JNI 21es Journées Nationales d'Infectiologie
Poitiers
et la région Nouvelle Aquitaine
Palais des Congrès du Futuroscope
du mercredi 9 septembre 2020
au vendredi 11 septembre 2020

Best-of
Résistance, nouvelles molécules

David Boutoille
Maladies Infectieuses et Tropicales, CHU de Nantes

Liens d'intérêt

- Boards : Astellas, MSD, Shionogi

- Invitations congrès : Correvio, Gilead, MSD

Bactéries à Gram négatif

Nouvelle définition : la résistance difficile à traiter

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America — hivma hiv medicine association

Impact of Difficult-to-Treat Resistance in Gram-negative Bacteremia on Mortality: Retrospective Analysis of Nationwide Surveillance Data

Kyungmin Huh,[1,2] Doo Ryeon Chung,[1,2] Young Eun Ha,[3] Jae-Hoon Ko,[1] Si-Ho Kim,[1] Min-Ji Kim,[4] Hee Jae Huh,[5] Nam Yong Lee,[5] Sun Young Cho,[1] Cheol-In Kang,[1] Kyong Ran Peck,[1] and Jae-Hoon Song[1,2]; for the Korean Antimicrobial Resistance Surveillance Network (KARS-Net) Investigators*

- Contexte : la classification en MDR et XDR ne rend pas forcément compte des difficultés thérapeutiques, et ne rend pas forcément compte de l'impact sur le pronostic.

- **DTR (difficult-to-treat resistance) = Résistance à tous les antibiotiques de 1ère ligne, spécifiquement les β-lactamines et les fluoroquinolones**

Méthodes


Clinical Infectious Diseases

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- Etude rétrospective sur 14 hôpitaux coréens.
- Bactériémies à BGN : *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumanii*

- Objectif : déterminer l'impact de la DTR sur la mortalité à 30 j

- 4 catégories :
  - DTR+
  - CR+/DTR- : résistance aux carbapénèmes, non DTR
  - ESCR+/DTR- : résistance aux céphalosporines (CP) et carbapénèmes, non DTR
  - FQR+/ESCR-CR- : résistance aux fluoroquinolones, sans résistance aux CP et carbapénèmes

Résultats

Clinical Infectious Diseases
MAJOR ARTICLE

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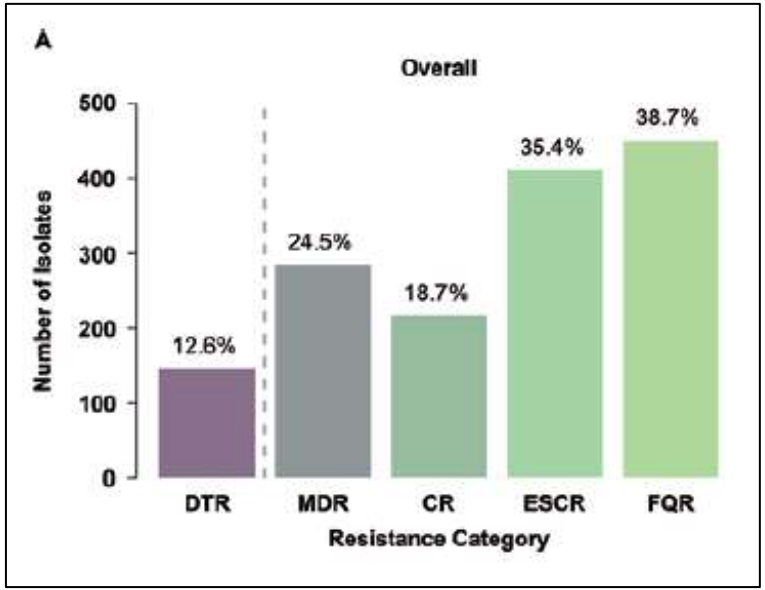

1167 épisodes :

- 147 (12,6 %) : DTR+
- 71 (6,1 %) : CR+ / DTR-
- 216 (18,5 %) : ESCR+ / DTR-
- 99 (8,5 %) : FQR+ / ESCR-CR-
- 634 (52,3 %) : autres

DTR :

- *A. baumanii* : 117 (79,6 %)
- *P. aeruginosa* : 26 (17,7 %)
- *K. pneumoniae* : 4 (1,4 %)
- *E. coli* : 0

