Tolerance and microbiological efficacy cefepim or piperacillin/tazobactam in combination with vancomycin as empirical antimicrobial therapy of PJI

C. Triffault-Fillit, E. Mabrut, K. Corbin, A. Becker, E. Braun, M. Tod, S. Goutelle, M.H. Fessy, C. Dupieux, F. Laurent, S. Lustig, C. Chidiac, T. Ferry, F. Valour, on behalf of the Lyon BJI study group

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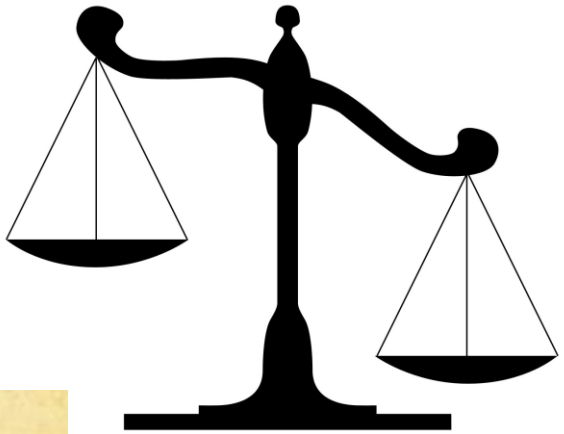
ciri Centre International de Recherche en Infectiologie

UCBL Lyon 1

Introduction

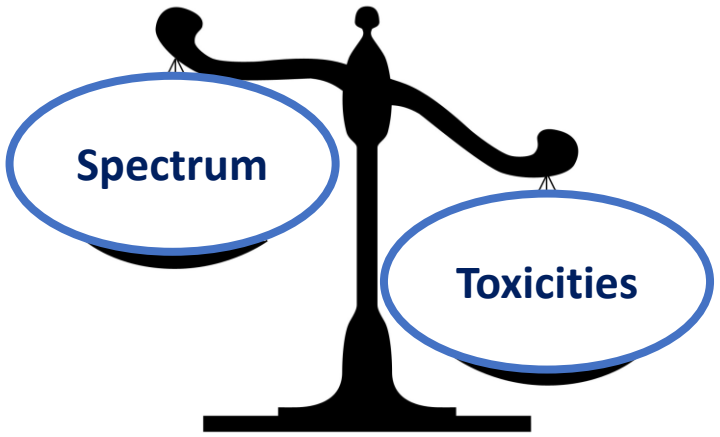
Empirical antimicrobial therapy : the right balance

Spectrum



Toxicities

Introduction



Main pathogens

Gram positive cocci : SA, CoNS *(> 65%),*
Streptococcus (20%),
Gram negative bacilli : *Enterobacteriaceae (20%)*

VANCOMYCIN + BROAD SPECTRUM BETA-LACTAMIN

- 3rd generation cephalosporin
- Piperacillin-Tazobactam

Osmon 2013, IDSA Guidelines, Hoyby 2014 ESCMID Guidelines

Introduction

Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-Tazobactam or Cefepime

Diane M. Gomes,[1] Carmen Smotherman,[2] Amy Birch,[1,3] Lori Dupree,[1,3] Bethany J. Della Vecchia,[1,3] Dale F. Kraemer,[2,4] and Christopher A. Jankowski[1,3]*

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Clinical Infectious Diseases

REVIEW ARTICLE

Systematic Review and Metaanalysis of Acute Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam

Drayton A. Hammond,[1,2] Melanie N. Smith,[3] Chenghui Li,[1] Sarah M. Hayes,[4] Katherine Lusardi,[2] and P. Brandon Bookstaver[5]

[1]Department of Pharmacy Practice, University of Arkansas for Medical Sciences, College of Pharmacy, and [2]Department of Pharmacy, University of Arkansas for Medical Sciences Medical Center, Little Rock; [3]Department of Pharmacy, Medical University of South Carolina, Charleston; [4]Department of Pharmacy, University of Minnesota Medical Center, Minneapolis; and [5]Department of Clinical Pharmacy and Outcome Sciences, College of Pharmacy at the University of South Carolina, Columbia

