis

Kühnen E et al, Infection 1987; 15: 422-4

PK/PD LCR du Linezolide

Lipophilic small molecule: Pharmacokinetiks of linezolid (MM 337 Da, partition coefficient 2.7) in serum and CSF in patients with Staphylococcus spp. ventriculitis

Dosing: 2 x 600mg linezolid/d

C_{maxS} after the first dose 12.4 ± 4.2mg/l

C_{maxCSF} after the first dose 6.6 ± 1.7mg/l

Steady State in serum and CSF after 5th dose

AUC_{CSF}/AUC_S, after first dose 1.0 ± 0.3

AUC_{CSF}/AUC_S, steady state 0.8 ± 0.3

Beer et al, AAC 2007; 51: 379-82

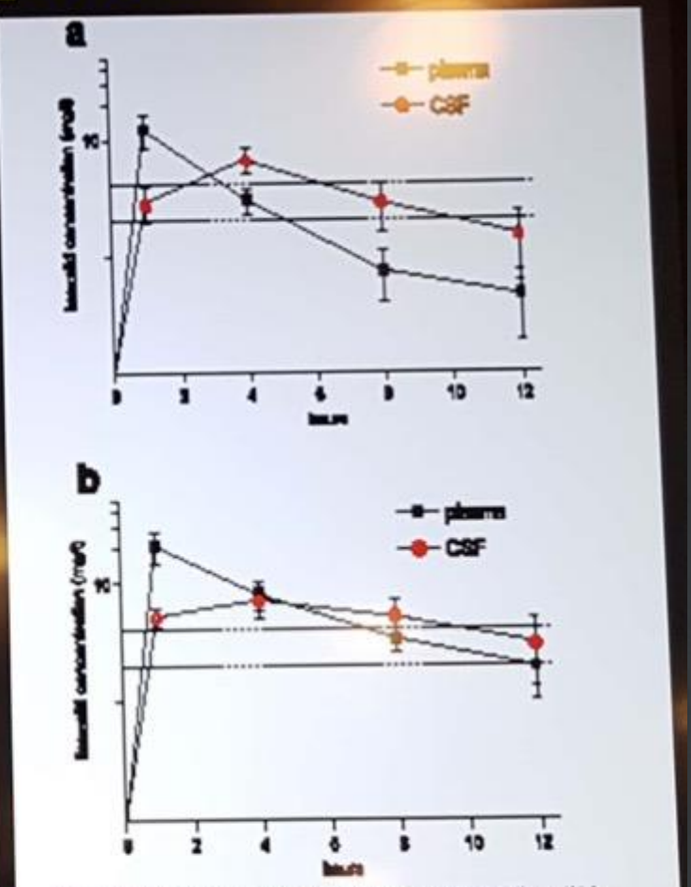
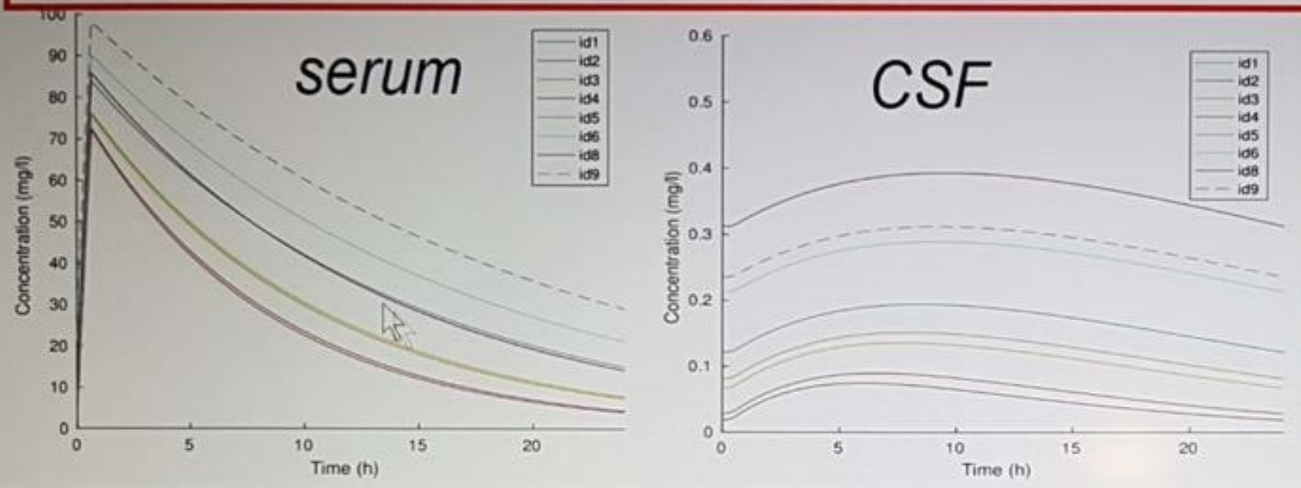


FIG. 1. Time-concentration curves (means ± SDs) of linezolid in plasma and CSF. (a) Profile after administration of a single intravenous dose of 600 mg ($n = 5$). (b) Profile after multiple intravenous doses (600 mg twice daily; $n = 5$). The dotted horizontal lines represent MICs (2 and 4 mg/liter) for susceptible pathogens.

PK/PD LCR de la Daptomycine

Daptomycin pharmacokinetics in nine patients with external ventricular drainage and healthcare-associated meningitis (10 mg/kg daptomycin i.v.)



Supplementary Figures 1 & 2: Estimated concentrations in plasma and CSF for each patient versus time

Table 2 Main pharmacokinetic parameters of daptomycin in plasma (compartment 1) and CSF (compartment 2)

Patients	PLASMA				CSF				CSF/serum ratio	
	AUC (h x mg/L)	C_{max} (mg/L)	t_{max} (H)	$T_{1/2}$ (h)	AUC (h x mg/L)	C_{max} (mg/L)	t_{max} (h)	$T_{1/2}$ (h)	AUC (%)	C_{max} (%)
1	965.9	83.87	0.67	9.38	4.00	0.19	8.60	7.15	0.41	0.23
2	574.7	72.15	0.67	5.58	1.51	0.09	6.74	4.54	0.26	0.12
3	728.9	76.36	0.67	7.08	2.61	0.14	7.67	6.17	0.35	0.18
4	590.7	72.55	0.67	5.74	1.17	0.08	6.04	3.43	0.20	0.10
5	713.4	75.91	0.67	6.93	2.98	0.15	7.90	7.21	0.42	0.20
6	1148.7	90.21	0.67	11.16	6.27	0.29	9.30	9.41	0.55	0.32
8	962.7	85.92	0.67	8.98	8.73	0.39	9.54	15.64	0.91	0.46
9	1366.3	98.15	0.67	13.27	6.81	0.31	9.30	8.60	0.50	0.32
Mean	881.4	81.89	0.67	8.51	4.26	0.21	8.14	7.77	0.45	0.24
SD	280.4	9.28		2.71	2.73	0.11	1.28	3.74	0.22	0.12

The AUC and C_{max} ratio values are also presented, suggesting a highly limited passage of the drug from plasma to the liquor

AUC area under the curve, *CSF* cerebrospinal fluid, C_{max} highest concentration, t_{max} time to peak

Piva S et al, Neurocrit Care 2019, Jan 3

PK/PD LCR vs BMR

Bacterial CNS infections with resistant bacteria

Strategy

- Quantitative in-vitro susceptibility testing
- Use in-vivo bactericidal antibiotics
- Ideal: CSF concentrations $\geq$ 10 x MIC (MBC)
- Increase dose, e.g. cefotaxime 300 mg/kg BW/d, maximum 24 g/d, or meropenem 15g/d
- If available, choose moderately lipophilic compound
- Consider intraventricular therapy

PK/PD LCR (6)

Only intraventricular injections produce reliable concentrations in the whole CSF compartment

Methotrexate: MM 454 Da,
„therapeutic concentration“
≥ 10^{-6}M ≈ 0.45mg/l

Shapiro WR et al, NEJM 1975; 293: 161-166

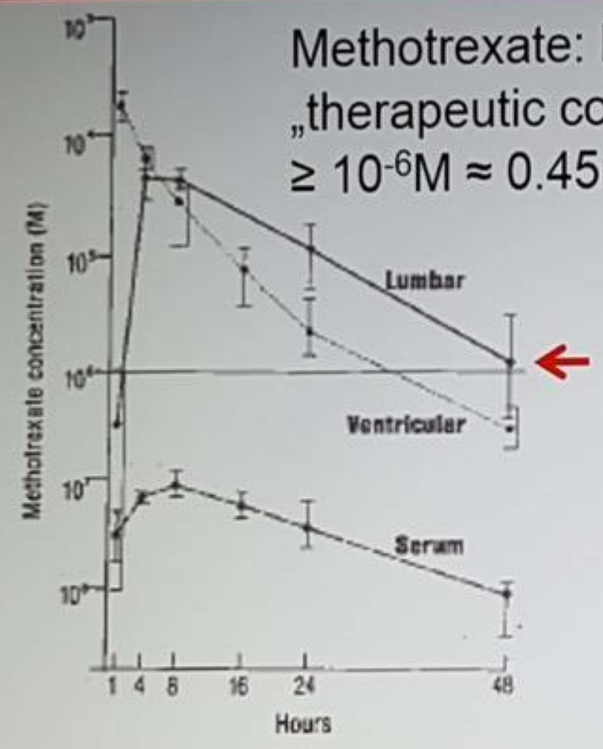


Figure 3. Methotrexate Distribution (Mean ±Range) in Five Studies after Administration of 6.25 Mg per Square Meter via the Ommaya Reservoir.

The ventricular concentration reached a peak of 2 × 10^{-4} M and then fell exponentially with a three-phase half-life of two, four and eight hours. Methotrexate rapidly distributed throughout the cerebrospinal-fluid space, reaching lumbar concentrations of 8 × 10^{-5} M at four hours. Lumbar and ventricular "therapeutic concentrations" were maintained for almost 48 hours. Low serum concentrations were maintained for 48 hours, indicating that the cerebrospinal fluid probably represented a "reservoir" for methotrexate to return to the systemic circulation.

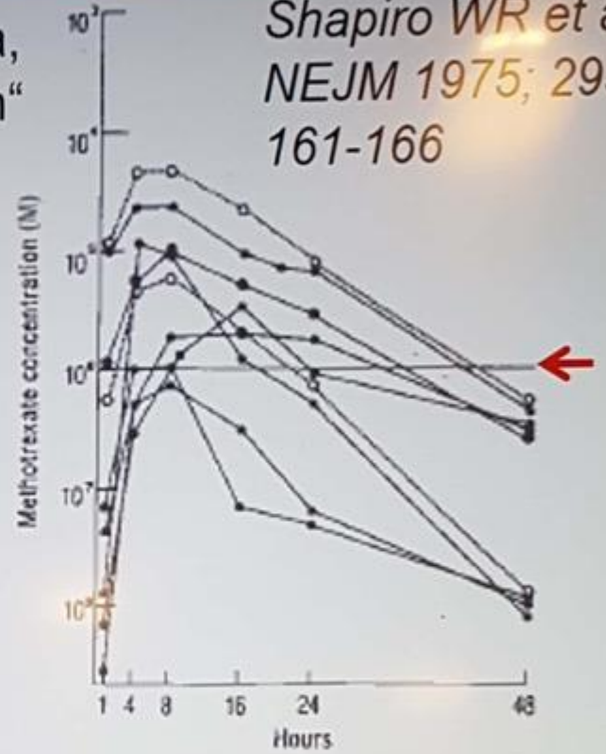


Figure 4. Intraventricular Methotrexate Concentration in Nine Individual Studies after Lumbar Administration.

Solid circles represent seven studies at a methotrexate dose of 6.25 mg per square meter. Open circles represent two studies at a methotrexate dose of 12.5 mg per square meter. There was considerable variation in the entry of methotrexate into the ventricle as compared to ventricular concentrations after Ommaya-reservoir injection (Fig. 3). Peak concentrations ranged from 6 × 10^{-7} M to 2.2 × 10^{-5} M, but there was no obvious relation between concentration and dosage. Although "therapeutic concentrations" were achieved in most of the studies, the "therapeutic concentrations" in five did not last for 24 hours.

