



Place des Nouveaux Antibiotiques

DESC Maladies Infectieuses Octobre 2007

B Guery
Maladies Infectieuses - CHRU Lille



Caractéristiques des drogues

- Larges spectres vs spectres étroits
- Oral et/ou IV
- Modification d'une classe existante vs. nouvelle classe

CLASSE EXISTANTE	NOUVELLE CLASSE
Quinopristine/dalfopristine	Linezolid
Tigecycline	Daptomycine
Dalbavancine, Oritavancine	Telithromycine
Ertapenème	



Pourquoi développer?

- Supériorité Microbiologique
 - Inhibition organismes résistants
- Avantage Pharmacologique
 - Fréquence de dosage
 - Facilité d'administration
- Sécurité d'administration



Design des études

- Indications cliniques et pathogènes rencontrés
 - Monomicrobien – *S. aureus* – IPTMc
 - Infection mixte – intra-abdominal
- Le pathogène potentiel guide la sélection de l'agent comparatif
 - Etroit – Infection urinaire, IPTM
 - Large – PAC, HAP, infection intra abdominale



Design de l'étude

- Type d'étude pour prouver la non-inferiorité
 - Aveugle
 - double ou investigateur
 - ouverte
- Taille des bras
 - Taux d'efficacité projeté
 - "delta"
 - Intervalle de Confiance 95%
- End Points – Clinique vs Microbiologique



Sélectionner delta

- Drogue supérieure au placebo, étude de supériorité
 - Mise en place d'un board de monitoring
- Gravité de l'infection affecte le delta
 - Peu grave: Impetigo, IU, gonococcie
 - Modérée: Bactériémie/Pneumonie Nosocomiale
 - Sévère (rare): Endocardite/Méningite
- Drogue équivalente au Tt standard
 - "Biocreep"



“Biocreep”

- Historique: drogues avec une efficacité inférieure au Tt standard...
- “Biocreep” – un produit accepté comme non inférieur qui n’est pas meilleur que le placebo



Delta

Taux de guérison prédit (%)	Delta (%)
90	10
80-89	15
<80	20



Impact des petits Delta

- Nombre de patients à inclure plus important
- Durée d'inclusion plus longue
- Etude multinationale
 - Populations différentes
 - Variabilité des contrôles (pratiques...)
- Coûts majeurs
 - Grosses firmes
 - Biotech



Stopper les biocreep

- “Biocreep”
 - Selection des comparatifs en collaboration avec les sociétés savantes
 - SPILF, SPLF, SRLF,
 - IDSA, SCCM, ATS
 - BTS.....
 -



Infections peu sévères

- Drogues orales
 - Infection peau et tissus mous
 - Sinusites
 - Otite moyenne
 - Bronchite
 - Infection urinaire
- Delta 10%



Infections sévères

- Drogues IV

Diagnosis	Expected Cure Rate (%)
Nosocomial Pneumonia	75-85
Hospitalized CAP	85-90
Intra-abdominal infection	85
cSST	80-88

Delta: 10%?

Paradoxe des infections à forte mortalité

- Tolérer un delta plus important dans les infections sévères type méningite-endocardite car la stérilisation du sang et du LCR sont des endpoints solides

<u>Indication</u>	<u>Mortality</u>
Meningitis	10-28%
Bacterial Endocarditis	
Viridans Strep	4-16
Enterococcus	15-25
<i>S. aureus</i>	24-47%



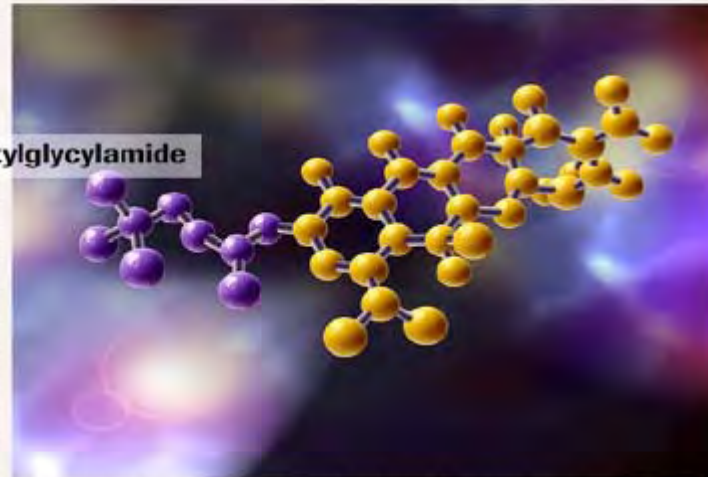
Conclusions sur le Delta

- Les infections communautaires
 - les biocreep sont les + fréquents
 - Un petit delta est donc approprié
 - le meilleur comparatif doit être sélectionné
- Dans les infections sévères
 - delta doit être basé sur des considérations cliniques et statistiques
 - comparatif doit être le Tt standard
 - Le delta peut être grand car les endpoint sont solides et l'incidence est basse

TYGACIL

Dérivé semi-synthétique de la minocycline, porteur d'un groupe t-butylglycylamide en position C9¹

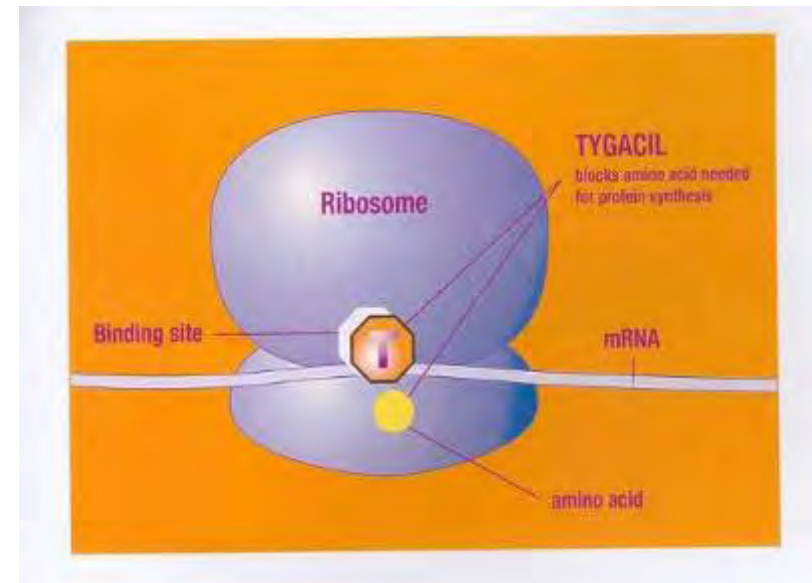
■ Groupe t-butylglycylamide



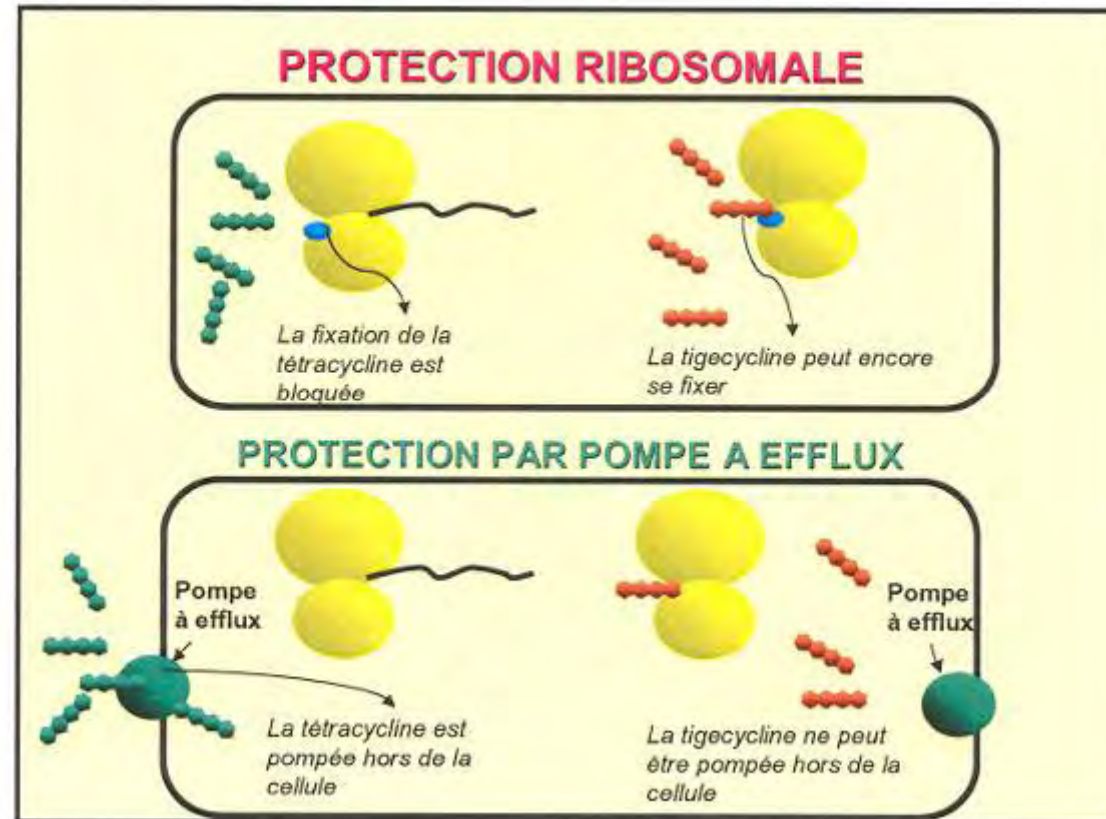
1. Chopra I. Glycylcyclines : third-generation tetracycline antibiotics. *Curr Opin in Pharmacology* 2001 ; 1 : 464-469.