Résultats

Clinical Infectious Diseases
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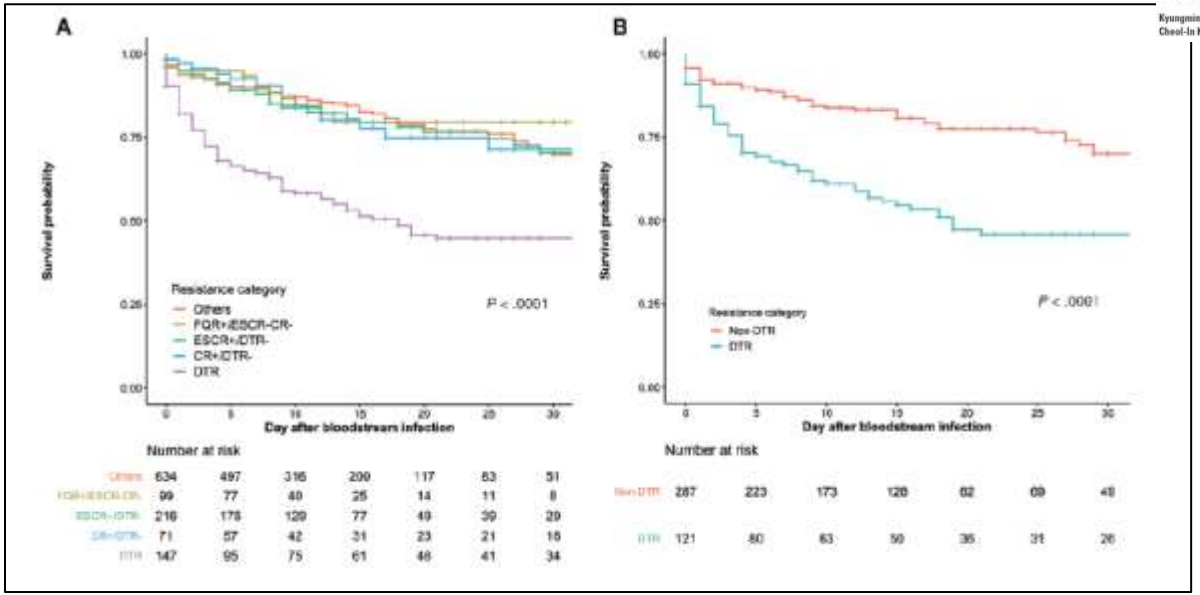

Seule la catégorie DTR sort comme FDR de mortalité

aOR : 3,48 [IC95 % : 1,82-6,79]

Analyse multivariée (A) et en score de propension (B)

Limite de l'étude : essentiellement *A. baumanii*

BLSE : du portage digestif à l'infection

Clinical Microbiology and Infection 26 (2020) 1046–1051

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Infections caused by extended-spectrum β-lactamase-producing Enterobacterales after rectal colonization with ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae*

L.A. Denkel [1,2], F. Maechler [1,2], F. Schwab [1,2], A. Kola [1,2], A. Weber [1,2], P. Gastmeier [1,2], F. Pfäfflin [3], S. Weber [4], G. Werner [5], Y. Pfeifer [5], M. Pietsch [6], R. Leistner [1,2,*]

- **Cohorte de patients hospitalisés à l'hôpital de la Charité, Berlin**
- **Stratégie de screening :**
  - Colonisation antérieure
  - Contact avec porteur
  - Hospitalisation à l'étranger < 6 mois
  - Hospitalisation en réanimation

- Etude de l'incidence des infections survenant durant l'hospitalisation après découverte d'une colonisation rectale à ESBL-E.
- En cas d'infection par la même bactérie, vérification de l'homologie entre souches par PFGE et WGS (pour KP)

Résultats

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266 675 patients hospitalisés pendant la période de l'étude

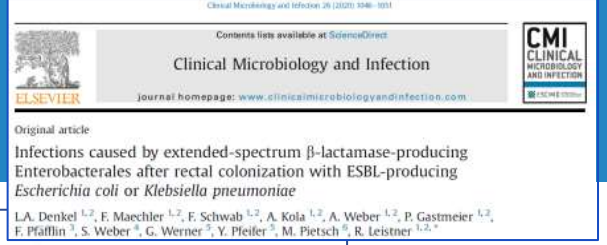
36 349 patients screenés (13,6 %)

2971 porteurs de E-BLSE :
- 2386 *E. coli*
- 585 *K. pneumoniae*

Porteurs de EC-BLSE :
- 3,9 % infections à EC-BLSE
- 5,1 % infections à autre bactérie

Porteurs de KP-BLSE :
- 6,8 % d'infections à KP-BLSE
- 7,7 % infections à autre bactérie

Résultats



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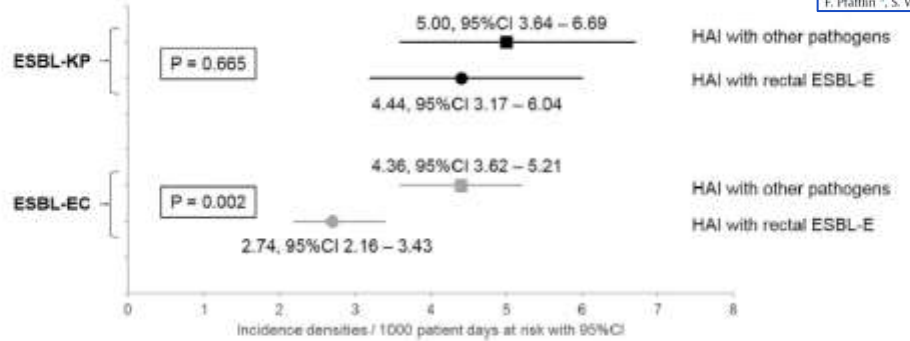