Risque convulsif des beta-lactamines

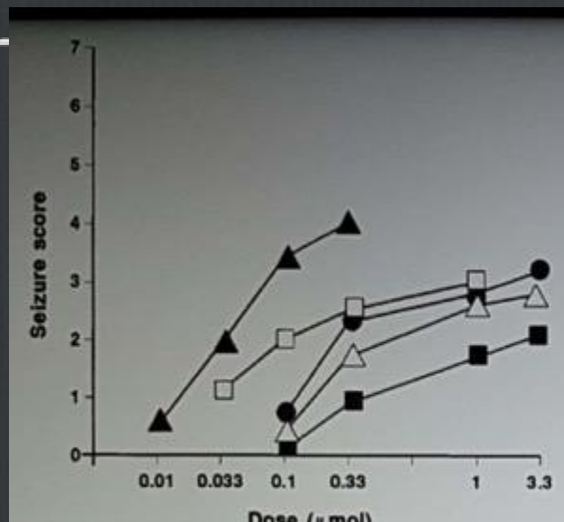


FIG. 5. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ▲, benzylpenicillin; □, aztreonam; △, amoxicillin; ●, ampicillin; ■, sulbenicillin.

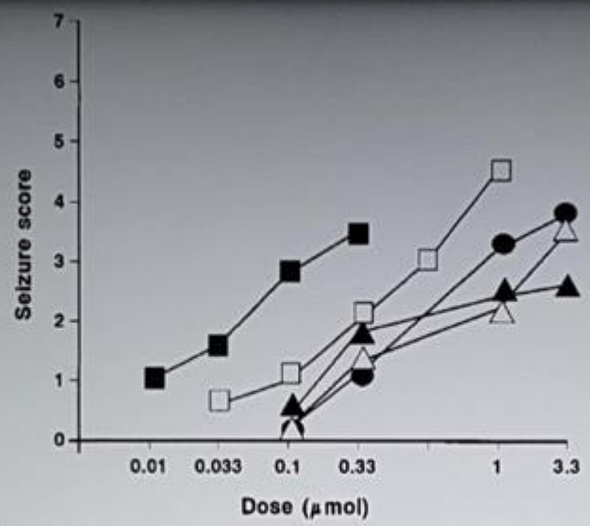


FIG. 6. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). □, azlocillin; △, piperacillin; ■, imipenem; ▲, mezlocillin; ●, meropenem.

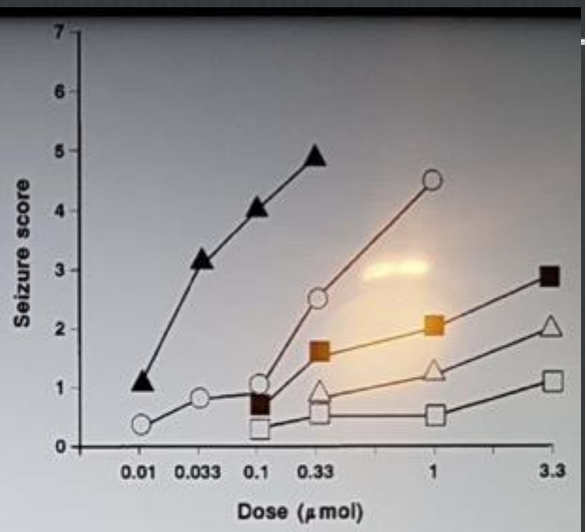


FIG. 7. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ▲, cefazolin; ○, cefoperazone; △, cefuroxime; □, cephradine; ■, Ro 23-9424.

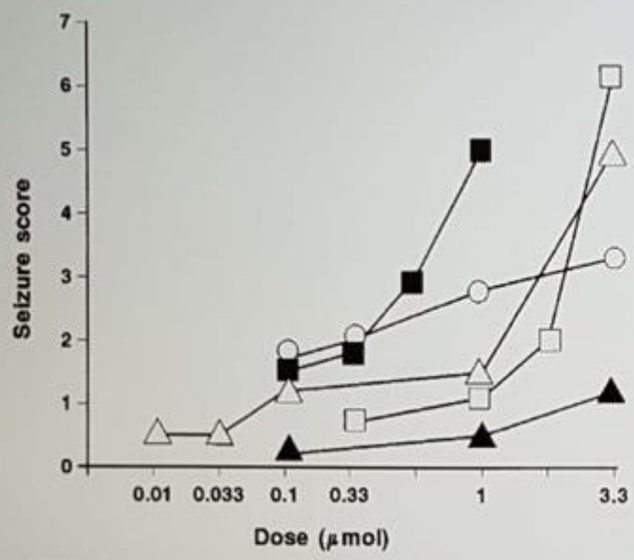


FIG. 9. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ■, ceftriaxone; ○, ceftazidime; △, cefotaxime; □, ceftizoxime; ▲, cefixime.

Pro-convulsive properties of β-lactam antibiotics

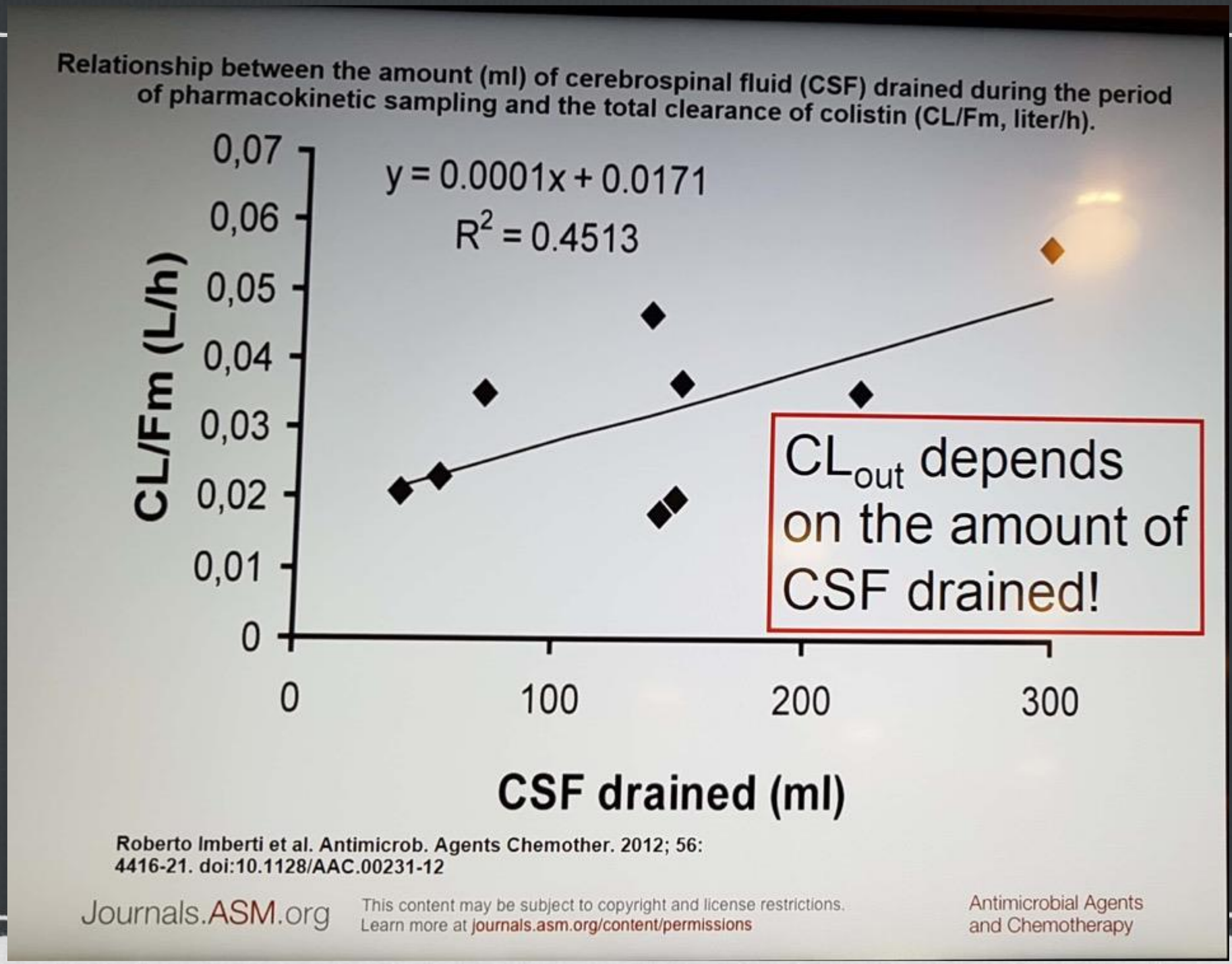
Adult male Wistar rats, injection into the lateral ventricle

Epileptogenic potency: cefazoline > benzylpenicillin = imipenem > ceftriaxone > meropenem >> cefotaxime

De Sarro A et al., Antimicrob Agents Chemother 1995; 39: 232-7

Intrathecal therapy with β-lactams unnecessary and dangerous!

PK/PD LCR :
attention débit DLE/DVE



ATB intraventriculaire

Intraventricular application of antibiotics

Antibiotic	Dose in adults	Severe reported side effects	References
Gentamicin	5 (4–10) mg every 24 h	(Temporary) hearing loss, epileptic seizures, aseptic meningitis, eosinophilic CSF pleocytosis	[38▪]
Tobramycin	5 (–10) mg every 24 h	Similar as gentamicin	[38▪]
Amikacin	30 (5–50) mg every 24 h	(Temporary) hearing loss	[38▪]
Streptomycin	Up to 1 mg/kg every (24–)48 h	(Temporary) hearing loss, epileptic seizures, radiculitis, transverse myelitis, arachnoiditis, paraplegia	[3▪▪]
Vancomycin	10–20 mg every 24 h	(Temporary) hearing loss	[3▪▪,39▪▪]
Colistin (polymyxin E) base (20000 IU = 1 mg)	250 000 IU every 12–24 h 125 000 IU (20 000–250 000 IU) every 24 h	Meningeal inflammation, with high doses epileptic seizures, loss of appetite, agitation, eosinophilia, edeme, pain, albuminuria	[3▪▪,40,41▪]
Daptomycin	5–10 mg every 24–72 h	Fever	[42,43]
Meropenem	10 mg every 12 h	None reported; beta-lactam antibiotics at high concentrations can cause epileptic seizures	[44]
Tigecycline	1 mg every 12 h and 49 mg i.v., 5 mg every 12 h and 45 mg i.v. 10 mg every 12 h and 40 mg i.v.	No severe side effects reported	[45▪]
	2 mg every 24 h, 2 mg every 12 h, 4 mg every 24 h		[46▪]
	3 mg every 24 h, 4 mg every 12 h		[47▪]
Amphotericin B	0.1–0.5 mg every 24 h	Tinnitus, fever, shivering + fever, Parkinson syndrome	[3▪▪]

CSF, cerebrospinal fluid; i.v., intravenous.

Simultaneous intravenous and intraventricular administration helps to reduce the selection of resistant bacteria! Combine colistin with a carbapenem!