Tigecycline: le mode d'action

- Inhibition de la synthèse protéique
- Par fixation au ribosome 30S
- Empêche la liaison d'ARNt



Conservation d'activité





Le mode d'action

- **Effet post antibiotique**
 - 8 à 9 h sur *S. pneumoniae*
 - 4 à 9h sur *E. coli*
- **Bactéricidie temps-dépendante (in vitro)**
 - *S. pneumoniae*
 - *H. influenzae*
 - *N. gonorrhoeae*



L'élimination et les interactions

- Biliaire: 59%
- Urinaire: 33%
- Cinétique indépendante de l'âge, sexe, poids, insuffisance rénale
- Pas d'interaction avec CY P450
- Pas d'interaction médicamenteuse (warfarine, digoxine)



Le spectre d'activité (1)

- Cocci à Gram positif:
 - Staphylocoques
 - Streptocoques
 - Enterocoques (ERV)

- Bacilles à Gram négatif aérobies
 - *Klebsiella, Enterobacter, Citrobacter, Acinetobacter*
 - *Haemophilus, Pasteurella*
 - *Neisseria*
 - *Salmonella*



Le spectre d'activité (2)

- **Résistances naturelles :**

- *Pseudomonas aeruginosa*
- *Proteus sp*
- *Providencia sp*
- *Morganella sp*



Le spectre d'activité (3)

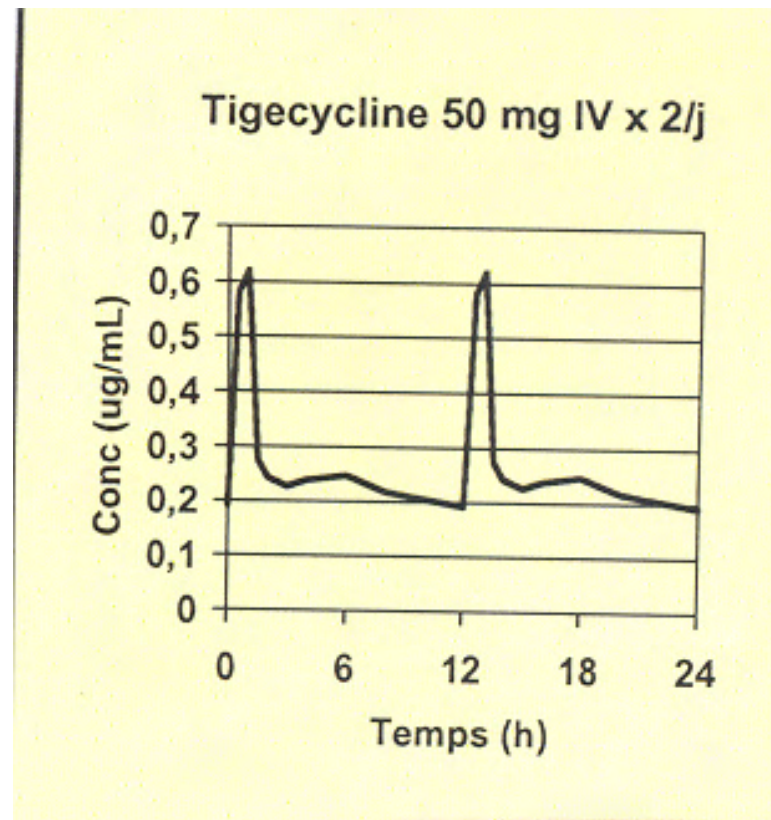
- Les bactéries anaérobies
 - Groupe *Bacteroides fragilis*
 - *Peptostreptococcus*
 - *Clostridium perfringens* et *Clostridium difficile*
- Les bactéries dites atypiques:
 - *Mycoplasma* et *chlamydia pneumoniae*
 - *Ureaplasma*
 - *Mycobacterium abscessus*, *chelonae*, *fortuitum*



La pharmacocinétique

- Volume de distribution: 8.2 L/kg (en comparaison, glycopeptides: 0.5 L/kg)
- Demi-vie sérique: 40 heures
- Fixation protéique: 78%

Evolution en 24h avec deux IV





Diffusion tissulaire

- Concentrations maximales (tigécycline marquée) dans foie, rein, rate, os
- ASC dans ces tissus 8 X supérieure au plasma
- $\frac{1}{2}$ vie dans l'os estimée à 200h
- ASC peau et poumon: 3 à 4 fois plasma



Relation CMI- pharmacocinétique

- Les espèces sensibles ont des CMI entre 0.12 et 1, voir 2 $\mu\text{g/ml}$
- Les concentrations sériques sont de l'ordre de 0.6 au pic (IV de 50mg) et 0.3 à l'équilibre
- Intérêt d'une dose de charge (100mg recommandés)
- Nécessité de validation dans les formes graves



Les validations cliniques

- Peau et tissus mous
 - Étude comparative, Tigé (100 mg en charge puis 50mg X 2 /j), 566 patients, vs Vanco/aztréonam (1g/2g /12h), 550 patients
 - Multicentrique internationale (200 centres, soit 5.7 cas /centre)



Peau et tissus mous

- Définition de cas

- Infection définie par 2 ou plus de signes suivants:
 - écoulement, érythème, fièvre, inflammation locale, et/ou GB > 10.000/mm³
- Infection qui était associée à l'un (ou plus) des éléments suivants:
 - nécessité de chirurgie
 - implication du tissu profond
 - Pathologie sous-jacente « significative » (diabète, pathologie vasculaire périphérique, neuropathie, insuffisance veineuse)



Les diagnostics cliniques

- Infections des tissu mous: 522
- Abscesses: 232
- Ulcères infectés: 53
- Brûlures: 18
- Autres: 8

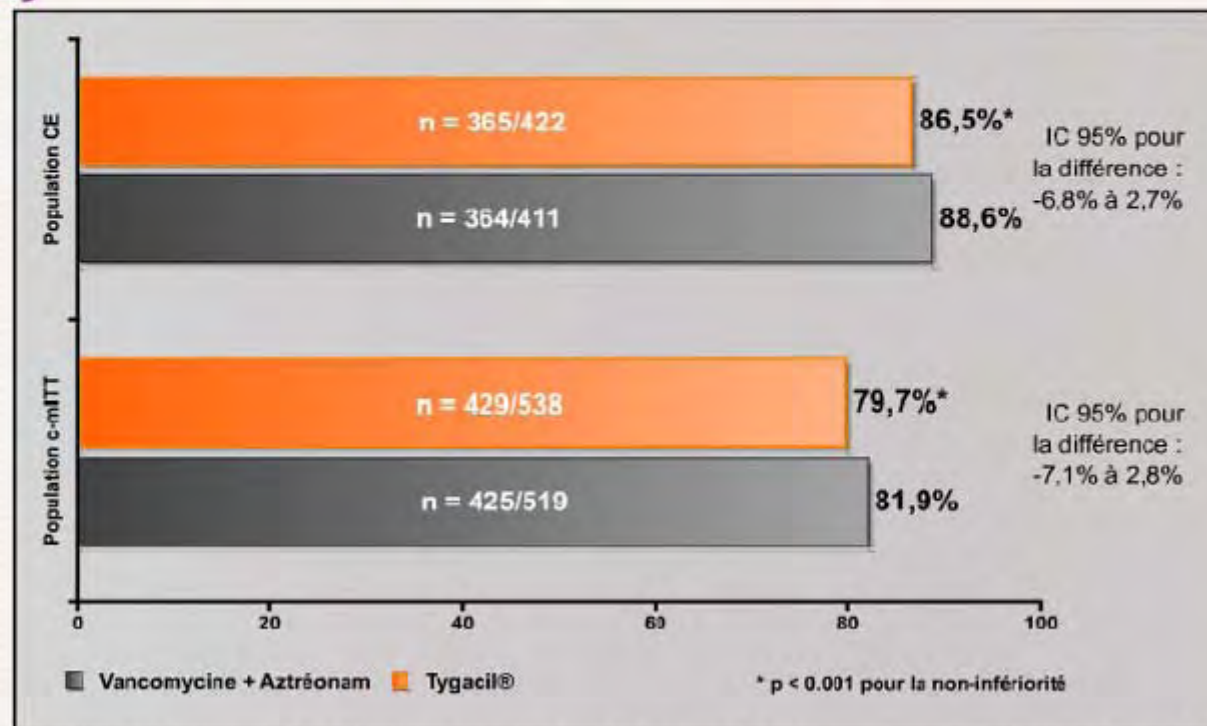


Définitions

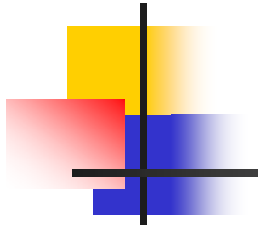
- The intent-to-treat (ITT) population comprised patients who received at least 1 dose of study drug.
- The modified ITT (MITT) subset comprised ITT patients infected with gram-positive pathogens at baseline.
- The clinically evaluable (CE) subset comprised ITT patients who received sufficient therapy (i.e., 7 days for outcome of success or 3 days for outcome of failure), received 80% of intended therapy, and underwent postbaseline assessment; patients were nonevaluable if they received potentially effective antibiotics for intercurrent illness.
- The microbiologically evaluable (ME) subset comprised CE patients infected with baseline gram-positive pathogens susceptible to both study drugs.