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Dale F. Kraemer,[2,4] and Christopher A. Jankowski[1,]

Clinical Infectious Diseases

REVIEW ARTICLE

Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults: A Systematic Review and Meta-Analysis

Megan K. Luther, PharmD[1–3]; Tristan T. Timbrook, PharmD, MBA, BPCS[1,2]; Aisling R. Caffrey, PhD, MS[1–4]; David Dosa, MD, MPH[3,4]; Thomas P. Lodise, PharmD, PhD[5]; Kerry L. LaPlante, PharmD, FCCP[1–4]

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Medical Sciences, College of Pharmacy, and [2]Department of Pharmacy, University of Arkansas for Medical Sciences Medical Center, uth Carolina, Charleston; [4]Department of Pharmacy, University of Minnesota Medical Center, Minneapolis; and [5]Department of at the University of South Carolina, Columbia

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Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-

Dia

Is the Combination of Piperacillin-Tazobactam and Vancomycin Associated with Development of Acute Kidney Injury? A Meta-analysis

Christopher A. Giuliano, Chandni R. Patel,[a] and Pramodini B. Kale-Pradhan,*
Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Science, Wayne State University, St. John Hospital and Medical Center, Detroit, Michigan

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Acute Kidney Injury in Adults: A Sy

and Meta-Analysis

Megan K. Luther, PharmD[1–3]; Tristan T. Timbrook, PharmD, MBA, BI
David Dosa, MD, MPH[3,4]; Thomas P. Lodise, PharmD, PhD[5]; Kerry L. LaPlante, PharmD, FCCP[1–4]

Metaanalysis of Acute Kidney
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Clinical Infectious Diseases
MAJOR ARTICLE

Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin–Tazobactam Compared to Those on Vancomycin and Cefepime

Bhagyashri Navalkele,[1,2] Jason M. Pogue,[2,7] Shigehiko Karino,[1,2] Bakht Nishan,[2] Madiha Salim,[2] Shantanu Solanki,[2] Amina Pervaiz,[2] Nader Tashtoush,[2] Hamadullah Shaikh,[2] Sunitha Koppula,[2] Jonathan Koons,[2] Tanveer Hussain,[2] William Perry,[2] Richard Evans,[3] Emily T. Martin,[3] Ryan P. Mynatt,[4] Kyle P. Murray,[5] Michael J. Rybak,[2,4,6] and Keith S. Kaye[1,2]

[1]Department of Medicine, Detroit Medical Center, and [2]Wayne State University School of Medicine, Detroit; [3]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [4]Department of Pharmacy Services, Detroit Receiving Hospital, [5]Department of Pharmacy Services, Huron Valley Sinai Hospital, [6]Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, and [7]Department of Pharmacy Services, Sinai-Grace Hospital, Detroit, Michigan

Metaanalysis of Acute Kidney
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Piperacillin/Tazobactam

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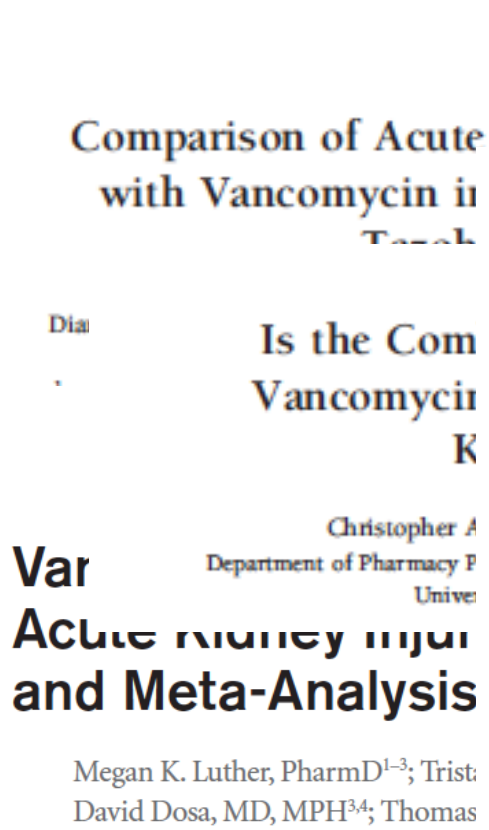
Introduction