Nau et al, Curr Opin Infect Dis 2018;31:57-68

PK/PD LCR (7) : Conclusion

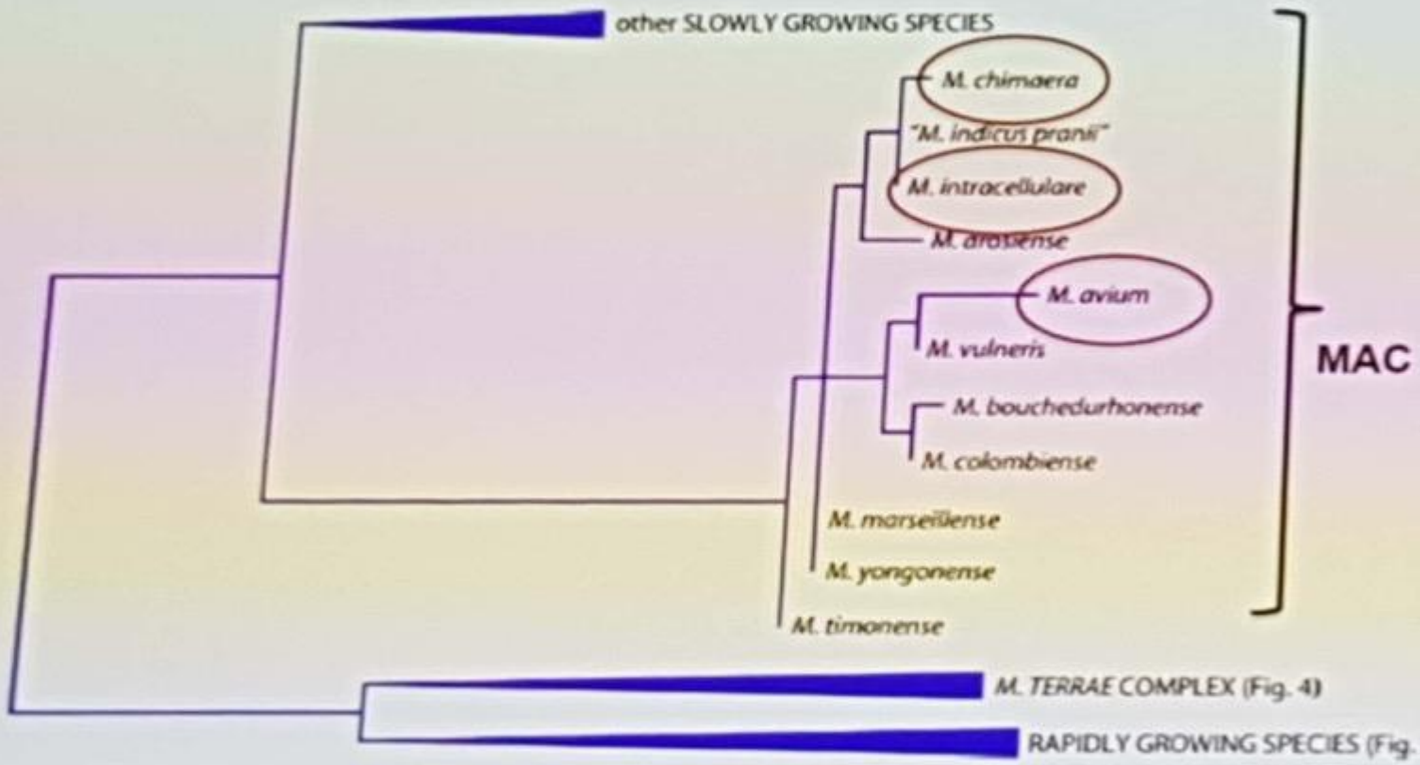
Take-home message

- After i.v. infusion: lumbar often higher than ventricular concentrations
- $T_{1/2}$ in CSF often longer than in serum
- CSF concentrations ≥ 10x MIC/MBC optimal
- Time-dependent antibiotics: avoid CSF levels below MIC
- Bacteria with reduced susceptibility:
  a) increase i.v. dose, if possible
  b) when drugs with similar activity are available, choose a low-molecular, moderately lipophilic compound
- Vancomycin, colistin, aminoglycosides, daptomycin: consider intraventricular injection.
  $V_d \approx 0.3l$, $t_{1/2} \approx 5\text{-}20h$

Classification des MAC

Mycobacterium avium Complex

12 Species



M. paraintracellulare
M. lepraemurium

FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

Tortoli E, et al. J System Evol Micro 2004;54:1277-1285.
van Ingen J, et al. Int J Syst Evol Microb 2018;68:36666
Tortoli E. Clin Micro Rev 2014;27:727-752

Traitement des MAC

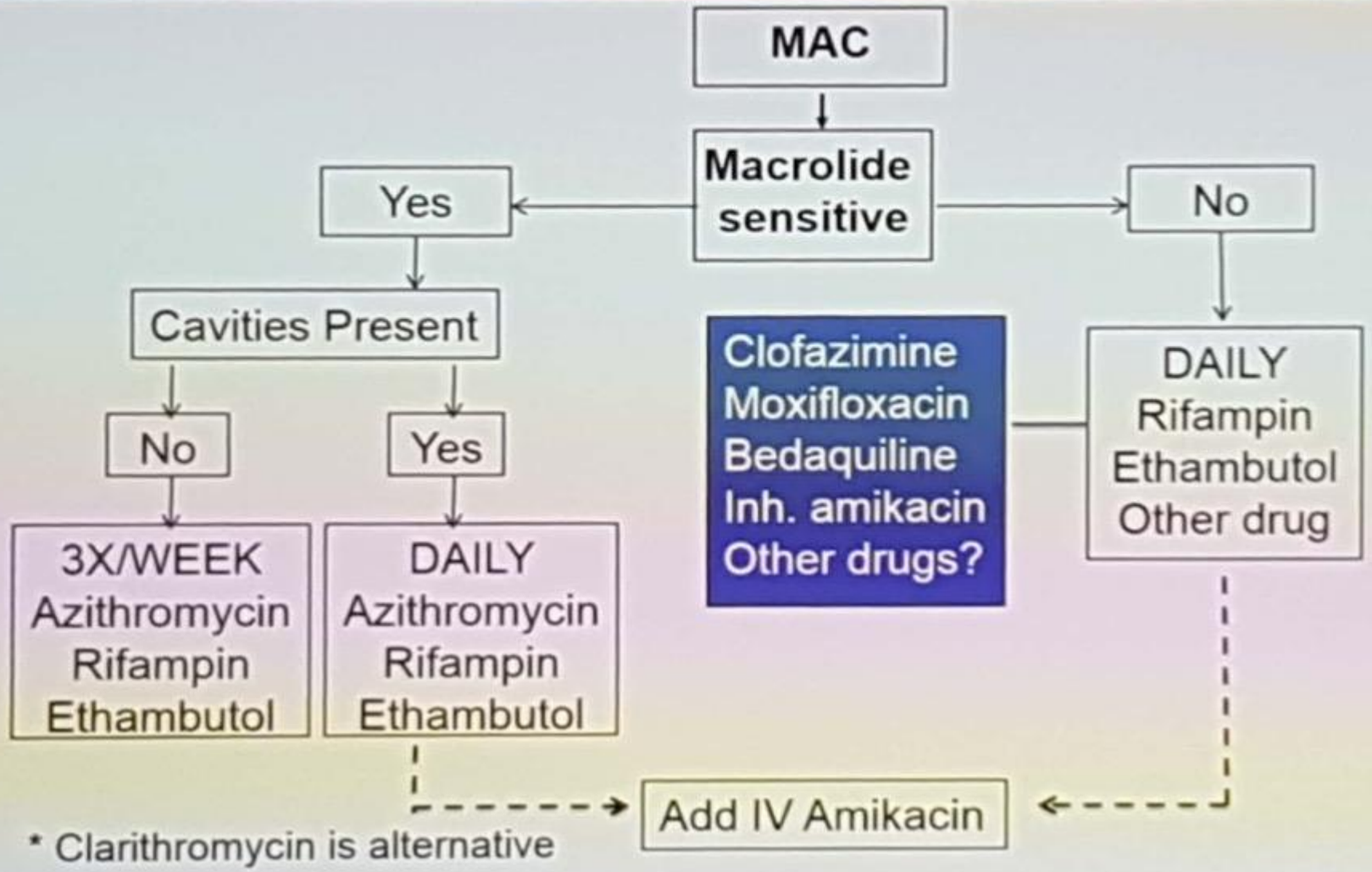
Treatment of Pulmonary *M. avium* complex

Questions being considered in revision of ATS/ESCMID/ERS/IDSA NTM guidelines

- Macrolide vs non-macrolide regimen
- Two vs three drug regimen
- Daily vs intermittent therapy
- Use of aminoglycosides
- Duration of therapy

Algorithme
de traitement des MAC

Treatment of Pulmonary *M. avium* complex



Duration :12 mos culture negativity

National Jewish Health
Science Transforming Life

Algorithme de traitement des MAC résistants aux macrolides

Treatment Outcomes for MAC

Macrolide Resistant

	Culture Conversion
Macrolide resistant	
No surgery/aminoglycoside	5%
Some surgery/aminoglycoside	15%
Surgery + prolonged aminoglycoside*	80%

* ≥ 6 months IV aminoglycoside

National Jewish Health
Science Transforming Life

Griffith DE, et al. AJRCCM 2006;174:928
Jeong BH, et al. AJRCCM 2015;191:96-103
Moon SM, et al. Antimicrob Agents Chemother; 2016
Wallace R, et al. Chest 2014;146:276-282
Koh WJ, et al. Eur Respir J 2017;50
Morimoto K, et al. Ann ATS 2016;11:1904

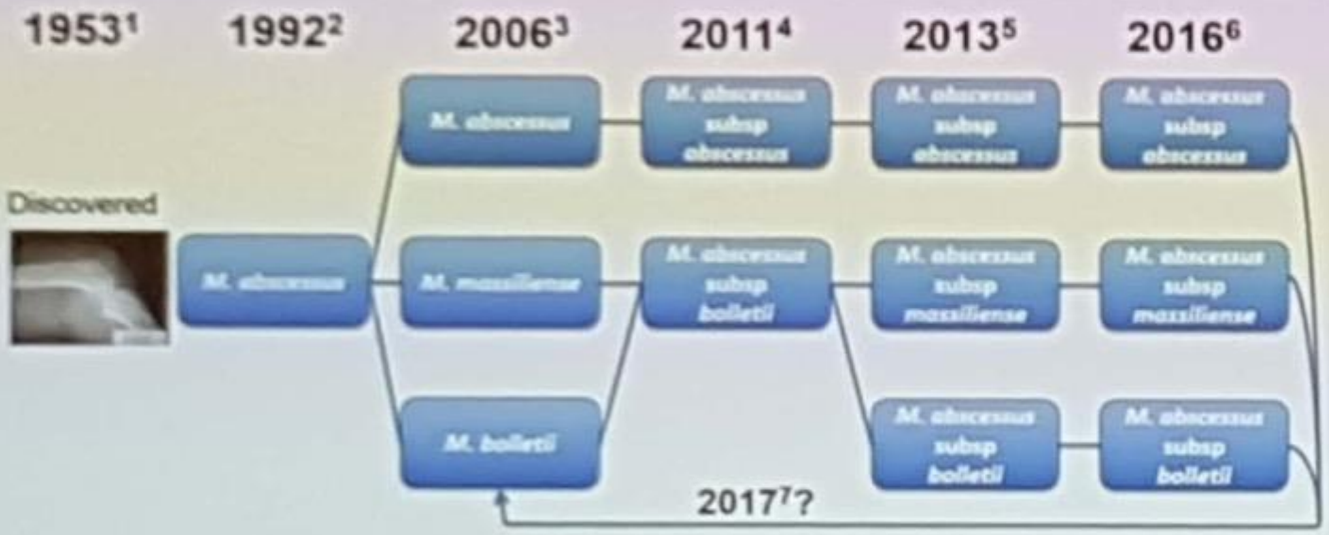
Cas du *Mycobacterium abscessus*

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

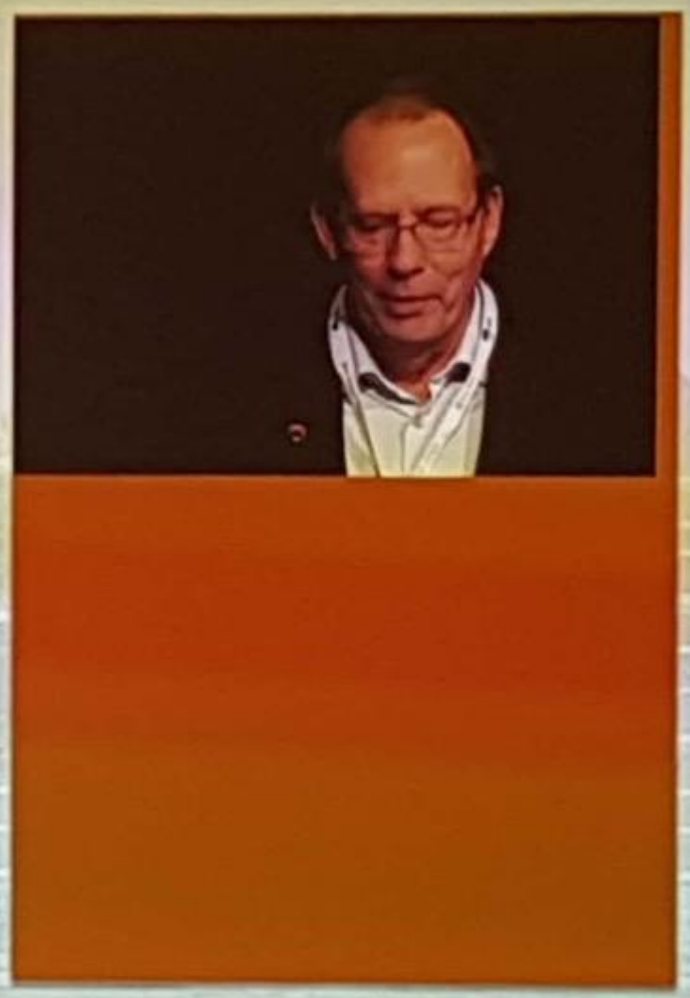
Chairs: Delia Goletti
Jakko van Ingen

13:18
Monday, 15 April 2019
HALL D

Mycobacterium abscessus
An Evolving Taxonomy



[1]Moore M J Invest Derm 1953;20:133
[2]Kusunoki S. Int J Syst Bacteriol 1992;42:240
[3]Adekambi T. Int J Syst Bacteriol 2006;56:133
[3]Adekambi T. Int J Syst Bacteriol 2006;56:2025
[4]Leao SC. Int J Syst Evol Microbiol 2011;61:2311
[5]Cho YJ. PLoS ONE 2013 8(11):e81560
[6]Tortoli E. Int J Syst Evol Microbiol 2016;66:4471
[7]Adekambi T. Int J Syst Evol Microbiol 2017;67:2726