► **TYGACIL® EN MONOTHERAPIE VERSUS L'ASSOCIATION VANCOMYCINE + AZTREONAM**

► **Taux de succès clinique dans la population cliniquement évaluable (CE) et dans la population en c-mITT (critère principal)**

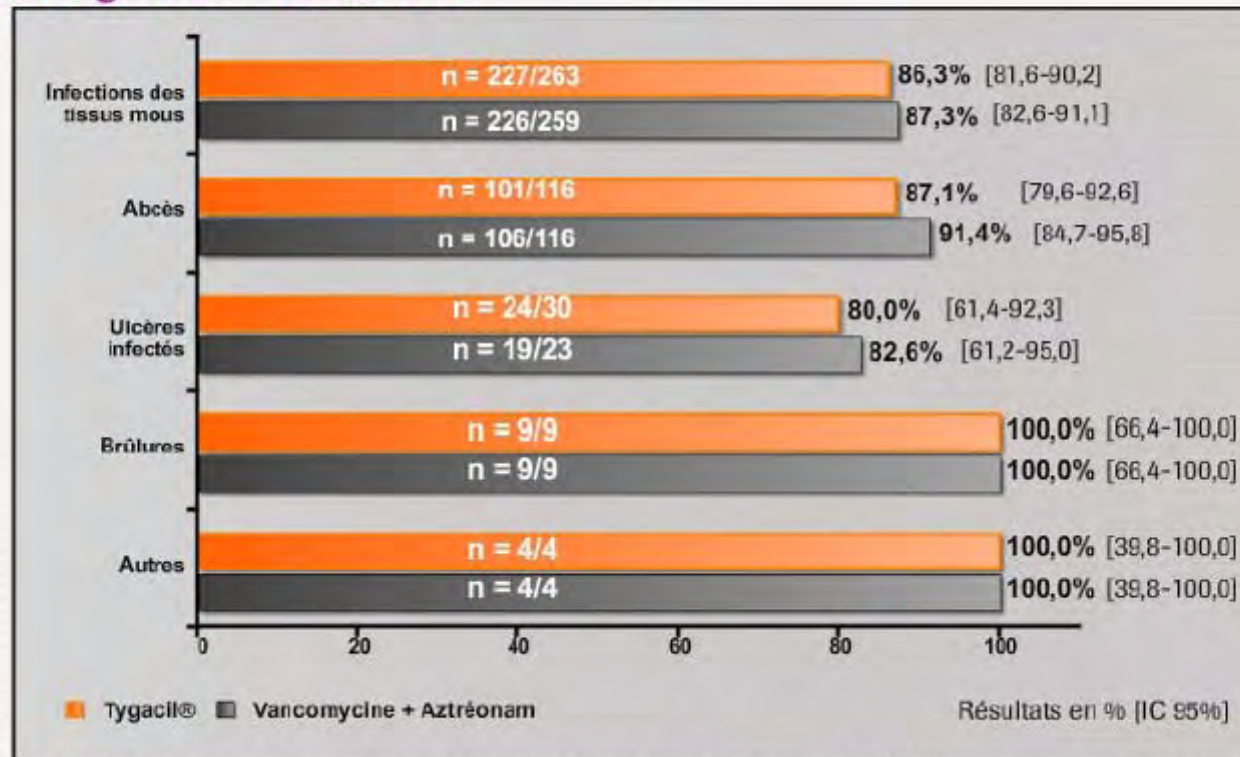


Efficacité et tolérance dans le traitement des infections compliquées de la peau et des tissus mous. D'après Ellis-Grosse LJ & al.

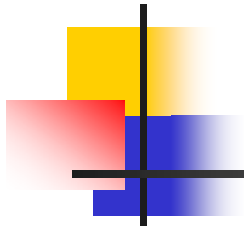


► **TYGACIL® EN MONOTHERAPIE VERSUS L'ASSOCIATION VANCOMYCINE + AZTREONAM : EFFICACITE EN FONCTION DE L'ETIOLOGIE DE L'INFECTION**

► **Taux de succès clinique dans la population CE en fonction de l'étiologie de l'infection**

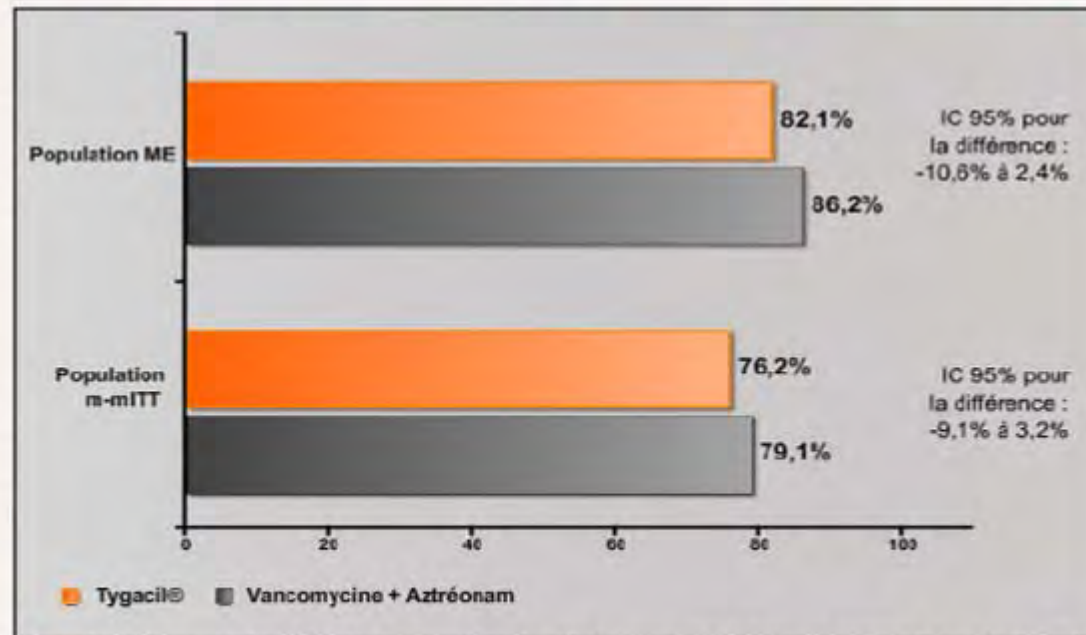


Efficacité et tolérance dans le traitement des infections compliquées de la peau et des tissus mous. D'après Ellis-Grosse EJ & al.



► **TYGACIL[®] : TAUX D'ERADICATION VERSUS L'ASSOCIATION VANCOMYCINE + AZTREONAM SUR LES GERMES IMPLIQUES DANS LES INFECTIONS DE LA PEAU ET DES TISSUS MOUS**

► **Taux d'éradication par patient dans la population microbiologiquement évaluable (ME) et dans la population en m-mITT**



Efficacité et tolérance dans le traitement des infections compliquées de la peau et des tissus mous. D'après Ellis-Grosse EJ & al.