Comparison of Acute Kidney Injury During Tre
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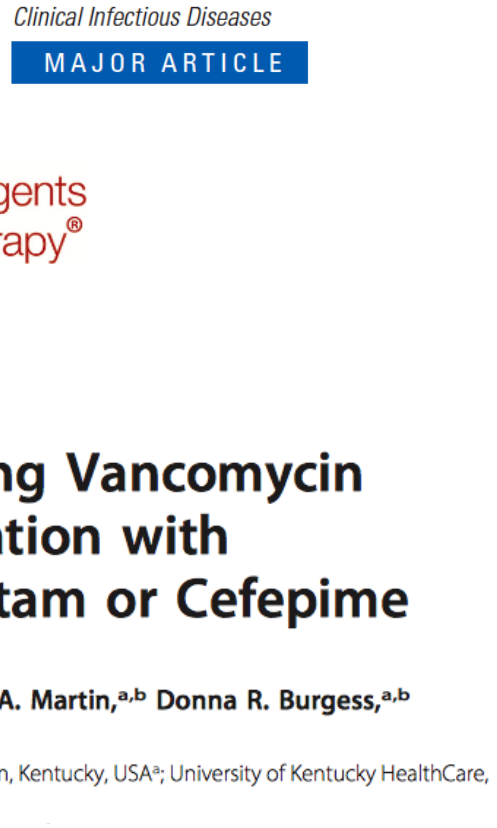


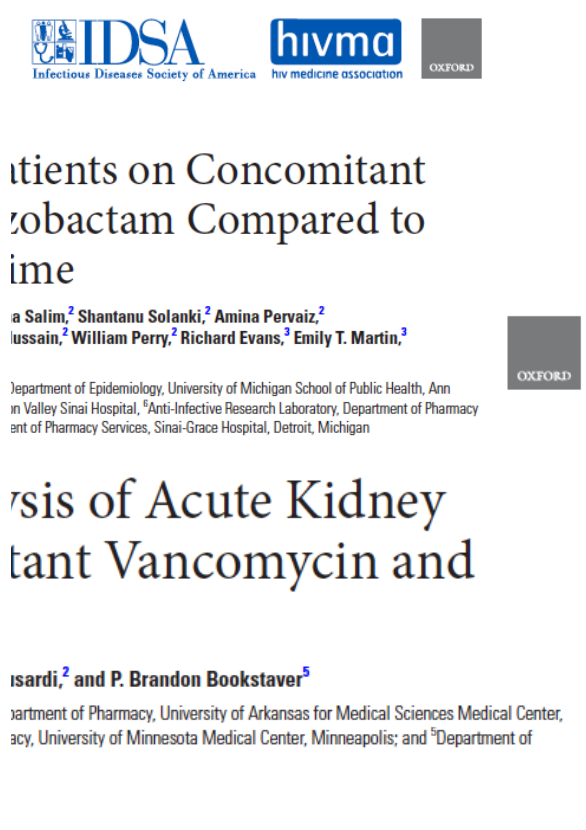
Clinical Infectious Diseases

MAJOR ARTICLE

Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime

W. Cliff Rutter,[a,b] Jessica N. Cox,[b] Craig A. Martin,[a,b] Donna R. Burgess,[a,b] David S. Burgess[a]

University of Kentucky College of Pharmacy, Lexington, Kentucky, USA[a]; University of Kentucky HealthCare, Lexington, Kentucky, USA[b]