13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

13:18
Monday, 15 April 2019
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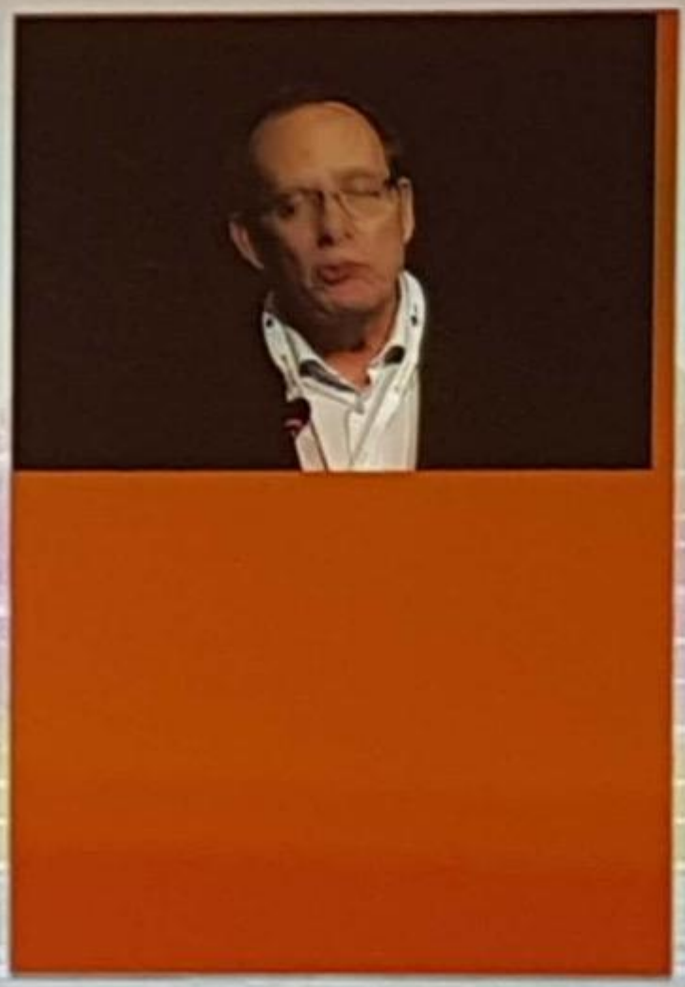
Proportions of *M. abscessus* complex subspecies

Study	Country	Total	M. abscessus	M. massiliense	M. bolletii
Zelazny, 2009	US	40	68%	28%	5%
Van Ingen, 2009	Netherlands	39	64%	21%	15%
Roux, 2009	France	50	60%	22%	18%
Harada, 2012	Japan	102	71%	26%	3%
Yoshida, 2013	Japan	143	63%	35%	2%
Nakanaga, 2014	Japan	115	60%	37%	3%
Morimoto, 2018	Japan	121	59%	44%	0%
Huang, 2013	Taiwan	79	43%	56%	1%
Kim, 2008	Korea	126	53%	45%	2%
Koh, 2011	Korea	158	44%	55%	1%
Lee, 2014	Korea	404	50%	49%	1%



Koh WJ, et al. Int J Tuberc Lung Dis 2014;18:1141
Morimoto K, et al. Respir Med 2018;145:14

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

13:21
Monday, 15 April 2019
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Macrolide Resistance: Implications for Treatment

Clarithromycin susceptibility results		Genetics	Subspecies	Susceptibility Phenotype	Use Macrolide
Days 3-5	Day 14				
Susceptible	Susceptible	Dysfunctional *erm*(41) gene	*M. massiliense*	Macrolide susceptible	Yes
Susceptible	Resistant	Functional *erm*(41) gene	*M. abscessus** *M. bolletii*	Inducible macrolide resistance	Possibly but don't count as active
Resistant	Resistant	23S rRNA point mutation	Any	Constitutive macrolide resistance	Only for anti-inflam purposes

* 10-15% have nonfunctional *erm*(41) gene due T to C substitution at position 28

Haworth C. et al Thorax 2017;72ii1-ii64

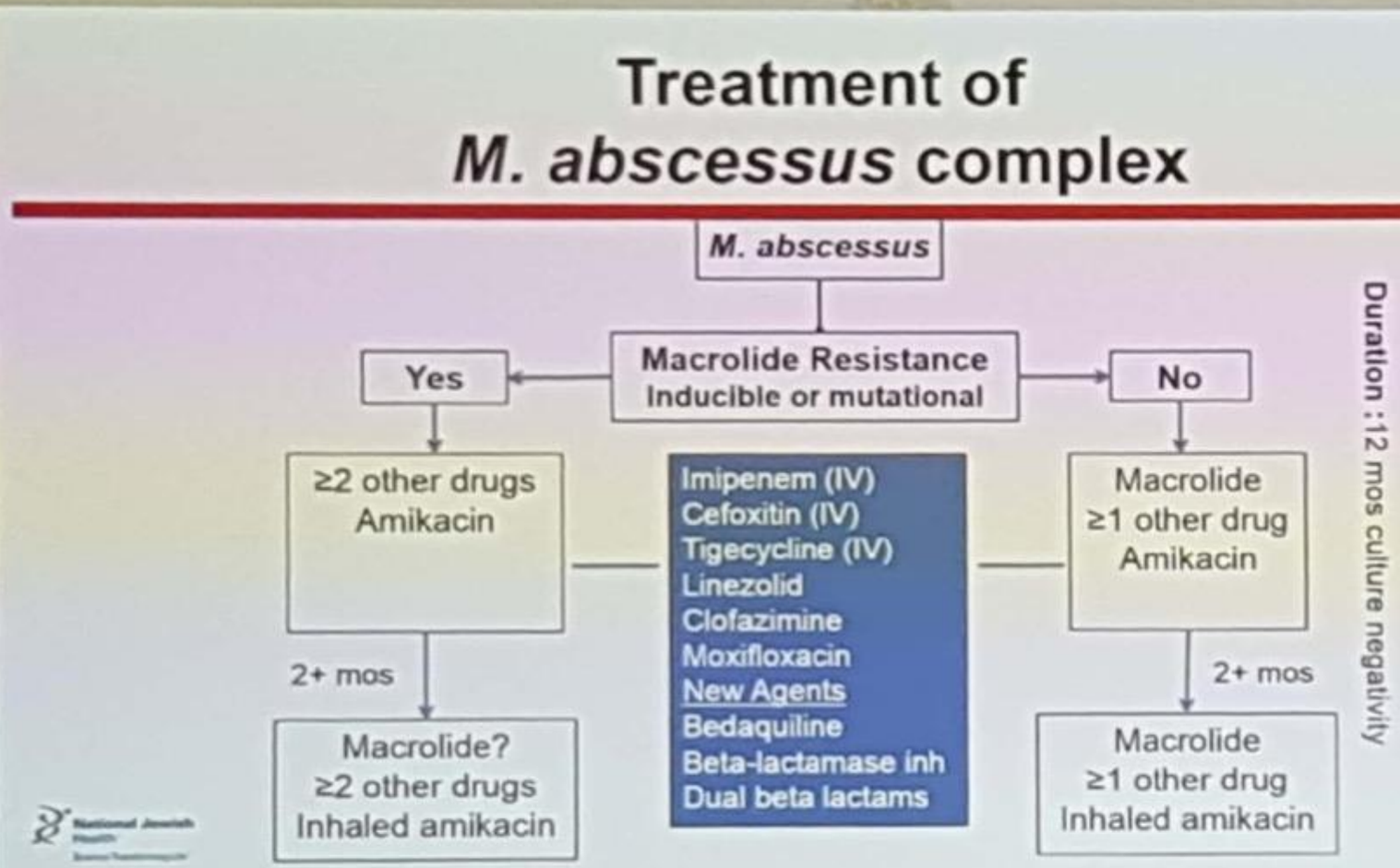
Algorithme de traitement des *Mycobacterium abscessus* complex

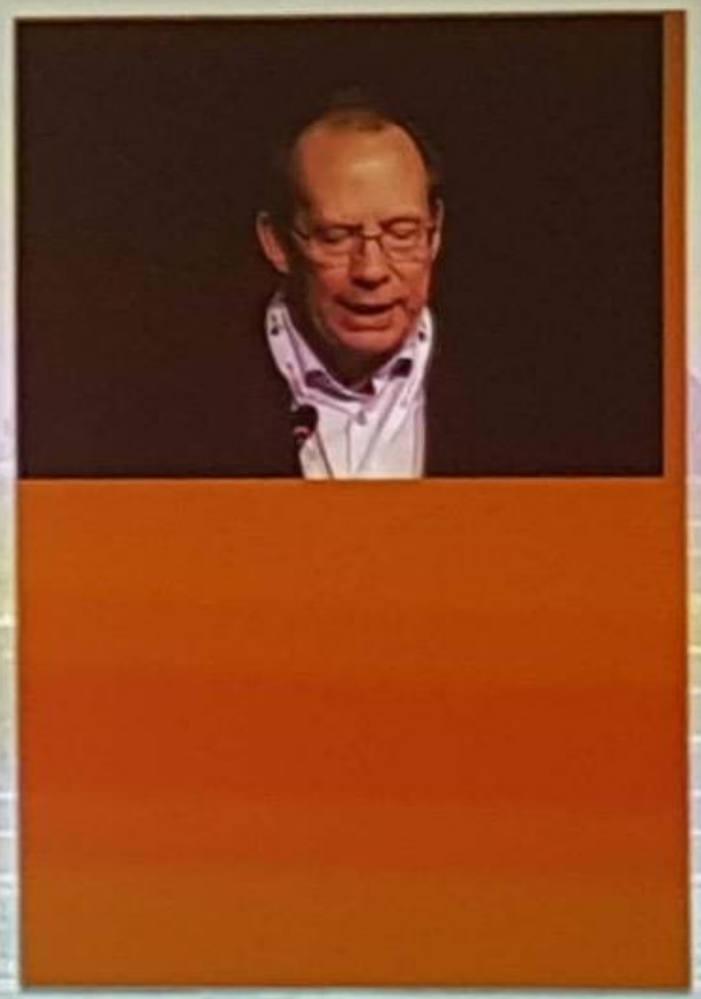
13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

13:24
Monday, 15 April 2019
HALL D

Treatment of *M. abscessus* complex





Traitement :
M. abscessus vs *M. massiliense*

Treatment Outcomes for *M. abscessus vs. M. massiliense*

Study	Population	Treatment	N	Sputum conversion	Failure to convert	Relapse
Koh, 2011	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	24 33	25% **88%**	58% **3%**	17% **9%**
Lyu, 2014	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	26 22	42% **96%**	27% **0%**	31% **5%**
Roux, 2015	Cystic Fibrosis	*M. abscessus* *M. massiliense*	12 7	25% **86%**	- -	- -
Park, 2017	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	19 17	**26%** **82%**	74% **18%**	55% **0%**

National Jewish Health
Science Transforming Life

Koh WJ, et al. Am J Respir Crit Care Med 2011;183:405-10
Choi H, et al. Antimicrob Agents Chemother 2016 epub
Park J, et al. CID 2017;64:301-8

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

14:26
Monday, 15 April 2019
HALL D

Treatment Outcomes with *M. abscessus*

Systematic Review and Meta-analysis

- 14 studies identified – eight provided individual patient data (303 patients)
- Treatment success was defined as culture conversion for ≥ 12 months while on treatment or sustained culture conversion without relapse until the end of treatment.
- Treatment success
  - Overall – 45.6%
  - *M. abscessus* subspecies *abscessus* – 33.0%
  - *M. abscessus* subspecies *massiliense* – 56.7%
- Imipenem, azithromycin, or parenteral amikacin associated with success in *M. abscessus* subspecies *abscessus*