Fig. 2. Incidence densities of healthcare-associated infection (HAI) (per 1000 patient days at risk) with 95% CI, Berlin, Germany, 2014/2015. Incidence densities were calculated for HAI with rectal extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) (●) and for HAI with other pathogens (■) among patients rectally colonised with ESBL-Escherichia coli (EC) (grey) or ESBL-*Klebsiella pneumoniae* (KP) (black). p values were calculated by Poisson test. 95% CI, 95% confidence interval.

- **KP = facteur de risque indépendant d'infection hospitalière après ajustement sur âge et comorbidités.**
- **En cas de survenue d'une infection durant l'hospitalisation :**
  - **Risque quasiment de 50 % que ce soit KP, si colonisation préalable**
  - **Pour *E. coli* : majorité d'infections liées à d'autres pathogènes.**

Limites de l'étude


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- 21 % des patients porteurs d'EC-BLSE en USI, vs 32 % pour les porteurs de KP-BLSE

- Incidence des HAI chez les non-porteurs ?

- Pas d'information sur les antibiotiques reçus avant HAI, ainsi que sur les procédures invasives, et présence de matériels étrangers.

Ceftolozane/Tazobactam

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

Lancet Infect Dis 2019; 19: 1299–311

- Essai phase 3 randomisé, de non-infériorité, en double-aveugle.
- 263 hôpitaux, 34 pays
- Pneumonies nosocomiales
- **3 g Ceftolozane/Tazobactam** toutes les 8 h
- Vs **1 g Meropénème sur 1 h** toutes les 8 h
- Durée 8-14 j (14 j pour les pneumonies à PA)
- Critère principal de jugement : mortalité à J30
- Critère secondaire : guérison clinique en fin de traitement

Caractéristiques de la population

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

Admitted to intensive care unit		
Yes	334 (92%)	334 (92%)
No	28 (8%)	30 (8%)
Previous antibacterial use*		
Yes	318 (88%)	323 (89%)
No	44 (12%)	41 (11%)
Primary diagnosis		
Ventilator-associated pneumonia	263 (73%)	256 (70%)
Ventilated hospital-acquired pneumonia	99 (27%)	108 (30%)
Clinical Pulmonary Infection Score		
≤6	25 (7%)	32 (9%)
7	29 (8%)	35 (10%)
8	45 (12%)	42 (12%)
>8	263 (73%)	254 (70%)

Résultats

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

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	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (–5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	–3·6 (–10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (–2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (–6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	–1·1 (–9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (–7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	–1·3 (–10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (–8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	–7·7 (–25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (–3·4 to 12·5)‡

Non-infériorité atteinte

Clinical Infectious Diseases
MAJOR ARTICLE

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Jason M. Pogue,[1] Keith S. Kaye,[2] Michael P. Veve,[3] Twisha S. Patel,[4] Anthony T. Gerlach,[5] Susan L. Davis,[6] Laura A Puzniak,[7] Tom M. File,[8] Shannon Olson,[9] Sorabh Dhar,[10] Robert A. Bonomo,[11] and Federico Perez[11]

Clinical Infectious Diseases® 2020;71(2):304–10

- Etude rétrospective, multicentrique, USA
- Infections par MDR PA (non-sensibilité à ≥ 1 AB dans ≥ 3 classes)
  ou XDR (non-sensibilité à toutes les classes sauf ≤ 2 classes différentes)
- Traitées au moins 48 h par Ceftolozane/Tazobactam ou Polymyxines IV ou Aminosides IV
- Polymyxines et aminosides inhalés autorisés dans les 2 bras
- Critère principal : guérison clinique