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ime

a Salim,[2] Shantanu Solanki,[2] Amina Pervaiz,[2]
lussain,[2] William Perry,[2] Richard Evans,[3] Emily T. Martin,[3]

OXFORD

Department of Epidemiology, University of Michigan School of Public Health, Ann
n Valley Sinai Hospital, [6]Anti-Infective Research Laboratory, Department of Pharmacy
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partment of Pharmacy, University of Arkansas for Medical Sciences Medical Center,
acy, University of Minnesota Medical Center, Minneapolis; and [5]Department of

Material & methods

Cohort matched study, in our reference center for the management of PJI in Lyon, between 2012 and 2018

227 Empirical antimicrobial therapies

Vancomycin / Piperacillin-tazobactam

Vancomycin / Cefepim

2012

01/01/2017

2018

n = 138

n = 89

Propensity matching score 1:1 (nearest neighbor)

Age
Baseline creatinin
Nephrotoxics

n = 89

n = 89

Results

				Piperacillin/tazobactam-vancomycin n=89	Cefepim-vancomycin n=89	p-value
Demographics						
	Sex (male)			49 (55.1%)	42 (47.2%)	0.294
	Age (years)			69 (61-77)	67 (58-75)	0.250
Comorbidities						
	BMI (kg/m^2)			29.4 (24.0-33.2)	28.4 (24.0-33.2)	0.800
	ASA score			2 (2-3)	2 (2-3)	0.783
	Modified Charlson comorbidity index			3 (2-4)	2 (2-4)	0.291
Baseline renal fonction						
	Creatinin level (umol/L)			60 (51-70)	60 (52-71)	0.955
	GFR (mL/min)			106.9 (79.8-140.7)	107.5 (85.0-138.9)	0.756
	Chronic kidney injury			32 (36.0%)	34 (38.2%)	0.877
	Other nephrotoxics			21 (23.6%)	33 (37.1%)	0.072

Results

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Results

			Piperacillin/tazobactam-vancomycin n=89	Cefepim-vancomycin n=89	p-value
EAT					
	Betalactam dose (mg/kg/d)		162.2 (133.3-176.5)	76.2 (63.2-89.6)	NA
	Vancomycin initial dose (mg/kg/d)		29.4 (25.0-33.3)	29.4 (25.0-33.3)	0.880
	Vancomycin trough concentration (mg/L)		17.4 (13.0-21.0)	14.4 (10.9-20.8)	0.032
	Appropriate EAT		77 (98.7%)	65 (98.5%)	1.000
EAT-related adverse events			27 (30.3%)	13 (14.6%)	0.019
	Delay (days)		8 (6-13.5)	8 (1-16)	0.568
	Grade CTCAE				
		1	11 (40.7%)	8 (61.5%)	0.314
		2	9 (33.3%)	4 (30.8%)	1.000
		3	7 (25.9%)	1 (7.7%)	0.236
	Acute kidney injury		23 (25.8%)	6 (6.7%)	$<10^{-3}$
	EAT discontinuation / AE		20 (22.5%)	5 (5.6%)	0.002
	Resolution		26 (96.3%)	12 (92.3%)	1.000