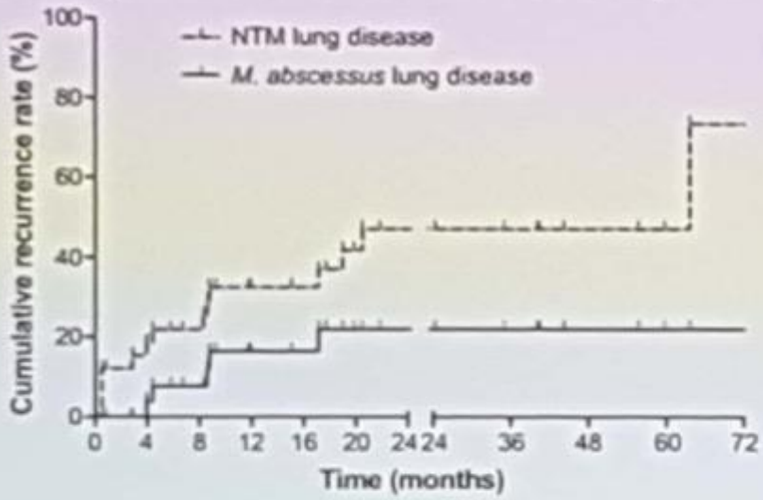
Kwak N, et al. ERJ 2019 epub

Charles Daley

Treatment of NTM

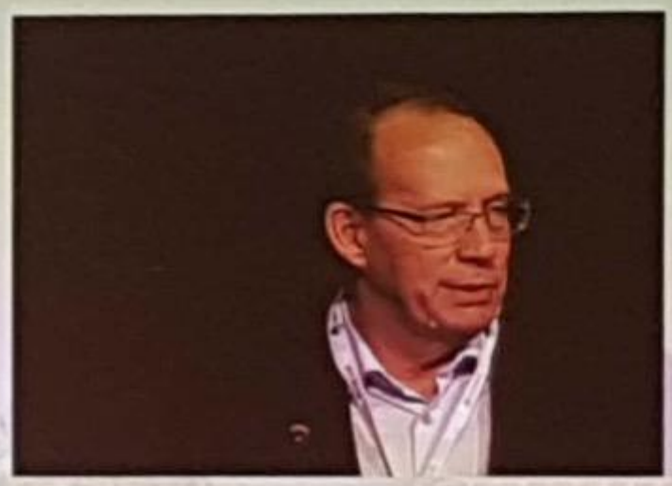
M. abscessus: Recurrence and Reinfection

77 consecutive patients with *M. abscessus* pulmonary disease



All recurrences had a different genotype pattern (rep PCR)

Koh WJ, et al. CID 2017;64:309-16



Charles Daley

Treatment of NTM

Traitement des Mycobactéries non tuberculeuses

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

14:31
Monday, 15 April 2019
HALL D

Summary

- The decision to treat should be based on at least three factors; patient, **organism** and goals of treatment
- Treatment of MAC pulmonary disease should include a macrolide-containing three drug regimen administered for 12 months beyond culture conversion
  - Aminoglycosides may be added for cavitary or macrolide resistant disease
  - Inhaled amikacin liposomal suspension may be added in treatment refractory cases
- Treatment of *M. abscessus* pulmonary disease should include at least three active drugs
  - A macrolide should be included when a nonfunctional erm(41) gene is present or when the status of the gene is unknown
- Duration of therapy: 12 months beyond culture conversion

Charles Daley

Treatment of NTM

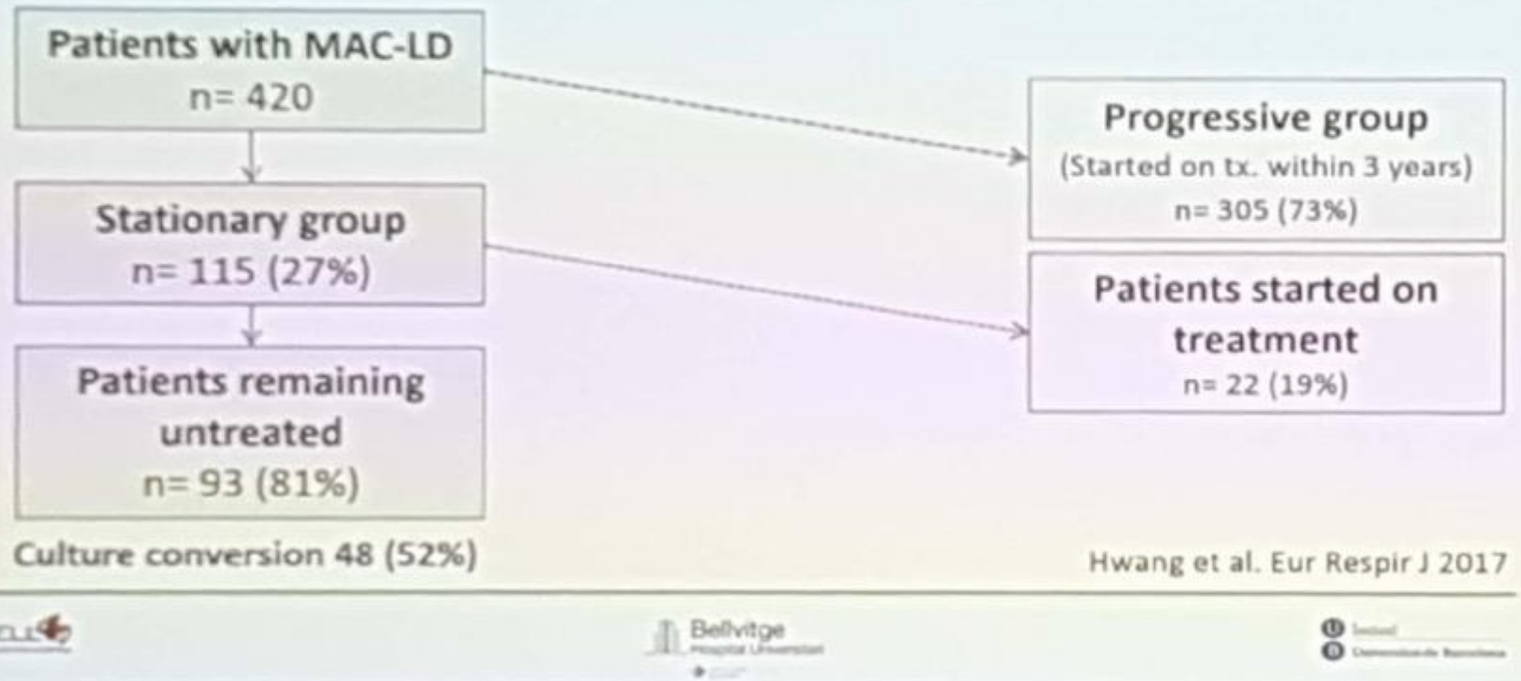
29th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Amsterdam, Netherlands
13 – 16 April 2019
ESCMID

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

14:36
Monday, 15 April 2019
HALL D

Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course



Hwang et al. Eur Respir J 2017

Miguel Santin

Challenging clinical cases of NTM

Facteurs de progression vers une mycobactériose maladie non tuberculeuse

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

14:37
Monday, 15 April 2019
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Factors associated to progression of NTM-LD

Patient-related factors	Mycobacterial factors
• Severe systemic symptoms	• Smear positivity
• Low BMI	
• Comorbidities	• ≥2 positive cultures
• Extensive disease	
• Fibrocavitary disease	• Mycobacterial species

Miguel Santin

Challenging clinical cases of NTM

How to continue Tx?

- Azithromycin-containing regimen:
  - Azithro + EMB + RMP
- Macrolide-free regimen:
  - EMB + RMP/RBT
  - EMB + RMP/RBT + FQ
  - EMB + RMP/RBT + Clofazimine
  - EMB + RMP/RBT + injectable or inhaled agent (ALIS)

Miguel Santin

Challenging clinical cases of NTM

13:30 - 15:30
Update on diagnosis and treatment of non-tuberculous mycobacteria (NTM)

Chairs: Delia Goletti
Jakko van Ingen

14:42
Monday, 15 April 2019
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Intermittent *vs.* daily therapy

Treatment Episodes With Initial Intermittent or Daily Macrolide/Azalide-Based Therapy For NB MAC Lung Disease **(Wallace RJ. Chest 2014)**

Episode	tiw, No. (%)	Daily, No. (%)
Regimen modification[a]		
Clarithromycin	3 of 74 (4)	14 of 21 (67)
Azithromycin	2 of 72 (3)	10 of 13 (77)
Clarithromycin + azithromycin	5 of 180 (3)	24 of 34 (71)

Modification of Initial Antibiotic Treatment **(Jeong BH AJRCCM 2015)**

	Daily Therapy (*n* = 99)	Intermittent Therapy (*n* = 118)	*P* Value
Early discontinuation of antibiotic treatment	15 (15%)	13 (11%)	0.366
Dose reduction of CLR	11/95 (12%)	1/26 (4%)	0.456
Change from AZM to CLR	0/12 (0%)	3/116 (3%)	NA
Discontinuation of RIF or RFB	4/99 (4%)	7/118 (6%)	0.527
Discontinuation of EMB	24/99 (24%)	1/118 (1%)	<0.001
Discontinuation of streptomycin	4/50 (7%)	—	NA
Total	46/99 (46%)	25/118 (21%)	<0.001

Miguel Santin

Challenging clinical cases of NTM

Summary

- An observational period for progression may be advisable before starting therapy in patients with NTM-LD (nodular/bronchiectatic disease)
- Therapy should based on the guidelines
- Recurrences, either during or after discontinuing therapy more often represent a new infection
- Surgery represents a reliable alternative for patients with refractory NTM-LD
- Intermittent symptoms-guided therapy is an option when the aim of treatment is to alleviate symptoms

Miguel Santin

Challenging clinical cases of NTM

Maladie de Weil/Leptospirose

16.00 - 18.00
Clinical tropical medicine: management of acute severe infection

Chairs: Nicholas J. Beeching
Kristine Moch

5 Key Points – Weil's Disease

- Weil's disease is a severe complication of leptospirosis that carries a **mortality rate of 5-15%**
- Clinical pearl = check **U/A** and **chest xray**
- **Empiric treatment** of febrile returned travelers with epidemiologic risk is likely prudent, though largescale protective efficacy data are scant
- Novel approaches are already disrupting the **diagnosis** of severe leptospirosis
- Given the increasing intersection of leptospirosis and health care resources, **management approaches** could be equally disrupted in the future

Medicine
UNIVERSITY OF TORONTO

ECCMID

Fièvres hémorragiques virales

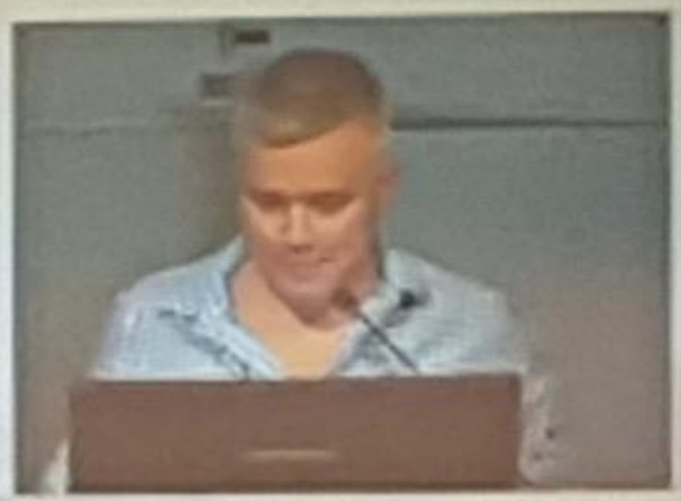
16:30 - 18:00
Clinical tropical medicine: management of acute severe infection

Chairs: Nicholas J. Beeching
Kristine Mach

16:51
HALL K

Viral hemorrhagic fever - numbers

Group	Virus	Reservoir	Vector	Cases/y	Lethality
Filovirus	Ebola, Marburg	Bat	Bat	28 000 (?)	50-90%
Arena-	Lassa	Rodent	Rodent	300 000	1-70%
Flavi-	Yellow Fever	Monkey Human	*Aedes mosquito*	200 000	20-50%
Flavi-	Dengue	Human	*Aedes*	500 000 DHF	4-5%
Bunya-	Rift Valley	Cattle, sheep, goat	*Aedes, culex*	Epidemics - >100 000	10-50%
Bunya-	Congo Crim	Hares, others	Ticks	Hundreds	10-50%