Table 2. Infection and Treatment-related Characteristics

Covariate	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/ Aminoglycoside (N = 100)	*P* Value
Severity of illness and infection-related variables			
Intensive care unit at infection onset	70	68	.76
No sepsis	14	11	.67
Sepsis	48	43	.57
Severe sepsis	15	23	.21
Septic shock	23	23	1.00
Severe sepsis or septic shock	38	46	.22
Vasopressors during therapy	30	34	.54
SOFA (sequential organ failure assessment) score[a]	8 (6–10) (n = 54)[b]	8 (5–10) (n = 63)[b]	.48
Polymicrobial infection	40	46	.39
Site of infection			
Ventilator-associated pneumonia	52	51	1
Hospital-acquired pneumonia	12	24	.04
Urinary tract	16	11	.41
Wound	13	8	.36
Other	7	6	
Presence of bacteremia	6	8	.58
Treatment-related variables			
Infectious diseases consult	100	92	.004
Time to active therapy (hours)[a]	55.5 (23–80.25)	43.5 (4.2–72.3)	.10
Time to study drug (hours)[a]	63.5 (45.3–92)	53.3 (5–93)	.08
Combination therapy	15	72	<.001
Aminoglycoside	0	2	
Polymyxin	0	2	
Ciprofloxacin	3	6	
Meropenem	0	36	
Cefepime	0	8	
Ceftazidime	0	2	
Piperacillin/Tazobactam	0	9	
Aztreonam	0	2	
Inhaled colistin	9	1	
Inhaled aminoglycoside	3	4	
In vitro activity of combination agent			
Susceptible	15	24	
Intermediate	0	17	
Resistant	0	31	
Duration of therapy (days)[a]	9.5 (7–14)	9 (6–14)	.17

[a]Median (interquartile range), otherwise data are presented as n (and percent as n = 100).
[b]Number of patients where all variables were available to calculate SOFA score.

Résultats

Clinical Infectious Diseases
MAJOR ARTICLE

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Table 3. Comparative clinical outcomes between Ceftolozane/Tazobactam and Polymyxin or Aminoglycoside treated patients

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)

- **Supériorité de Ceftolozane/Tazobactam sur Polymyxines ou Aminosides, sur le succès clinique et la survenue d'insuffisance rénale.**
- 250 patients dans chaque groupe auraient été nécessaires pour étudier l'impact sur la mortalité.

- **Posologies non données pour polymyxine/aminosides, du fait d'une hétérogénéïté importante des stratégies de doses.**


Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

Imipénème/Relebactam

CID, mis en ligne Août 2020

- Etude de phase 3, internationale, randomisée, double-aveugle, de non-infériorité
- Pneumopathies acquises à l'hôpital ou sous ventilation mécanique.
- Prélèvement respiratoire bas < 48h : présence d'un pathogène carbapénème-R
- < 24h antibiothérapie efficace dans les 72h précédant l'inclusion

RESTORE-IMI 2 : design

- Randomisation 1:1 :

Imipénème/Cilastatine/Relebactam 500 mg/500 mg/ 250 mg toutes les 6h

Pipéracilline/Tazobactam 4g/500 mg toutes les 6h

- Durée 7-14 j

- Critère de jugement principal : Mortalité à J28

Charactéristiques des patients

Characteristic	IMI/REL (n = 264)	PIP/TAZ (n = 267)	Total (N = 531)
Geographic region			
Americas	59 (22.3)	71 (26.6)	130 (24.5)
United States	5 (1.9)	15 (5.6)	20 (3.8)
Europe	166 (62.9)	160 (59.9)	326 (61.4)
Asia and Australia	39 (14.8)	36 (13.5)	75 (14.1)
APACHE II score			
<15	139 (52.7)	140 (52.4)	279 (52.5)
≥15	125 (47.3)	127 (47.6)	252 (47.5)
Mean (SD)	14.6 (6.2)	14.8 (6.7)	14.7 (6.4)
Median (range)	14.0 (2–31)	14.0 (1–37)	14.0 (1–37)
Primary diagnosis			
Nonventilated HABP	142 (53.8)	131 (49.1)	273 (51.4)
Ventilated HABP/VABP	122 (46.2)	136 (50.9)	258 (48.6)
Ventilated HABP	31 (11.7)	35 (13.1)	66 (12.4)
VABP	91 (34.5)	101 (37.8)	192 (36.2)