Peau et tissus mous: analyse critique

- Eparpillement des patients
- Flou de la définition de cas
- Peu d'information sur la gravité initiale (hémocultures positives pour 23 patients seulement)
- Comparateurs



Infections intra-abdominales compliquées

- Comparative, double aveugle: tigécycline (100 mg en charge puis 50mg/12h) vs imipenem/cilastatine 500 mg/6h)
- Multicentrique internationale (220 centres)
- 1002 patients évaluable (4.5/centre)



Gravité à l'inclusion

- APACHE II > 15: 22 patients
- APACHE II < 15: 1002

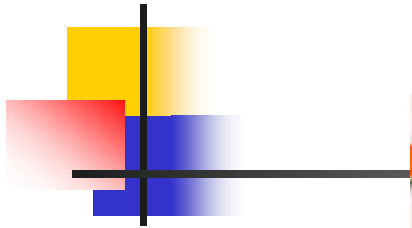


CARACTÉRISTIQUES DÉMOGRAPHIQUES INITIALES DES PATIENTS m-ITT

Caractéristiques	Tigécycline (n = 631)	Imipénem-cilastatine (n = 631)
Foyer de l'infection intra-abdominale initiale, nombre (%) de patients		
Appendicite compliquée	319 (50,6)	307 (48,7)
Cholécystite compliquée	81 (12,8)	95 (15,1)
Abcès intra-abdominal	68 (10,8)	58 (9,2)
Perforation intestinale	67 (10,6)	59 (9,4)
Divericulite compliquée	39 (6,2)	49 (7,8)
Perforation gastrique/duodénale	33 (5,2)	36 (5,7)
Péritonite	21 (3,3)	22 (3,5)
Autres diagnostics ^a	3 (0,5)	5 (0,8)

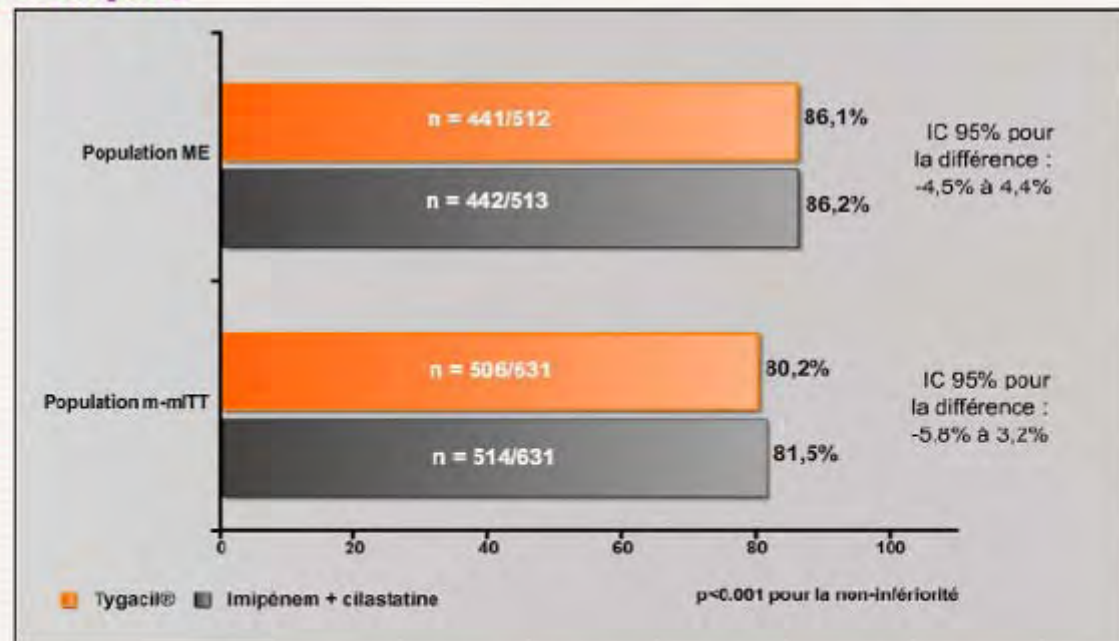
^a Les autres diagnostics étaient les suivants : hématome infecté, affection pelvienne inflammatoire, sub-occlusion intestinale aiguë, inflammation abdominale aiguë, infection pelvienne, abcès tubo-ovarien, abcès tubaire droit, hématome sous-phrénique gauche infecté, salpingite compliquée, pyosalpinx, péritonites due à un abcès ovarien gauche (abcès local), salpingites purulentes droite et gauche, perforation d'un kyste ovarien gauche suppurée, abcès intra-abdominal après ablation d'un kyste ovarien, salpingite aiguë avec péritonite purulente, avortement septique incomplet avec traumatisme et perforation de l'utérus.

Efficacité et tolérance dans le traitement des infections intra-abdominales compliquées. D'après Babinchak T & al.

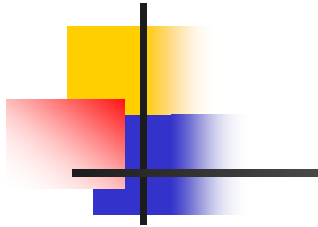


▶ **TYGACIL® : EN MONOTHERAPIE VERSUS L'ASSOCIATION IMIPENEM-CILASTATINE**

- ▶ **Taux de succès clinique dans la population microbiologiquement évaluable (ME) et dans la population en intention de traiter microbiologiquement modifiée (m-mITT) (critère principal)**

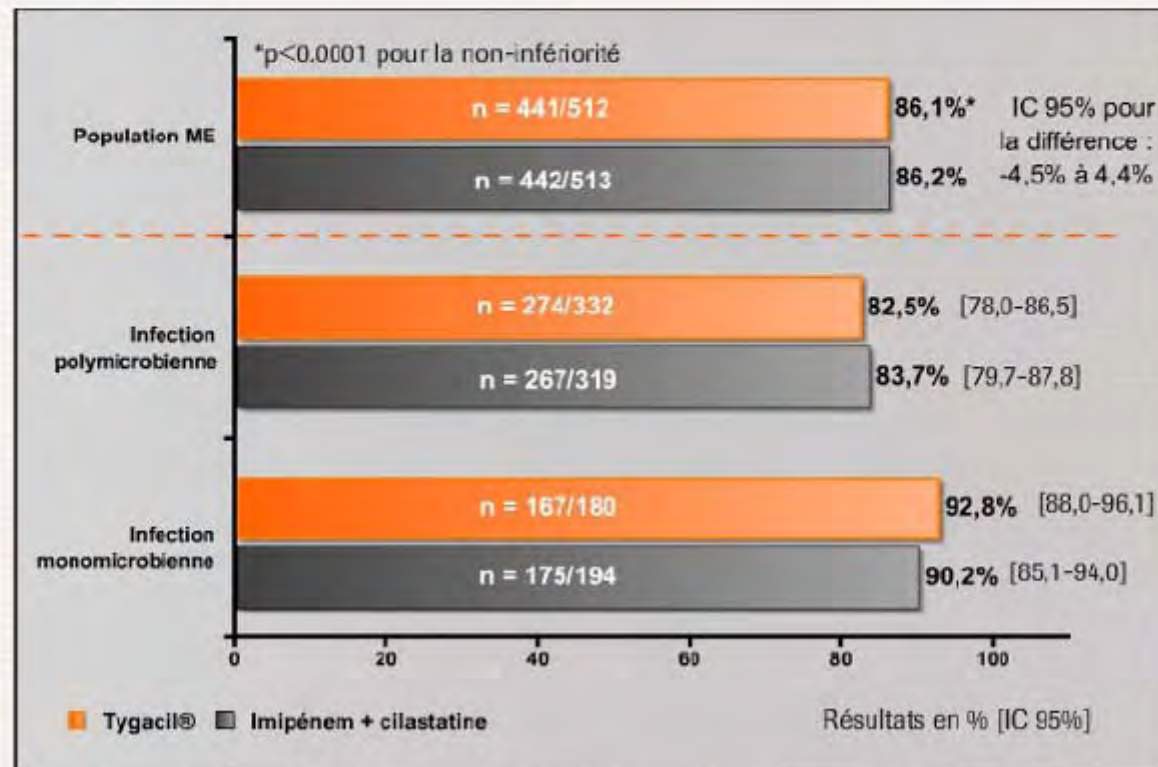


Efficacité et tolérance dans le traitement des infections intra-abdominales compliquées. D'après Babinchak T & al.



► **TYGACIL® : EN MONOTHERAPIE VERSUS L'ASSOCIATION IMIPENEM-CILASTATINE : TAUX D'ERADICATION**

► **Taux d'éradication dans la population ME, selon que l'infection était mono ou polymicrobienne**



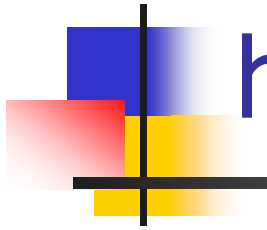
Efficacité et tolérance dans le traitement des infections intra-abdominales compliquées. D'après Babinchak T & al.



Guérison par pathogènes

	Tigecycline ME n / N (%)	Imipenem ME n / N (%)
<i>S. aureus</i> (MSSA)	26/29 (89.7)	22/24 (91.7)
<i>S. anginosus</i>	102/120 (85.7)	61/81 (75.3)
<i>E. cloacae</i>	14/16 (87.5)	16/17 (94.1)
<i>E. faecalis</i>	25/33 (75.8)	35/47 (74.5)
<i>E. coli</i>	281/329 (85.4)	298/343 (86.9)
<i>K. oxytoca</i>	19/20 (95.0)	18/20 (90.0)
<i>K. pneumoniae</i>	46/52 (88.5)	53/60 (88.3)

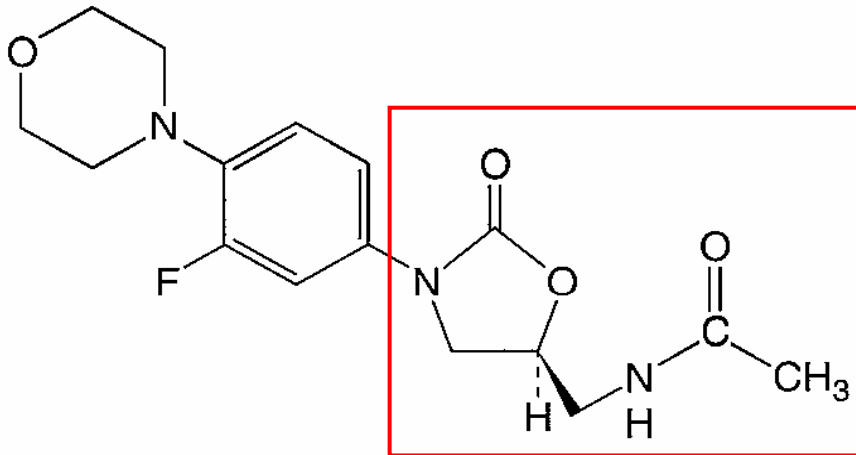
Le prenez vous dans votre
hôpital?