Björn Blomberg

ECCMID

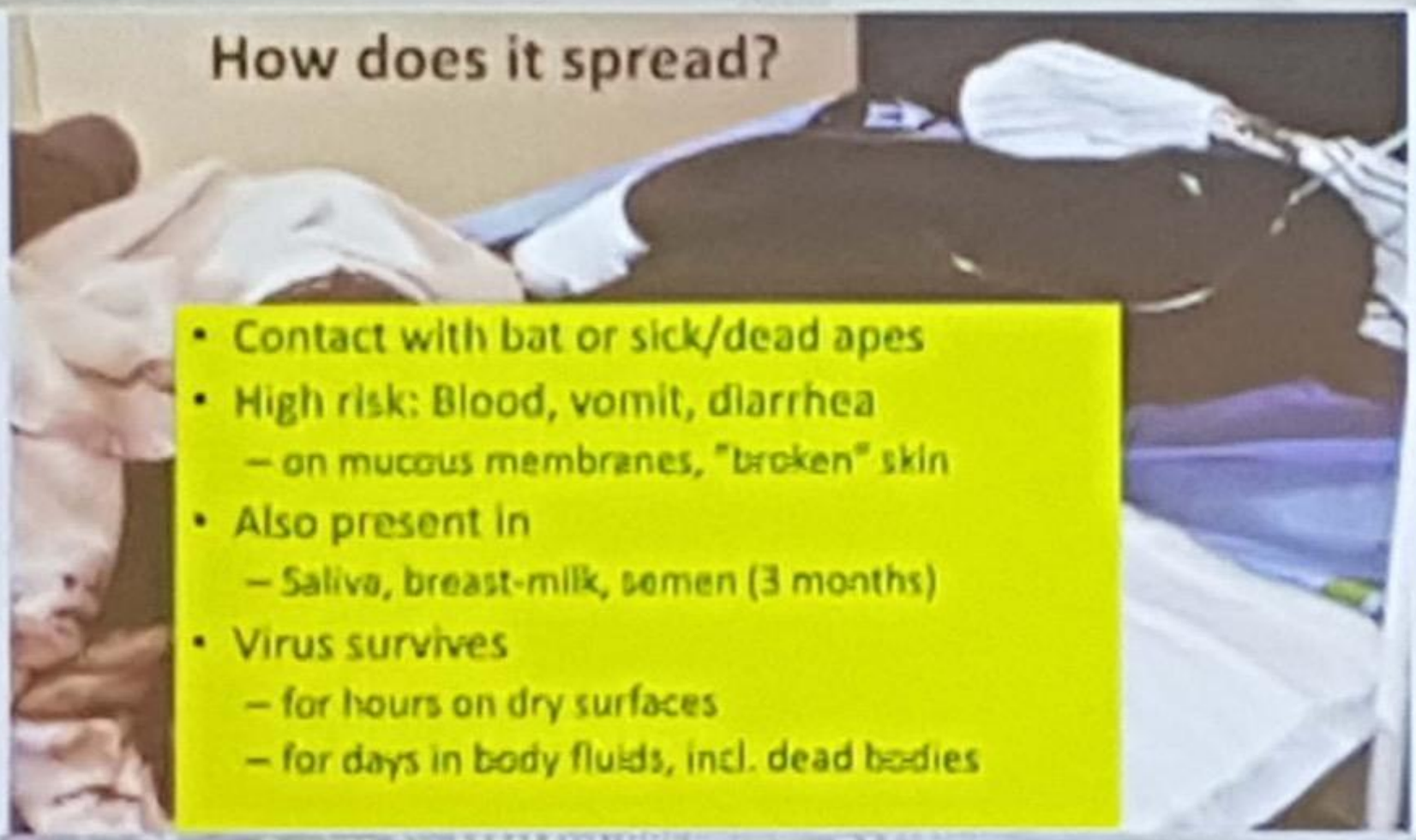
ESCMID

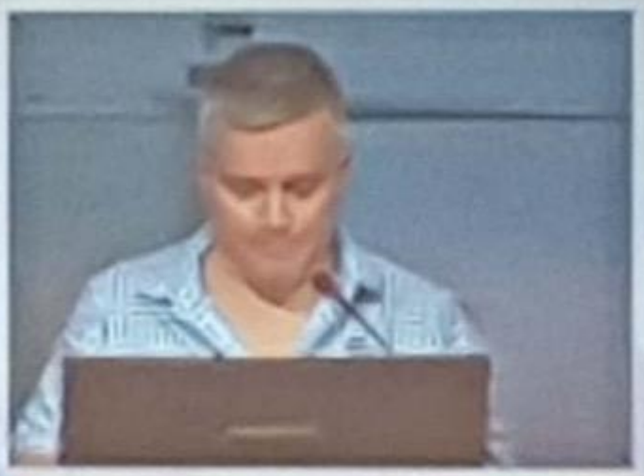
Contagiosité des fièvres hémorragiques

16:00 - 18:00
Clinical tropical medicine: management of acute severe infection

Chairs: Nicholas J. Beeching
Kristine Macfie

16:53
HALL K





Björn Blomberg

Haemorrhagic fever (focus on Ebola)

ECCMID

ESCMID

Supportive therapy – different phases

Stage	Time since symptoms (days)	Features	Management
Early febrile	0-3	Fever, weak, myalgia, lethargy	Oral hydration Able to care for self
Gastrointestinal	3-10	+ diarrhea, vomiting, abdominal pain	Needs intravenous fluids
Complicated	7-12	+ bleeding, shock, organ failure, neruological complications	Fluid therapy Vital organ support Seizure control Pain management

Modified from Malvy, Lancet 2019

Supportive therapy - I

Problem	Intervention	Remarks
Other infections	Malaria Tx Broadspectrum antibiotic Doxycyclin	Malaria – similar symptoms Translocation of bacteria from gut Doxycyclin – rickettsia etc
Shock	Fluid, crystalloids * Vasopressor	Liberal fluid therapy, but... Avoid «third-spacing»
Bleeding	Blood-Tx Platelets, plasma, vit-K	Malnutrition -> vitamin K Low fibrinogen* -> plasma
Electrolytes	Add potassium?	* Availability of lab testing
Hypoxemia	O2 therapy * Respirator	
Renal failure	Fluid, furosemid * Dialysis	Renal failure >50% Associated with fatal outcome

* Not available in low-resource areas

Modified from Malvy, Lancet 2019

Supportive therapy - II

Problem	Intervention	Remarks
Nausea, vomiting	Metoclopramide, ondesartron	
Pain	Paracetamol, Tramadol Opiates	Avoid NSAIDS, ASA – bleeding Transdermal opiates – avoid punctures
Ulcer	Ulcer prophylaxis	Extremely stressful – stress ulcer
Seizures	Benzodiazepines	
Malnutrition	Oral > enteral	Oral if possible Nasogastric tube – bleeding?

Modified from Malvy, Lancet 2019

Immunothérapie pour les infections à *C. difficile*

Antitoxin antibody-mediated therapies for *C. difficile* infection

Passive immunotherapies

- Systemic:
  - Humanised antitoxin mAbs
  - Polyclonal IVIg
- Oral
  - IgAbulin
  - Hyperimmune bovine Ig concentrate
  - Mucomilk (polyclonal-antibody enriched whey protein concentrate)

Active immunotherapies/toxin-based vaccines

- Systemic:
  - PF-06425090 (Pfizer; phase III)
    - Genetically and chemically detoxified TcdA and TcdB
  - VLA84 (Valneva; phase II)
    - Recombinant chimeric protein linking binding domains of TcdA and TcdB

Recommandations sur la durée de traitement des PAC

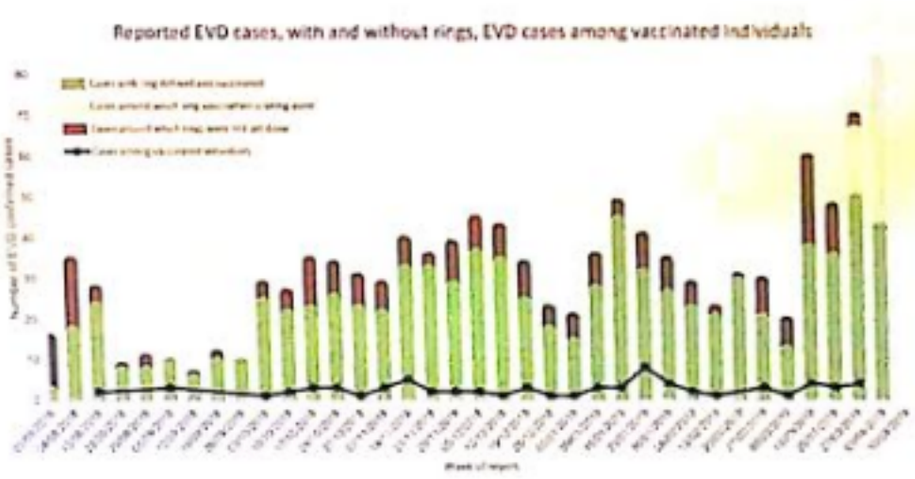
Duration: Guideline Recommendations

Guideline	Duration (days)
IDSA/ATS (2007;2019 pndg)	Minimum of **5 days**, should be afebrile for 48–72 h, and no more than 1 CAP-associated sign of clinical instability. (level I) A longer duration of therapy if resistant pathogen or complicated by extrapulmonary infection, such as meningitis or endocarditis (level III).
ERS (2011)	The duration of treatment should generally **not exceed 8 days** in a responding patient [C2]. **Biomarkers, particularly Procalcitonin, may guide shorter duration**
BTS (2009;2015; NICE 2014))	offer a **5 day** course of antibiotic therapy for patients with low severity CAP; consider a 7-**10** day course of antibiotic therapy for patients with moderate **and high severity** CAP (may need to be extended to 14 or 21 days according to clinical judgement; for example, *S aureus* or Gram-negative enteric bacilli pneumonia is suspected or confirmed. [C]
ATS/IDSA VAP (2016)	**7 day** course; Procalcitonin guidance + clinical response
ERS VAP (2017)	**7-8 days**; Procalcitonin not routine but serial levels good practice in selected patients (e.g., MDRO; immunocompromised)

Vaccin contre Ebola

Ebola Virus Disease

Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response.



- 71 infected people among 93695 people at risk vaccinated
- The estimated vaccine efficacy for those with onset of illness 10 day or more post vaccination is 97.5%, 95% CI [92.4 – 99.1] and for those with EVD regardless of timing of onset of illness is 88.1%, 95% CI [79.9-92.9].

https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf?ua=1 Access 12th April 2019

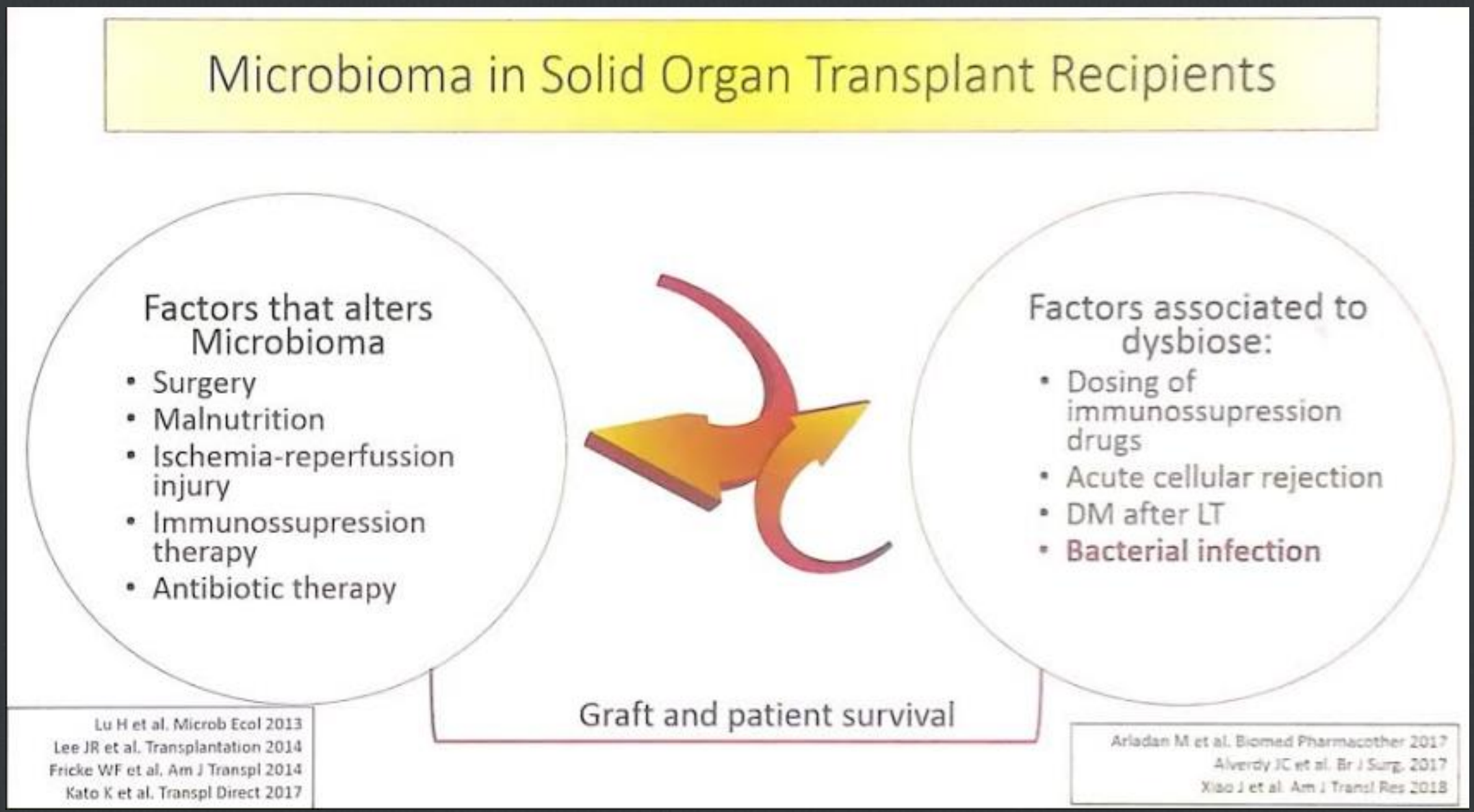
Sensibilité aux ATB et Indice développement humain

	High HDI (n=295)	Middle HDI (n=187)	Low HDI (n=128)	Total (n=610)	p value
Antibiotic not used	27 (9·2%)	6 (3·2%)	0 (0·0%)	33 (5·4%)	<0·001
Sensitive to antibiotic	92 (31·2%)	56 (29·9%)	40 (31·2%)	188 (30·8%)	..
Resistant to antibiotic	49 (16·6%)	37 (19·8%)	46 (35·9%)	132 (21·6%)	..
Sensitivity not available	127 (43·1%)	88 (47·1%)	42 (32·8%)	257 (42·1%)	..