Results

Univariate analysis

	AKI	No AKI	p-value	OR (95%CI)	p-value
Demographics					
Sex (male)	13 (44.8%)	78 (52.3%)	0.544	0.740 (0.333-1.645)	0.459
Age (years)	69 (61.73%)	67 (69-75)	0.604	1.014 (0.981-1.048)	0.415
Comorbidities					
BMI (kg/m^2)	32.4 (33.0-34.7)	28.5 (23.9-33.0)	0.040	1.073 (1.014-1.135)	0.014
ASA score	2 (2-3)	2 (2-3)	0.010	2.632 (1.328-5.218)	0.006
Modified Charlson comorbidity index	3 (3-4)	3 (2-4)	0.081	1.193 (1.008-1.411)	0.040
Baseline renal fonction					
Creatinin level (umol/L)	65 (56-74)	60 (51-70)	0.079	1.000 (0.995-1.005)	0.899
GFR (mL/min)	98.7 (78.2-135.3)	108.3 (84.8-140.7)	0.186	0.993 (0.983-1.003)	0.196
Chronic kidney injury	13 (44.8%)	53 (35.6%)	0.402		
Other nephrotoxics	10 (34.5%)	44 (29.5%)	0.660	1.256 (0.541-2.917)	0.596
EAT					
Piperacillin-tazobactam	23 (79.3%)	66 (44.3%)	0.001	4.821 (1.855-12.526)	0.001
Piperacillin-tazobactam dose (mg/kg/d)	164.9 (134.6-187.5)	162.2 (133.3-176.5)	0.531	1.004 (0.991-1.018)	0.512
Cefepime dose (mg/kg/d)	78.6 (67.4-81.9)	75.9 (63.2- 90.9)	0.676	0.937 (0.944 -1.032)	0. 565
Metronidazole	3 (10.3%)	15 (10.3%)	1.000	1.000(0.270-3.703)	1.000
Vancomycin initial dose (mg/kg/d)	28.8 (26.3-31.7%)	29.4 (25.0 – 33.3)	0.650	1.003 (0.941-1.070)	0.916
Vancomycin trough max (mg/L)	17.8 (12.7-23.1)	15.6 (11.7-20.7)	0.356	1.025 (0.976-1.078)	0.323

Results

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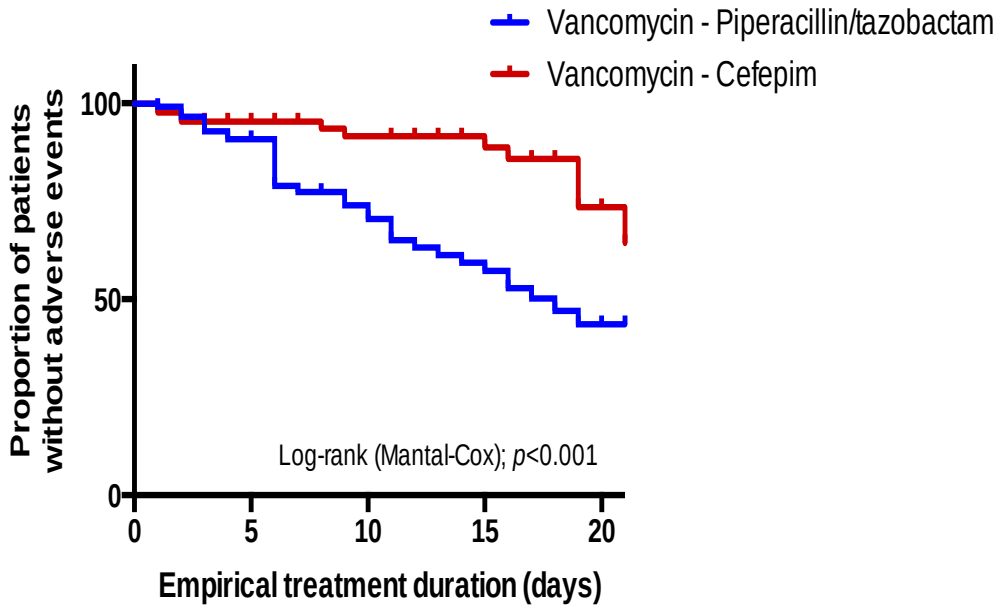
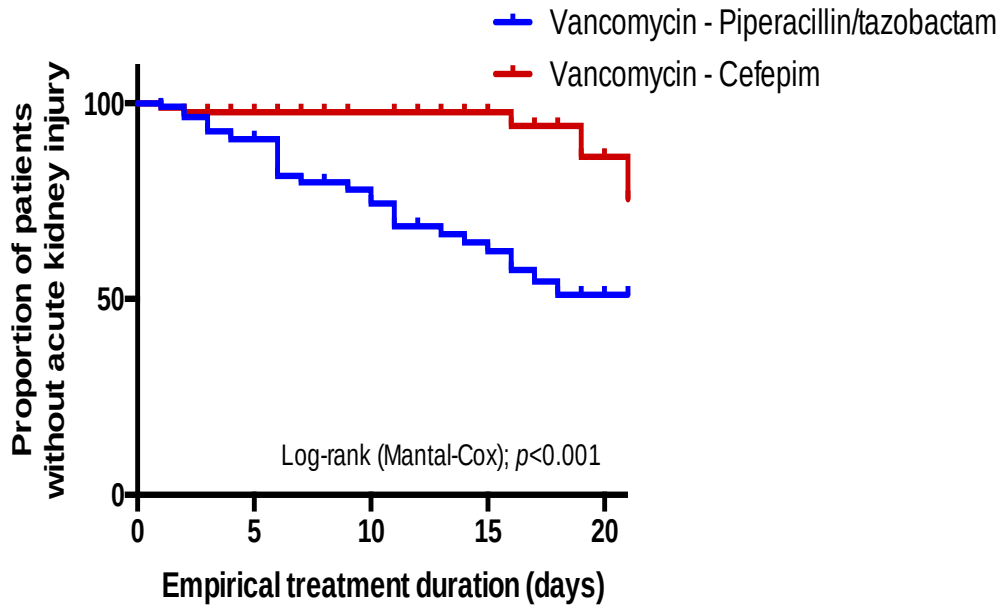
Results