Microbiologie

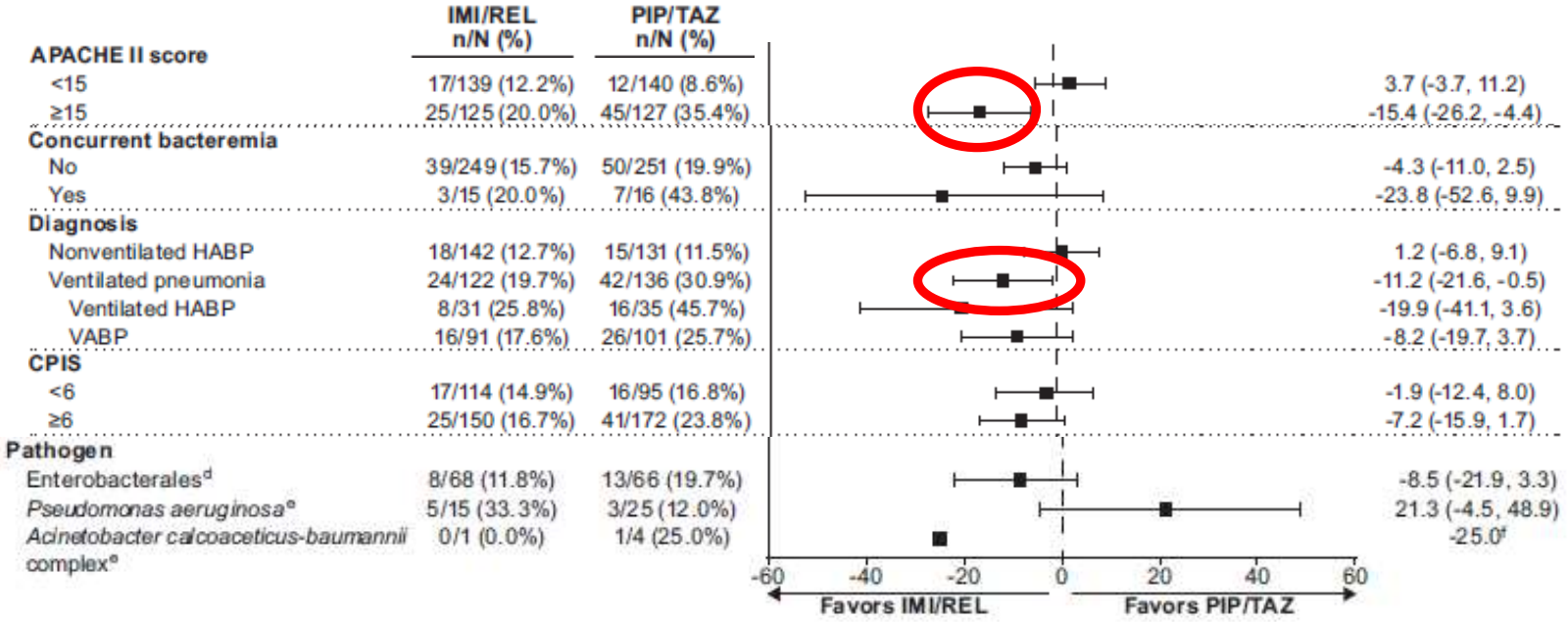
Characteristic	IMI/REL (n = 264)	PIP/TAZ (n = 267)	Total (N = 531)
No. of baseline LRT pathogens			
Monomicrobial	160 (60.6)	160 (59.9)	320 (60.3)
Polymicrobial	55 (20.8)	58 (21.7)	113 (21.3)
None	49 (18.6)	49 (18.4)	98 (18.5)
Baseline LRT pathogen (≥10% in either treatment arm)[c]	(n = 215)	(n = 218)	(N = 433)
Klebsiella pneumoniae	58 (27.0)	53 (24.3)	111 (25.6)
Pseudomonas aeruginosa	34 (15.8)	48 (22.0)	82 (18.9)
Acinetobacter calcoaceticus-baumannii complex	32 (14.9)	36 (16.5)	68 (15.7)
Escherichia coli	30 (14.0)	37 (17.0)	67 (15.5)
MSSA	23 (10.7)	22 (10.1)	45 (10.4)

Résultats

Endpoint	IMI/REL, no./No. (%)[a]	PIP/TAZ, no./No. (%)[a]	Adjusted Difference[b], % (95% CI)
Primary endpoint			
Day 28 all-cause mortality (MITT)	42/264 (15.9)	57/267 (21.3)	−5.3 (−11.9 to 1.2)[c]
Key secondary endpoint			
Favorable clinical response at EFU (MITT)	161/264 (61.0)[d]	149/267 (55.8)[d]	5.0 (−3.2 to 13.2)[e]
Other secondary endpoints			
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	−3.5 (−10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9)[d]	135/218 (61.9)[d]	6.2 (−2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	−3.7 (−13.6 to 6.4)