Numbers are n (%), unless otherwise indicated. All tests are χ^2 tests.

Table 3: Sensitivity of organism by Human Development Index (HDI) from patients with a surgical site infection who had a wound swab taken

Microbiote altéré chez le transplanté d'organe solide



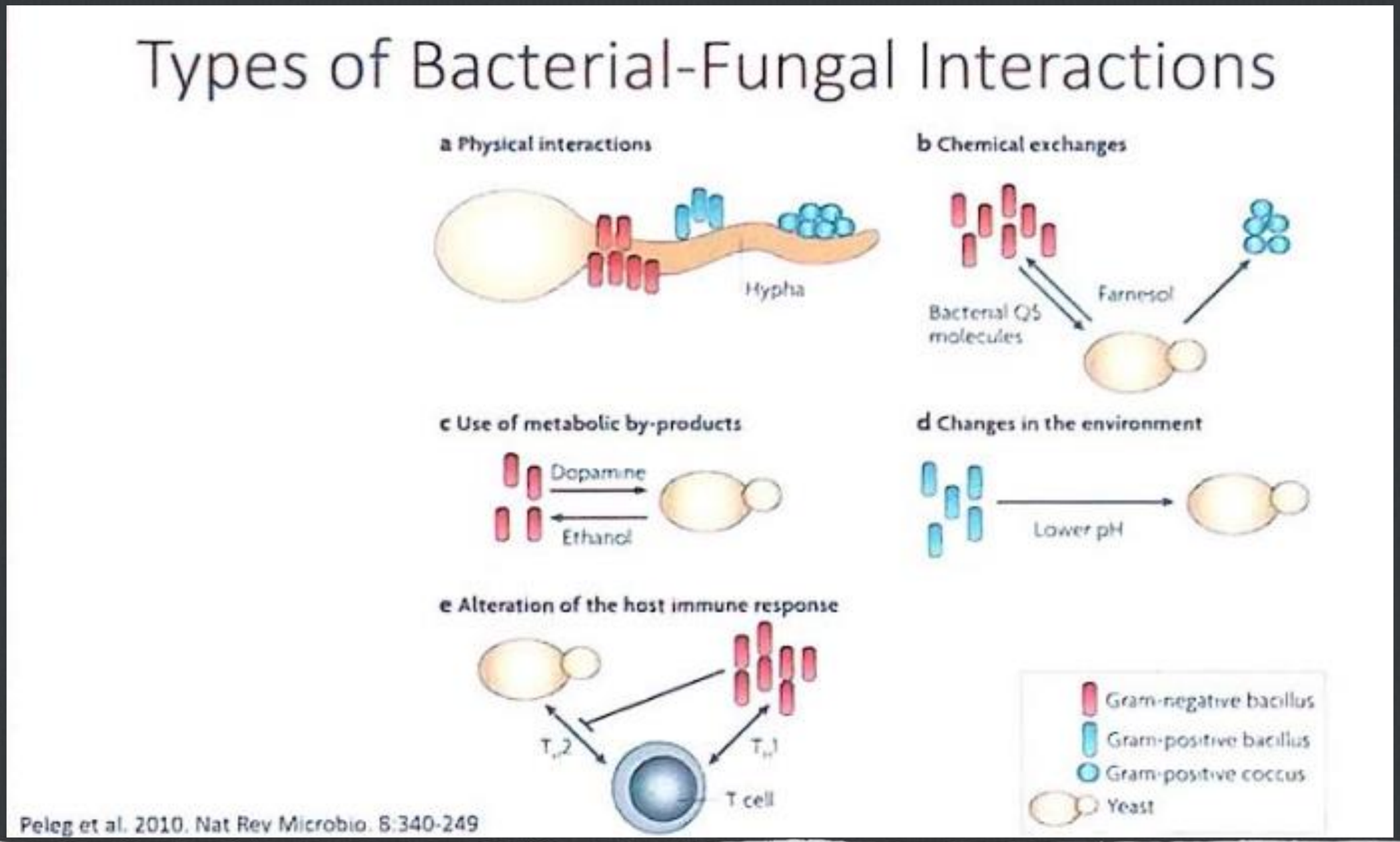
Synergie des beta-lactamines

Synergy with β-lactams

β-lactam	Type of study	Synergy		Ref.
		Yes	No	
AMP	Case report / in vitro	X		Sakoulas AAC 2012
CPT, AMP, CRO, CFZ	In vitro (included DNS)	X		Sakoulas AAC 2014
CRO	In vitro SEV with DNS		X	Hall JAC 2014
AMP, CBP	In vitro PK/PD	X		Werth JAC 2015
CPT, ERT, AMP	In vitro PK/PD	X		Smith AAC 2015
CPT, **ERT**, FEP, CRO*, CFZ*, CTO	In vitro	X		Smith JAC 2015
AMP, ERT, CRO*, CFZ*, **CPT**	In vitro	+/-		Hindler AAC 2015

AMP – ampicillin; CBP – ceftobiprole; CFZ – cefazolin; CPT – ceftaroline; CRO – ceftriaxone; CTO – cefotaxime; ERT – ertapenem, FEP – cefepime; PIP – piperacillin

Interactions Bactérie-Champignon



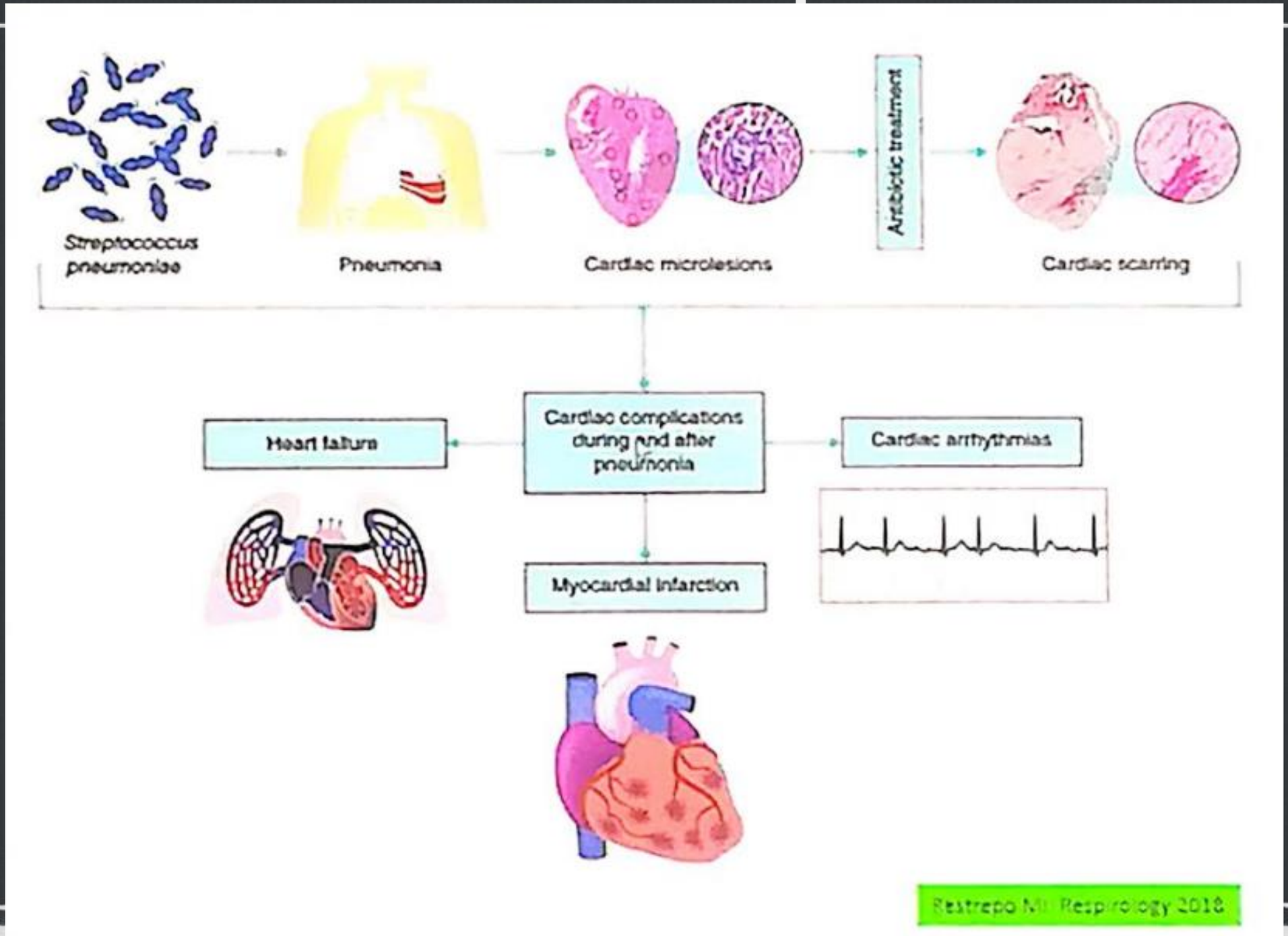
Recommandations du traitement des infections à *C. difficile* : data ?