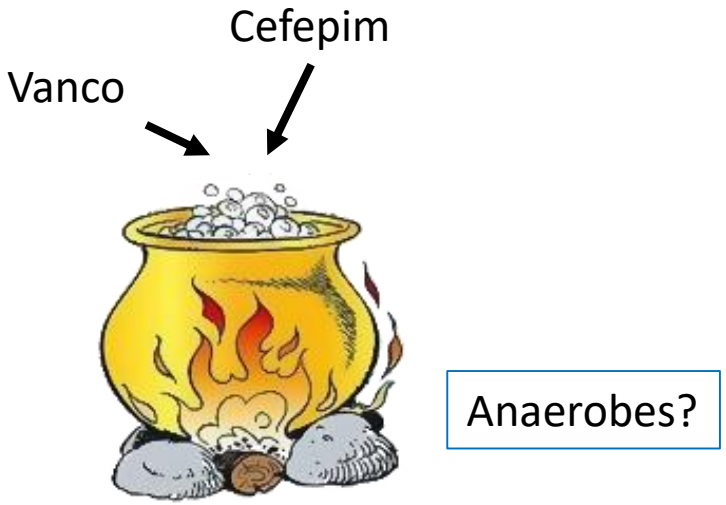
Multivariate analysis

	Adjusted odds ratio	95% CI	p-value
Piperacillin-tazobactam	5.439	1.949-15.178	0.001
IMC	1.064	0.999-1.133	0.055
ASA	1.020	0.824-1.263	0.854
Charlson	2.174	0.932-5.071	0.072





Discussion



Anaerobes?

Coverage : V/PT 98.7% vs V/C 98.5% (*p*=1.000)
Non documented infection 18%

Discussion

Cefepim

Vanco

+ Metronidazole

Anaerobes?

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Vanco + Piperacillin-tazobactam

Prior documentation
BMR

Discussion

Vanco + Cefepim + Metronidazole

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Vanco + Piperacillin-tazobactam

Prior documentation BMR

Median AE delay : 8 days

Discussion

Vanco + Cefepim + Metronidazole

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Vanco + Piperacillin-tazobactam

Prior documentation BMR

Median AE delay : 8 days

Earlier targeted antimicrobial therapy ?

Discussion – Conclusion

Vanco + Cefepim + Metronidazole

Anaerobes?