Non-infériorité pour le critère principal et les critères secondaires

Résultats : mortalité à J28

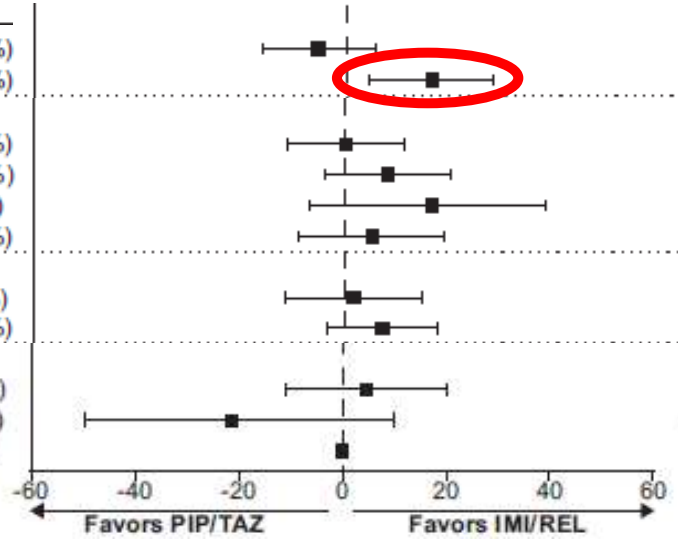


	IMI/REL n/N (%)	PIP/TAZ n/N (%)	
APACHE II score			
<15	17/139 (12.2%)	12/140 (8.6%)	3.7 (-3.7, 11.2)
≥15	25/125 (20.0%)	45/127 (35.4%)	-15.4 (-26.2, -4.4)
Concurrent bacteremia			
No	39/249 (15.7%)	50/251 (19.9%)	-4.3 (-11.0, 2.5)
Yes	3/15 (20.0%)	7/16 (43.8%)	-23.8 (-52.6, 9.9)
Diagnosis			
Nonventilated HABP	18/142 (12.7%)	15/131 (11.5%)	1.2 (-6.8, 9.1)
Ventilated pneumonia	24/122 (19.7%)	42/136 (30.9%)	-11.2 (-21.6, -0.5)
Ventilated HABP	8/31 (25.8%)	16/35 (45.7%)	-19.9 (-41.1, 3.6)
VABP	16/91 (17.6%)	26/101 (25.7%)	-8.2 (-19.7, 3.7)
CPIS			
<6	17/114 (14.9%)	16/95 (16.8%)	-1.9 (-12.4, 8.0)
≥6	25/150 (16.7%)	41/172 (23.8%)	-7.2 (-15.9, 1.7)
Pathogen			
Enterobacterales[d]	8/68 (11.8%)	13/66 (19.7%)	-8.5 (-21.9, 3.3)
Pseudomonas aeruginosa[e]	5/15 (33.3%)	3/25 (12.0%)	21.3 (-4.5, 48.9)
Acinetobacter calcoaceticus-baumannii complex[e]	0/1 (0.0%)	1/4 (25.0%)	-25.0[f]

Supériorité dans le sous-groupe avec score APACHE ≥ 15, et le sous-groupe des patients ventilés

Résultats : réponse clinique favorable

	IMI/REL n/N (%)	PIP/TAZ n/N (%)	
APACHE II score			
<15	90/139 (64.7%)	98/140 (70.0%)	-5.3 (-16.2, 5.8)
≥15	71/125 (56.8%)	51/127 (40.2%)	16.6 (4.3, 28.5)
Diagnosis			
Nonventilated HABP	95/142 (66.9%)	87/131 (66.4%)	0.5 (-10.7, 11.7)
Ventilated pneumonia	66/122 (54.1%)	62/136 (45.6%)	8.5 (-3.7, 20.5)
Ventilated HABP	15/31 (48.4%)	11/35 (31.4%)	17.0 (-6.8, 39.1)
VABP	51/91 (56.0%)	51/101 (50.5%)	5.5 (-8.6, 19.4)
CPIS			
<6	67/114 (58.8%)	54/95 (56.8%)	1.9 (-11.4, 15.3)
≥6	94/150 (62.7%)	95/172 (55.2%)	7.4 (-3.4, 18.0)
Pathogen			
Enterobacterales[d]	45/68 (66.2%)	43/66 (65.2%)	4.7 (-10.9, 20.0)
Pseudomonas. aeruginosa[e]	7/15 (46.7%)	17/25 (68.0%)	-21.3 (-49.7, 10.0)
Acinetobacter calcoaceticus-baumannii complex[e]	1/1 (100.0%)	4/4 (100.0%)	0.0[f]



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journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Colistin plus meropenem for carbapenem-resistant Gram-negative infections: *in vitro* synergism is not associated with better clinical outcomes

Amir Nutman [1,2,*], Jonathan Lellouche [1], Elizabeth Temkin [1], George Daikos [3,4], Anna Skiada [3,4], Emanuele Durante-Mangoni [5,6], Yael Dishon-Benattar [7,8], Roni Bitterman [7], Dafna Yahav [2,9], Vered Daitch [2,9], Mariano Bernardo [5,6], Domenico Iossa [5,6], Oren Zusman [10], Lena E. Friberg [11], Johan W. Mouton [12], Ursula Theuretzbacher [13], Leonard Leibovici [2,10], Mical Paul [2,14], Yehuda Carmeli [1,2]on behalf of the AIDA Study Group[1]

- Analyse secondaire de l'essai AIDA : Colistine vs Colistine + méropénème dans les infections à BGN carbapénème-R
- Détermination de synergie in vitro pour Colistine + méropénème
- (171 souches : 131 *A. baumanii*, 37 entérobactéries, 3 *P. aeruginosa*)