ZYVOXID

Linezolid Zyvoxid®



**Fonction
oxazolidinone**

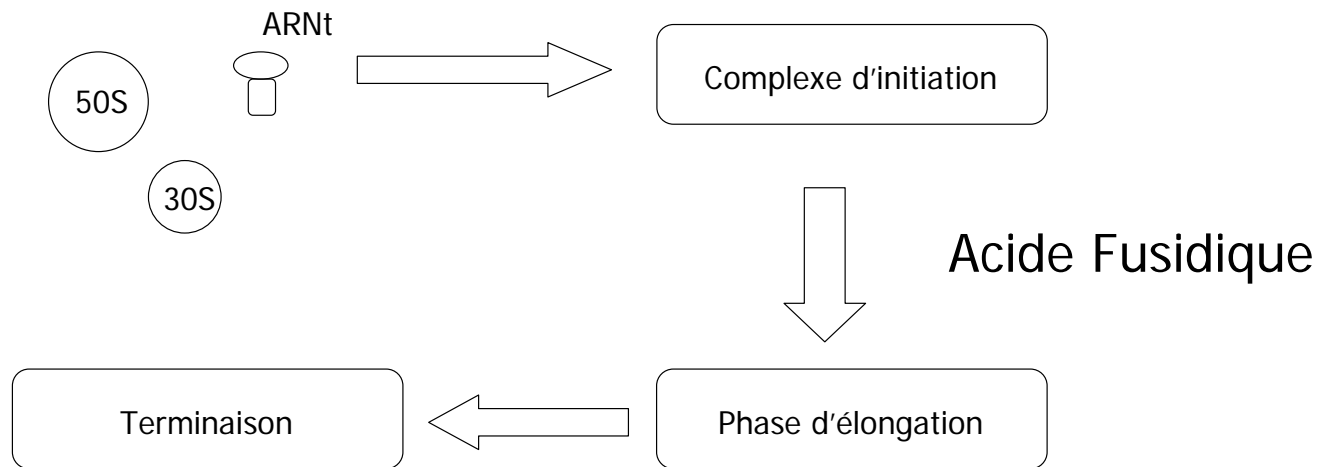
**Nouvelle classe
antibiotique**

**Agent semi-
synthétique**

Mode d'action

Synthèse protéique

Linézolide



Aminosides, Macrolides,
Streptogramines, tétracyclines,
Chloramphénicol



Le spectre d'activité (1)

Espèces sensibles

- Aérobie à Gram +

- *Enterococcus faecalis*
- *Enterococcus faecium**
- *Staphylococcus aureus**
- Staphylocoques à coagulase négative
- *Streptococcus agalactiae**
- *Streptococcus pneumoniae**
- *Streptococcus pyogenes**
- Streptocoques du groupe C
- Streptocoques du groupe G

- Anaérobies à Gram +

- *Clostridium perfringens*
- *Peptostreptococcus anaerobius*
- *Peptostreptococcus sp*

- **Espèces résistantes**

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Neisseria sp*
- *Enterobacteriaceae*
- *Pseudomonas sp*



Le spectre d'activité (2)

- SARM
- ERV
- GISA
- *S.pneumoniae* résistant à la pénicilline et à l'érythromycine



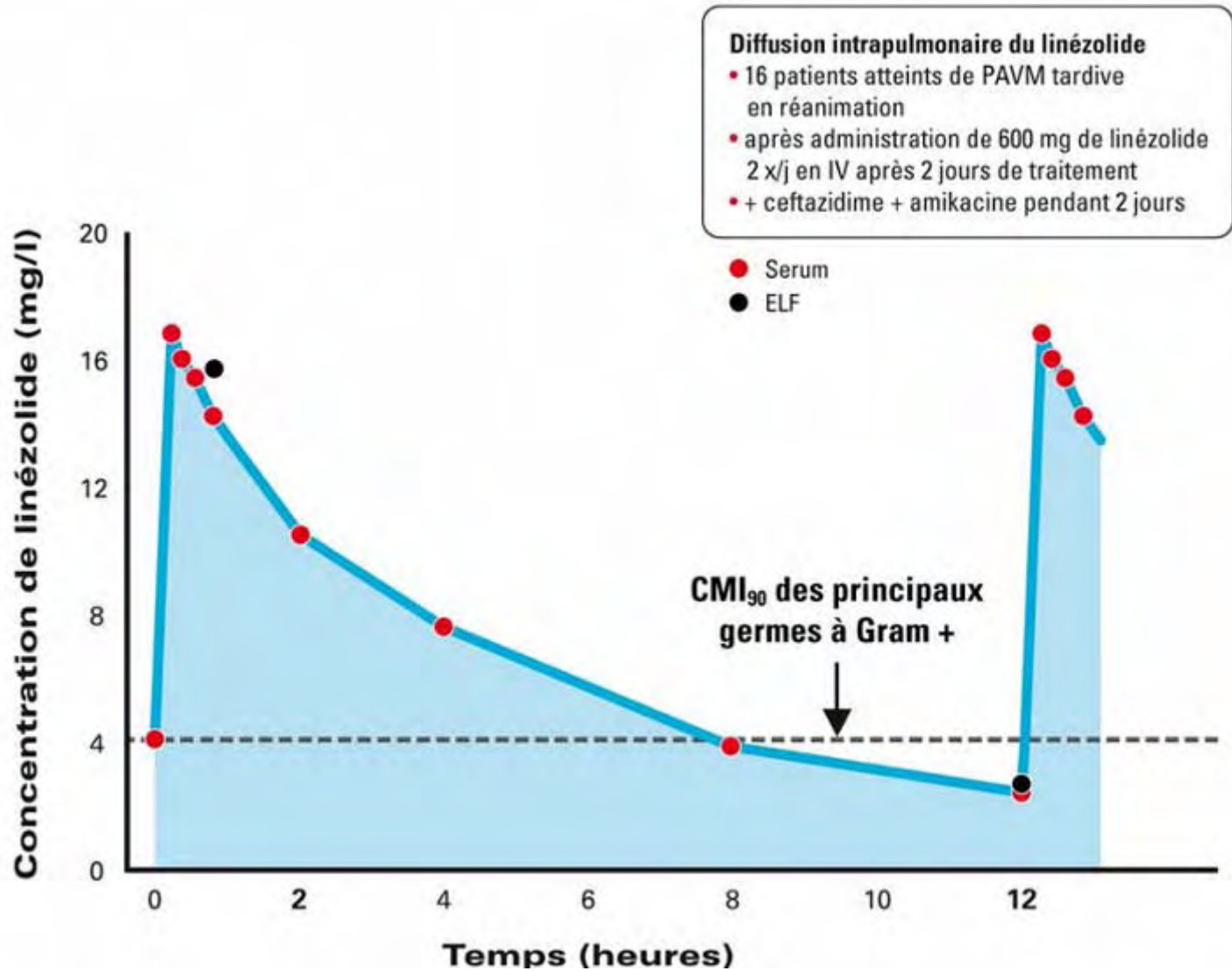
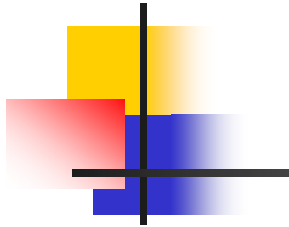
Pharmacologie

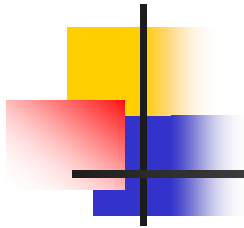
- Bactéricidie et concentration sont indépendants
- EPA
 - 3 à 4 h pour *S. aureus* et *S. pneumoniae*
 - 0.8 h pour *Enterococcus*
- Absorption – 100%
- Distribution ubiquitaire
- Pas d'ajustement en cas HD