Coverage : V/PT 98.7% vs V/C 98.5% (*p*=1.000)
Non documented infection 18%

Daptomycin
Linezolid
~~Vanco~~
Piperacillin-tazobactam

Prior documentation BMR

Median AE delay : 8 days

Earlier targeted antimicrobial therapy ?

Acknowledgements

Thank you for your attention

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Acknowledgements

Lyon BJI Study group

Coordinator: Tristan Ferry
Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Patrick Miailhes, Florence Ader, Sandrine Roux, Claire Triffault-Fillit, Agathe Becker, Anne Conrad, Marielle Perry, Cécile Pouderoux, Marie-Elodie Langlois, Fatiha Daoud, Johanna Lippman, Evelyne Braun, Christian Chidiac
Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Romain Gaillard, Stanislas Gunst, Julien Roger, Charles Fiquet, Michel-Henry Fessy, Anthony Viste, Quentin Ode, Gaël Gaudin, Tanguy Ledru, Adrien Van Haecke, Quentin Ode, Marcelle Mercier, Florie Alech-Tournier, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Sébastien Martres, Franck Trouillet, Yannick Herry, Cédric Barrey, Emmanuel Jouanneau, Sophie Brosset, Brice Gérenton, Ali Mojallal, Fabien Boucher, Hristo Shipkov, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizal
Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo
Microbiologists – Frederic Laurent, Céline Dupieux, Laetitia Berraud, Camille Kolenda, Jérôme Josse
Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile
PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle
Clinical Research Assistant and data manager – Eugénie Mabrut

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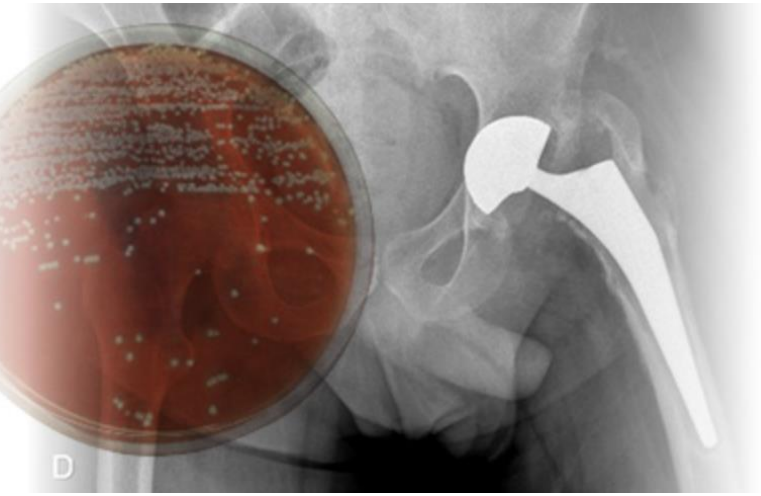

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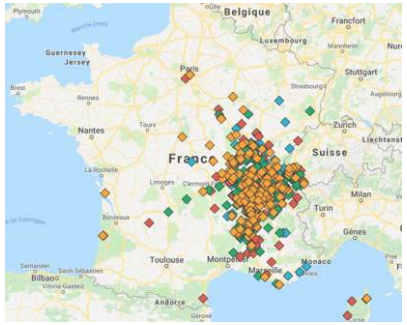

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Material & methods

Cohort matched study, in our reference center for the management of PJI in Lyon, between 2012 and 2018

Inclusion criteria

All adult patients (>18 years) managed for a PJI who received an empirical antimicrobial therapy

Prosthetic joint infection

Clinical, morphological, microbiological and therapeutic criteria

Adverse events (AE)

- Classification according to the National Cancer Institute (CTCAE)
- AKI definition according to current guidelines (KDIGO 2012) – creatinin baseline increase ≥ 0.3mg/ml
- Prospective collection of the AE characteristics (V/C) – Retrospective for V/PT