Synergie : 75 => 74 % d'échecs cliniques
Antagonisme : 20 => 55 % d'échecs cliniques
Indifférence : 78 => 75,6 % d'échecs cliniques

Infections à bactéries à Gram +

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD; Matthew A. Roberts, PhD; Alan Cass, MBBS, PhD; David L. Paterson, MBBS, PhD; Hong Foo, MBBS; Mical Paul, MD; Stephen D. Guy, MBBS; Adrian R. Tramontana, MBBS; Genevieve B. Walls, MBChB; Stephen McBride, MBChB; Narin Bak, MBBS, MPH; Niladri Ghosh, MBBS; Benjamin A. Rogers, MBBS, PhD; Anna P. Ralph, MBBS, PhD; Jane Davies, MBBS, PhD; Patricia E. Ferguson, MBBS, PhD; Ravindra Dotel, MBBS; Genevieve L. McKew, MBBS; Timothy J. Gray, MBBS(Hons); Natasha E. Holmes, MBBS(Hons), PhD; Simon Smith, MBChB; Morgyn S. Warner, MD, PhD; Shirin Kalimuddin, MBBS, MPH; Barnaby E. Young, MBBS; Naomi Runnegar, MBBS; David N. Andresen, MBBS; Nicholas A. Anagnostou, MBBS; Sandra A. Johnson, BSc, MPH; Mark D. Chatfield, MSc; Allen C. Cheng, MBBS, PhD; Vance G. Fowler Jr, MD, MHS; Benjamin P. Howden, MBBS, PhD; Niamh Meagher, MBiostat; David J. Price, PhD; Sebastiaan J. van Hal, MBChB, PhD; Matthew V. N. O'Sullivan, MBBS, PhD; Joshua S. Davis, MBBS, PhD; for the Australasian Society for Infectious Diseases Clinical Research Network

JAMA. 2020;323(6):527-537.

Essai CAMERA II

- Etude ouverte, randomisée.
- 27 sites, 4 pays (Australie, Singapour, Israël, Nouvelle-Zélande).

- Août 2015 à juillet 2018.
- 352 patients avec bactériémie à SARM.

Vancomycine ou Daptomycine - monothérapie (n = 178)
- association avec Flucloxacilline, Cloxacilline, ou Céfazoline 7 j (n = 174)

Vancomycine : dosée pour obtenir des résiduelles de 16 – 20 mg/L
Daptomycine : 6-10 mg/kg/j

Cloxa et Flucloxacilline : 2 g toutes les 6 h
Cefazoline (si allergie péni) : 2 g toutes les 8 h

Critères de jugement

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Critère de jugement principal = critère composite :

- Mortalité J90
- Bactériémie persistante J5
- Récidive microbiologique
- Echec microbiologique

Critères secondaires :

- Mortalité J14, J42, J90
- Bactériémie persistante J2 et J5
- Insuffisance rénale aiguë
- Durée de ttt IV
- Récidive microbiologique
- Echec microbiologique

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Table 2. Characteristics of Patients During the Trial in the Primary Analysis Population

Characteristics	Combination Therapy (n = 174)	Standard Therapy (n = 178)
Final diagnosis of infective endocarditis, No. (%)[a]	26 (15)	16 (9)
Received vancomycin, No. (%)[b]	171 (98)	178 (100)
Received daptomycin, No. (%)[b]	7 (4)	6 (3)
Trough vancomycin level, mean (SD), μg/mL		
Day 1	15.1 (8.1)	14.7 (7.3)
Day 2	17.9 (9.1)	17.2 (8.0)
Day 3	20.1 (7.6)	19.2 (7.5)
Received any nonstudy antibiotic during days 1-7, No. (%)[c]	53 (30)	48 (27)
Infectious diseases consultation, No. (%)	168 (97)	171 (96)
Presumed infected source removed, No. (%)	77/106 (73)	84/105 (80)
Time to removal of infected source, median (IQR), d[d]	0.0 (−1.0 to 2.0)	0.0 (−1.0 to 2.0)
Echocardiogram performed, No. (%)	161 (93)	168 (94)
Transthoracic	151 (87)	151 (85)
Transesophageal	61 (35)	68 (38)

Table 3. Primary and Secondary Outcomes

Outcomes	No./Total No. (%) Combination Therapy	Standard Therapy	Risk Difference, % (95% CI)	*P* Value
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

Pas de différence sur la mortalité
Arrêt de l'essai à 80 % du recrutement prévu

Survenue d'une insuffisance rénale : 28 % pour la cloxacilline et la flucloxacilline
4 % pour la céfazoline

Limites

JAMA | Original Investigation

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- Résultats limités à l'association vancomycine + pénicilline M.
- Très peu de daptomycine.

- Large utilisation des pénicillines M et peu de la céfazoline.