Linezolid

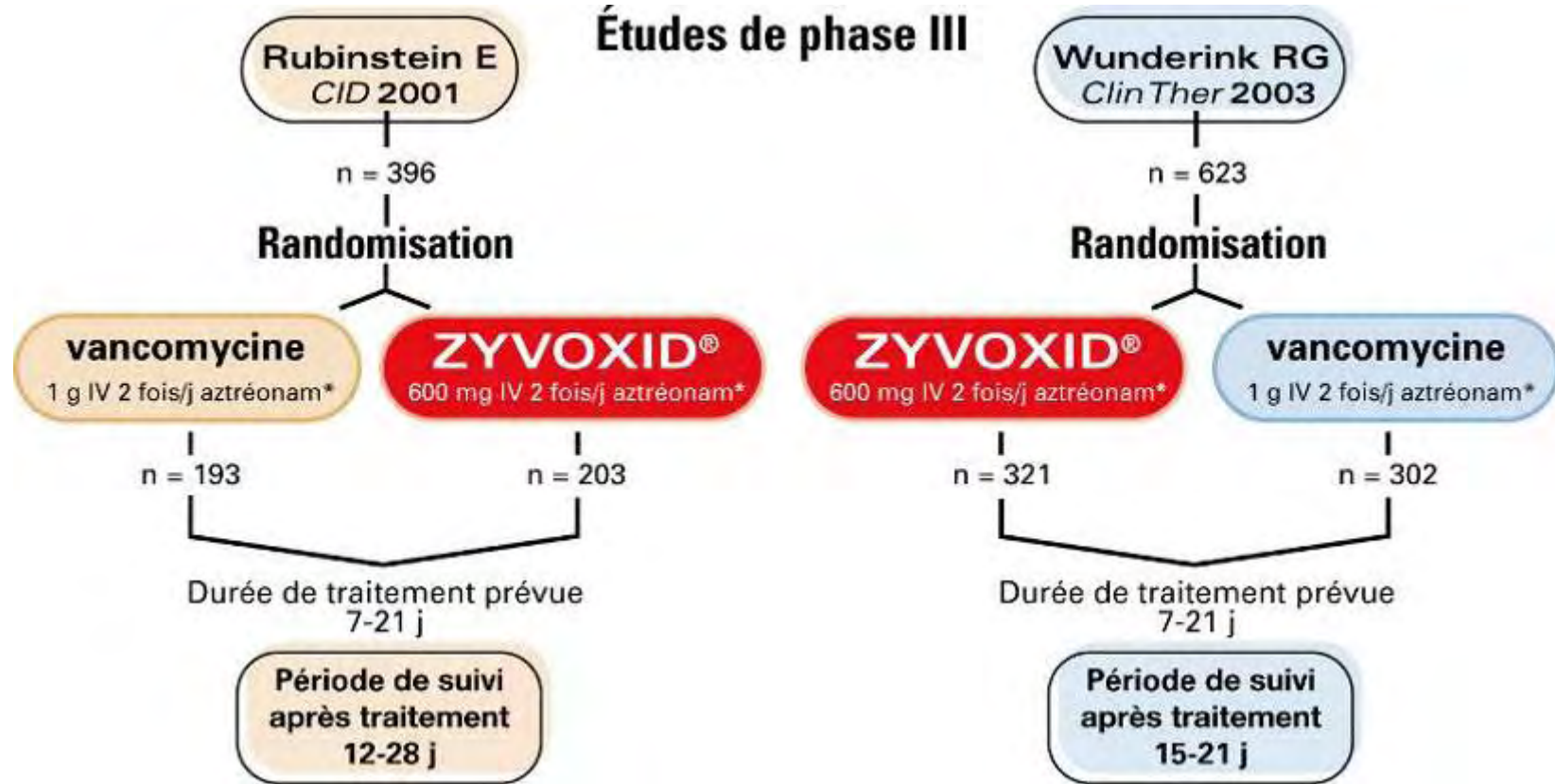
Adverse Effects

- Gastrointestinal – nausea, vomiting, diarrhea (6 to 8 %)
- Headache – 6.5%
- Thrombocytopenia – 2 to 4%
 - Most often with treatment durations of > 2 weeks
 - Therapy should be discontinued – platelet counts will return to normal
- Blindness