Evidence for treatment recommendations of initial CDI episode *(Randomized, controlled trials)*

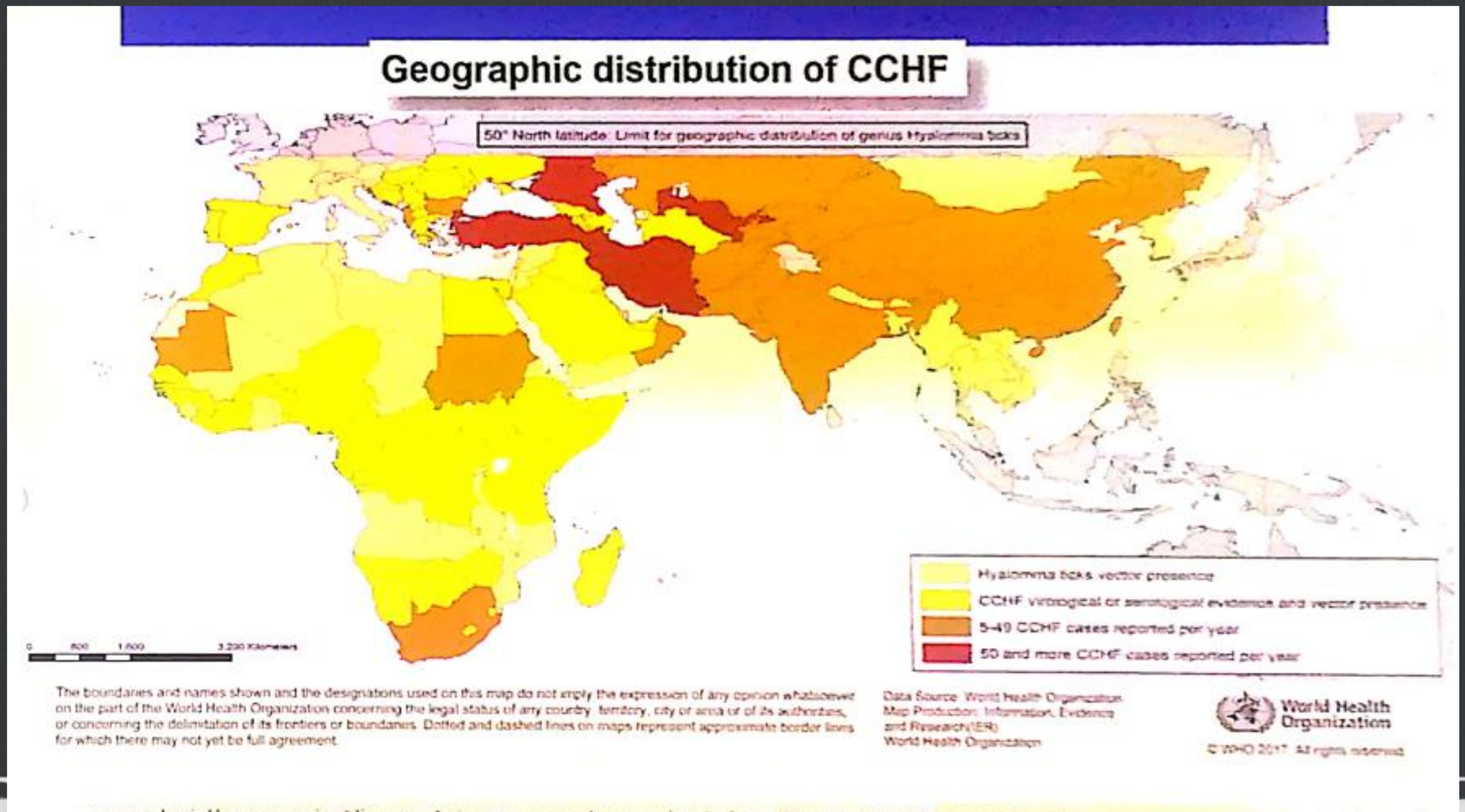
Outcome	N Participants (studies)	Percent resolution	Relative Risk (95%CI)	*P*	Quality of evidence (GRADE)
Metronidazole (MTR) vs. vancomycin (VAN)					
Initial cure	843 (5*)	78 (MTR) 87 (VAN)	0.89 (0.85, 0.96)	0.0008	ΦΦΦΦ high
Sustained response	843 (5*)	63 (MTR) 73 (VAN)	0.87 (0.79, 0.96)	0.003	ΦΦΦΦ high
Fidaxomicin (FDX) vs. vancomycin (VAN)					
Initial cure	1,005 (2**)	88 (FDX) 86 (VAN)	1.0 (0.98, 1.1)	0.36	ΦΦΦΦ high
Sustained response	1,005 (2**)	71 (FDX) 57 (VAN)	1.2 (1.1, 1.4)	<0.0001	ΦΦΦΦ high

**Teasley Lancet 1983, Wenisch CID 1996, Zar CID 2007, Johnson CID 2014*
***Louie NEJM 2011, Cornely Lancet ID 2012*

Evènements cardio-vasculaires lors des infections invasives à Pneumocoque

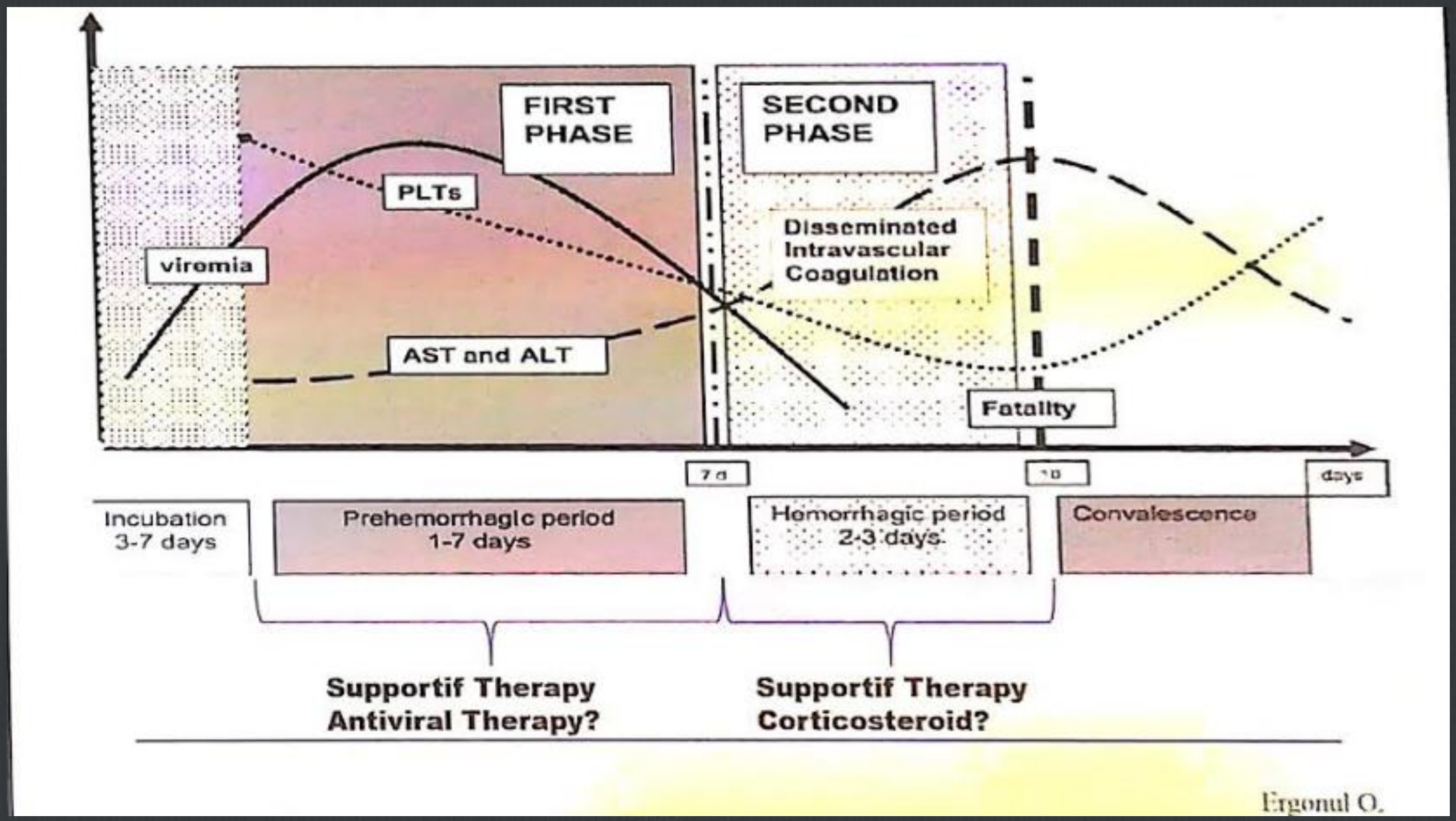


Epidémiologie de la Fièvre de Crimée-Congo



www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/Global_CCHFRisk_2017.jpg?ua=1

Différentes phases de la Fièvre de Crimée-Congo



Etude REACH : effet d'une intervention multimodale d'hygiène retrouvant un effet significatif sur l'acquisition d'une infection à VRE (Staph aureus, C. difficile = NS)

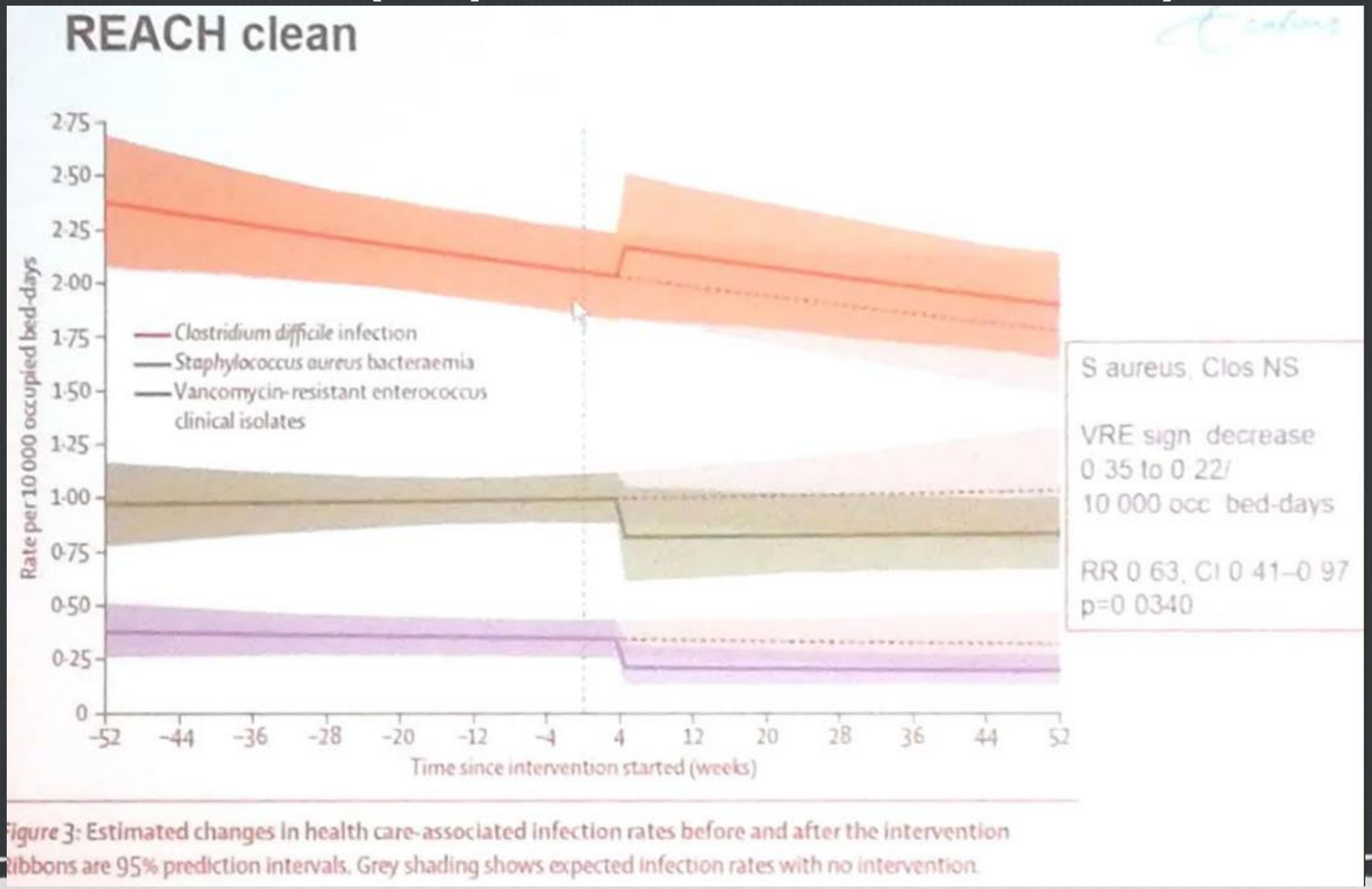


Figure 3: Estimated changes in health care-associated infection rates before and after the intervention
Ribbons are 95% prediction intervals. Grey shading shows expected infection rates with no intervention

Résistance au Linézolide

Resistance to linezolid

Acquired mechanisms of resistance. Clinical isolates

Microorganisms	Mechanism of resistance	Cross-R
S. aureus *S. epidermidis* *S. haemolyticus* CoNS	**Mutations 23S rRNA** G2576T, T2500A, others G2576T, G2603T,C2534T,T2504A G2474T, G2447T, others G2576T G2576T, others	Pleuromutilins (only unidirectional)
S. aureus *S. epidermidis* *S. haemolyticus; S. cohnii;* *S. capitis*, other CoNS	**Acquisition of Cfr methyltransferase** Methylation at A2503G (23S rRNA) Phenotype $PhLOPS_A$ *cfr-1* and *cfr-2* genes Transferable	Phenicols Lincosamides Pleuromutilins Streptogramin A 16-member ring macrolides
S. aureus CoNS	**Mutations ribosomal proteins L3, L4**	Macrolides Phenicols
S. aureus CoNS	**Ribosomal protection OptrA protein** Transferable	Phenicols
S. aureus CoNS	**Ribosomal protection PoxtA protein** Transferable	Phenicols Tetracyclines

Mycobiome des patients en réa