Nouveaux antibiotiques

Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

Marcus Y Chen, Anna McNulty, Ann Avery, David Whiley, Sepehr N Tabrizi, Dwight Hardy, Anita F Das, Ashley Nenninger, Christopher K Fairley, Jane S Hocking, Catriona S Bradshaw, Basil Donovan, Benjamin P Howden, David Oldach, on behalf of the Solitaire-U Team

Lancet Infect Dis 2019; 19: 833–42

- Etude ouverte
- Multicentrique (USA, Australie)

- Infection génitale par le gonocoque, homme ou femme

- **Solithromycine (Cempra Pharmaceuticals, USA) :** macrolide de 4ème génération, qui reste actif sur la plupart des souches résistantes à l'azithromycine.
  - 1000 mg PO dose unique
  - Vs Ceftriaxone 500 mg IM + Azithromycine 1 g PO

- Critère de jugement principal : éradication microbiologique à J7 ± 2

	Solithromycin (n=123)	Ceftriaxone plus azithromycin (n=129)	Difference (95% CI)
Primary outcome			
Eradication	99 (80%)	109 (84%)	−4·0% (−13·6 to 5·5)*
Persistence	8 (7%)	0	..
Indeterminate	16 (13%)	20 (16%)	..
Secondary outcomes†			
Eradication of genital gonorrhea			
Overall	97/105 (92%)	107/107 (100%)	−7·6 (−14·3 to −3·9)
Women	5/5 (100%)	5/5 (100%)	..
Men	92/100 (92%)	102/102 (100%)	..
Eradication of pharyngeal gonorrhea			
Overall	15/16 (94%)	19/19 (100%)	−6·3 (−28·8 to 11·6)
Women	2/2 (100%)	1/1 (100%)	..
Men	13/14 (93%)	18/18 (100%)	..
Eradication of rectal gonorrhea			
Overall	5/6 (83%)	12/12 (100%)	−16·7 (−57·4 to 11·6)
Women	1/1 (100%)	1/1 (100%)	..
Men	4/5 (80%)	11/11 (100%)	..
Eradication of gonorrhea at all anatomical sites (by-patient analysis)‡			
Overall	95/104§ (91%)	107/107 (100%)	−8·7 (−15·7 to −4·6)
Women	5/5 (100%)	5/5 (100%)	..
Men	90/99 (91%)	102/102 (100%)	−9·1 (−16·4 to −4·8)
Heterosexual men	20/21 (95%)	24/24 (100%)	−4·8 (−23·0 to 9·7)
Men who have sex with men	70/78 (90%)	78/78 (100%)	−10·3 (−19·0 to −5·3)

Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

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Non-infériorité non atteinte

Le faible taux d'éradication dans les 2 groupes est lié au nombre de patients qui ne se sont pas présentés à la visite de J7.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

December 2019 Volume 63 Issue 12 e01733-19

Estimating the Size of the U.S. Market for New Antibiotics with Activity against Carbapenem-Resistant *Enterobacteriaceae*

Cornelius J. Clancy,[a] M. Hong Nguyen[a]

Calcul d'un marché annuel aux USA de 289 M $ pour les antibiotiques anti-CRE (169 – 439)

Ventes entre février 2018 et Janvier 2019 :

- Ceftazidime/Avibactam 92,4 M $
- Meropenem/Vaborbactam 7,9 M $
- Plazomicine 0,7 M $

Allergan a vendu Ceftazidime/Avibactam
Medicines Company a vendu Meropenem/Vaborbactam du fait de retours sur investissement insuffisants.

Archaogen a fait faillite après avoir perdu > 450 M $ pour le développement de la Plazomicine.

Published in final edited form as:
N Engl J Med. 2019 August 08; 381(6): 503–505. doi:10.1056/NEJMp1905589.

Sustainable Discovery and Development of Antibiotics — Is a Nonprofit Approach the Future?

Travis B. Nielsen, Ph.D., Eric P. Brass, M.D., Ph.D., David N. Gilbert, M.D., John G. Bartlett, M.D., Brad Spellberg, M.D.

- **Incitations financières pour la recherche sur nouveaux antibiotiques :**
  - Combacte
  - ND4BB
- **En 2019 : 42 antibiotiques étaient en développement clinique ou préclinique, contre 6 en 2004.**
- **Le nombre d'antibiotiques approuvés chaque année par la FDA a triplé ces 6 dernières années.**

- **Mais marché de niches, avec drogues concurrentielles, et des besoins qui ne sont toujours pas satisfaits Faillite d'Archaogen.**

- **Plaidoyer pour la création d'organisations à but non lucratif qui assureraient recherche, développement et commercialisation des nouveaux antibiotiques, sur le modèle de :**
  - TB Alliance : pour la Bedaquiline
  - Medicines for Malaria Venture : artesunate

- **Merci pour votre attention**