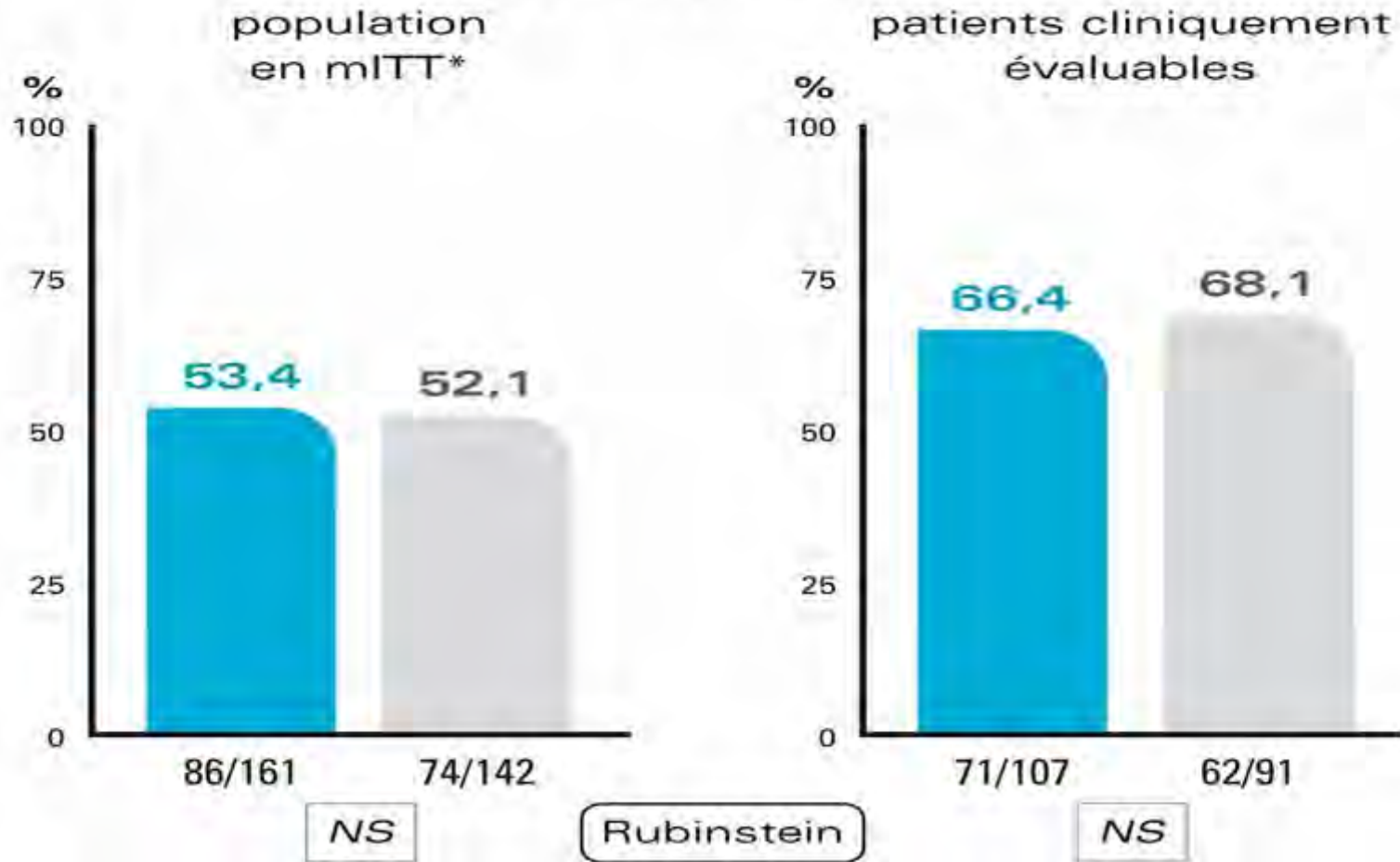




Études de phase III



Guérison clinique



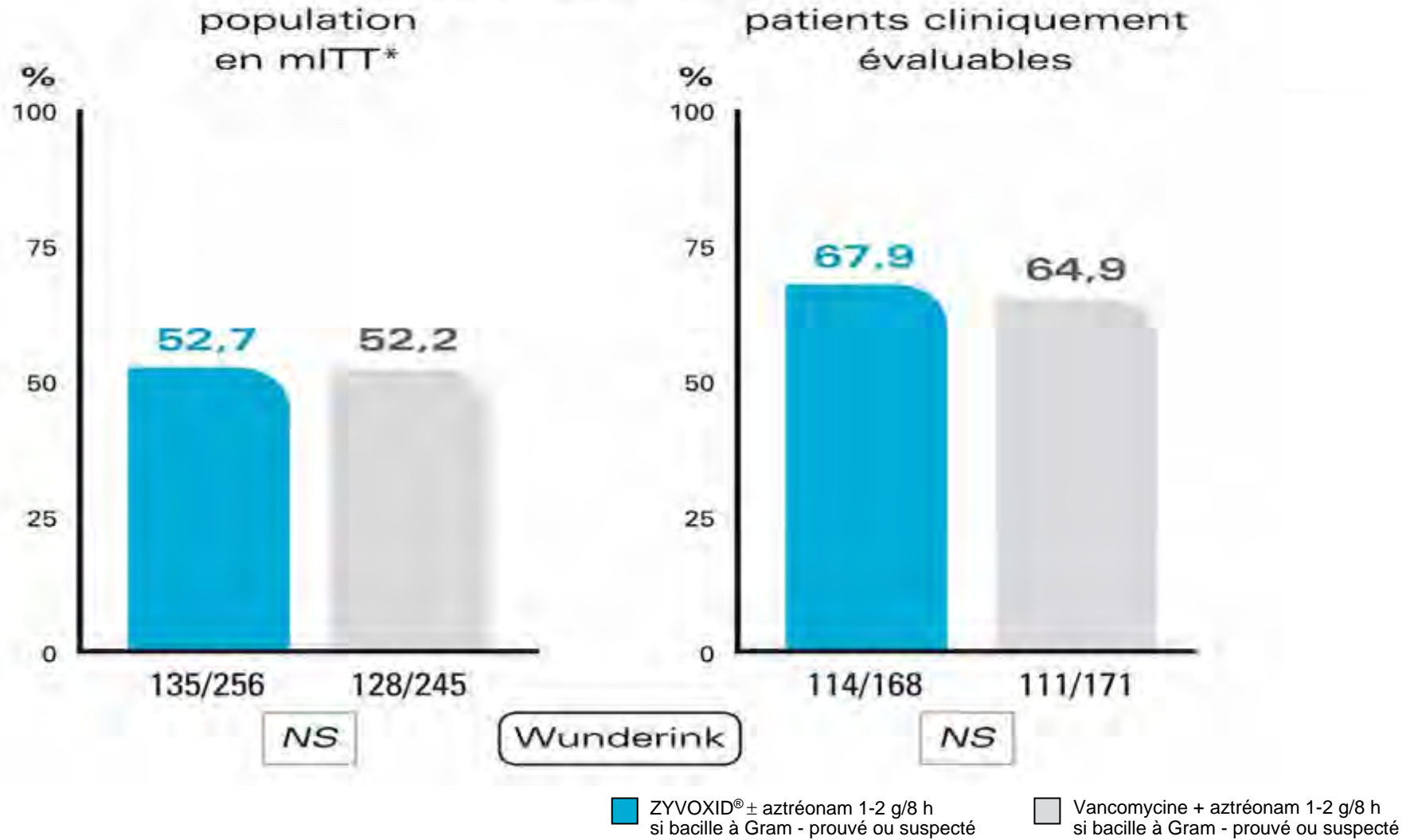
ZYVOXID® ± aztréonam 1-2 g/8 h
si bacille à Gram - prouvé ou suspecté

Vancomycine + aztréonam 1-2 g/8 h
si bacille à Gram - prouvé ou suspecté

* mITT : en intention de traiter modifiée.

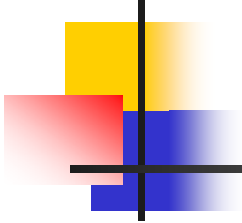
1) Rubinstein E et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis* 2001; 32(3): 402-12.

Guérison clinique



* mITT : en intention de traiter modifiée.

1) Wunderink RG et al. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003; 25(3): 980-92



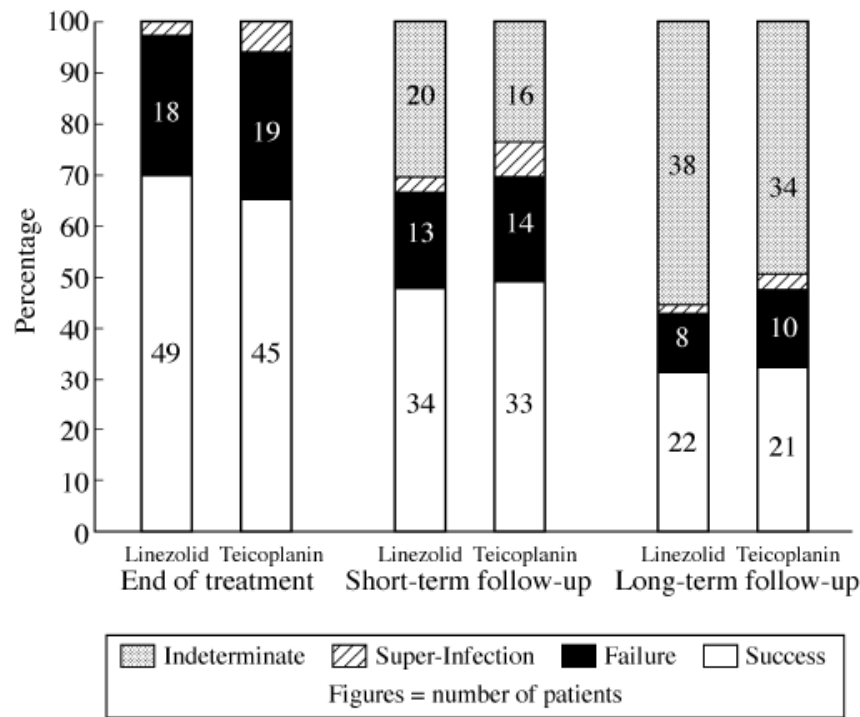
Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study

Table 3. Baseline pathogens in the ITT population

Pathogen	Linezolid (<i>n</i> = 100)	Teicoplanin (<i>n</i> = 102)
MRSA	45 (45.0)	37 (36.3)
MSSA	12 (12.0)	5 (4.9)
CoNS	16 (16.0)	20 (19.6)
VRE	1 (1.0)	1 (1.0)
Vancomycin-sensitive enterococci	7 (7.0)	9 (8.8)
Other	0 (0.0)	1 (1.0)
No pathogen isolated	19 (19.0)	29 (28.4)

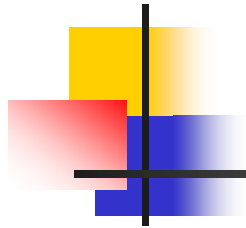
- Pneumonies nosocomiales, Infections peau et tissus mous, Bactériémies, Ostéomyélites, Arthrites septiques....!

Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study

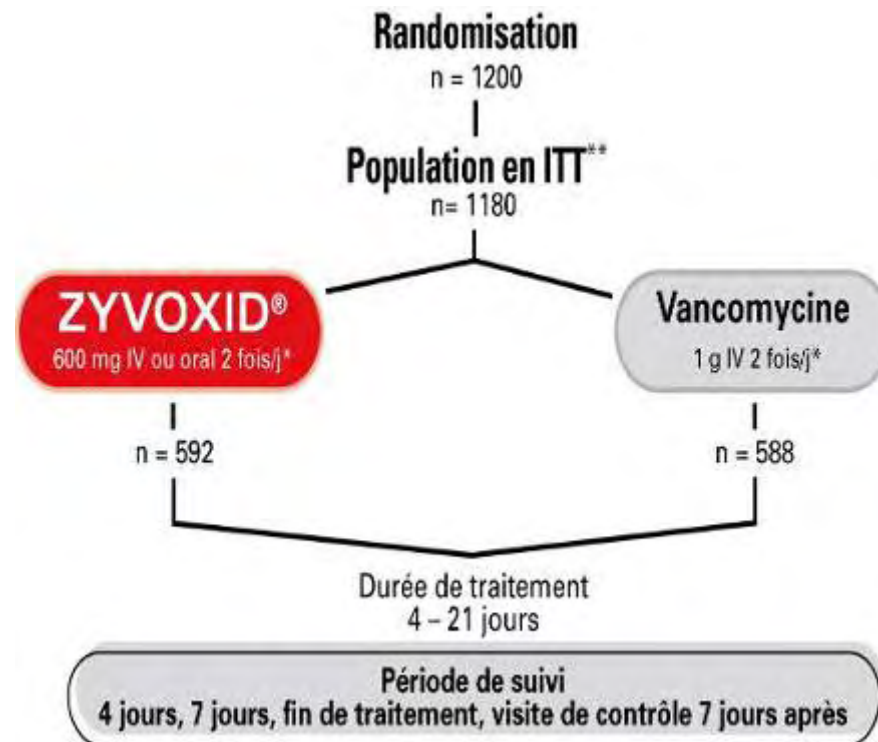


Linezolid was superior at initial clearance of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization (end of treatment, 51.1% versus 18.6%, $P = 0.002$).

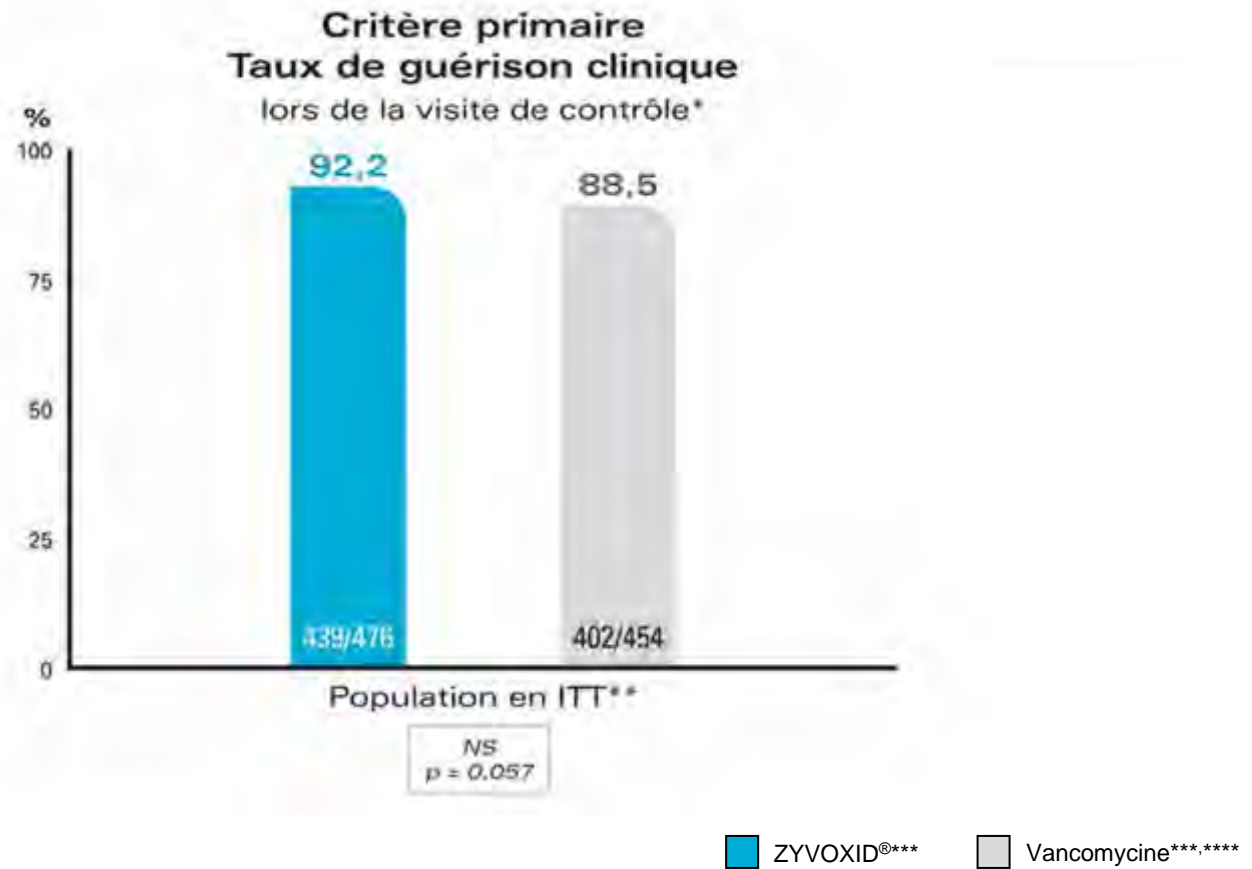
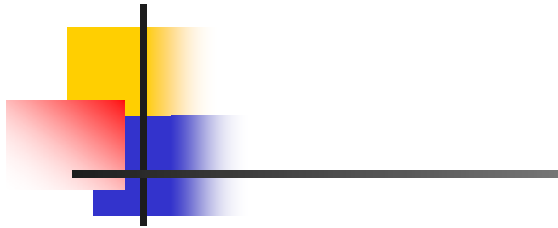
Figure 3. Microbiological outcomes in modified intention-to-treat population (MITT).



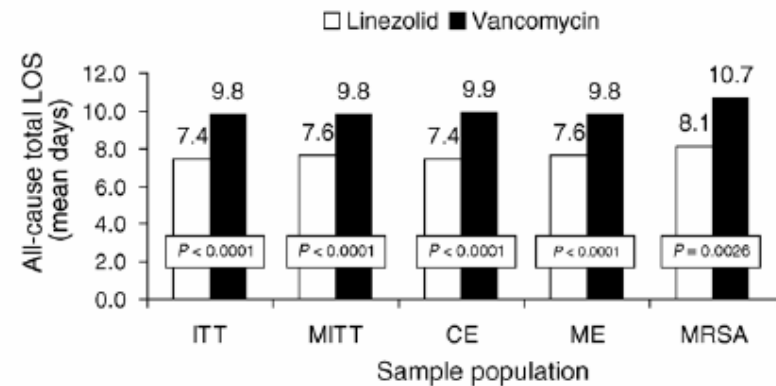
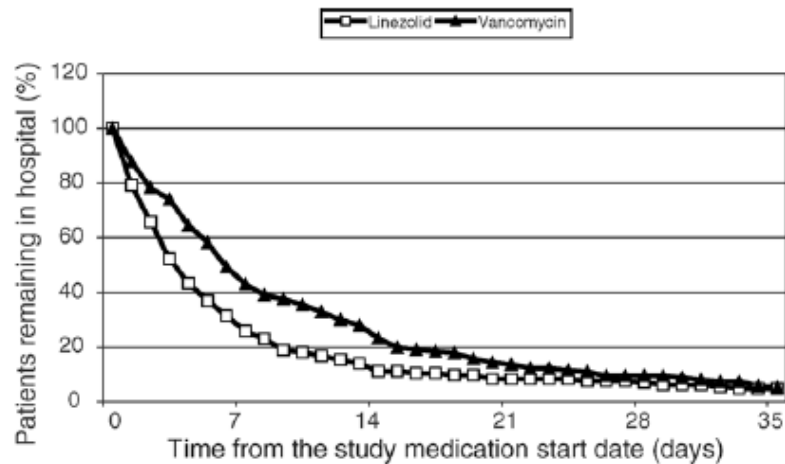
- Etude multicentrique, internationale
 - randomisée, ouverte,
 - contrôlée avec comparateur,
 - comparant l'efficacité clinique, la tolérance de 2 protocoles utilisés pour traiter les infections compliquées de la peau et des tissus mous à bactéries Gram + méti-R, suspectées ou prouvées



* + aztréonam (ou autre) si infection concomitante à gram- documentée ou suspectée.** En intention de traiter.
Weigelt J et al. Linezolid CSSTI Study Group. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections.
Antimicrob Agents Chemother 2005 Jun; 49(6): 2260-6.



Linezolid reduces length of stay and duration of intravenous treatment compared with vancomycin for complicated skin and soft tissue infections due to suspected or proven methicillin-resistant *Staphylococcus aureus* (MRSA)

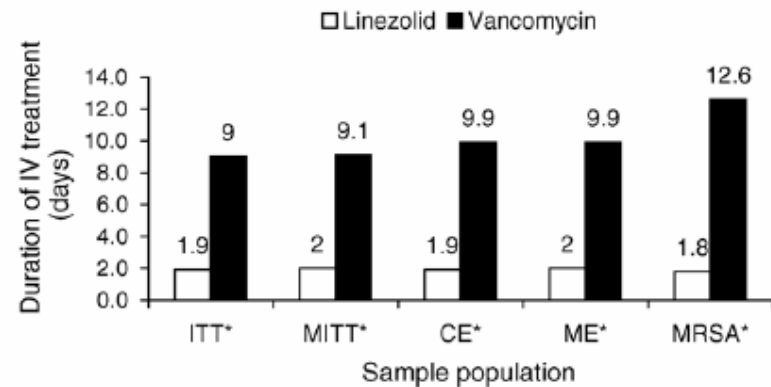


Study-infection-related re-admission rates by treatment

Population	Re-admission rate (%)		Difference ^a	P-value
	Linezolid	Vancomycin		
Intent-to-treat	3.4	2.4	1.0	0.3058
Modified intent-to-treat	2.8	2.6	0.2	0.8688
Clinically-evaluable	3.1	2.8	0.3	0.7813
Microbiologically-evaluable	2.6	3.0	-0.4	0.7415
MRSA	4.2	2.7	1.5	0.4983

MRSA, methicillin-resistant *Staphylococcus aureus*.

^a Difference between the linezolid and vancomycin groups.



Treating Foot Infections in Diabetic Patients: A Randomized, Multicenter, Open-Label Trial of Linezolid versus Ampicillin-Sulbactam/ Amoxicillin-Clavulanate

- Etude randomisée ouverte multicentrique
- Infection pied diabétique
- Ampic-sulbactam ou Amox-clav vs linezolid
- 7 à 28j de traitement
- Ratio 2/1

Table 1. Baseline demographic and clinical characteristics of the intent-to-treat population.

Characteristic	Linezolid arm (n = 241)	Aminopenicillin/ β -lactamase inhibitor arms (n = 120)
Demographic		
Male sex	171 (71)	86 (72)
Race		
White	206 (85)	100 (83)
Black	27 (11)	16 (13)
Other	8 (3)	4 (3)
Age, mean years \pm SD	63 \pm 12	62 \pm 13
Type-2 diabetes, % of patients	61	52
Type of infection ^a		
Infected ulcer	190 (79)	93 (78)
Cellulitis	101 (42)	60 (50)
Deep soft-tissue infection	37 (15)	16 (13)
Paronychia	12 (5)	11 (9)
Osteomyelitis	57 (24)	20 (17)
Other	8 (3)	5 (4)

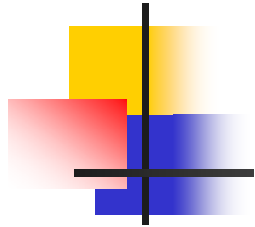
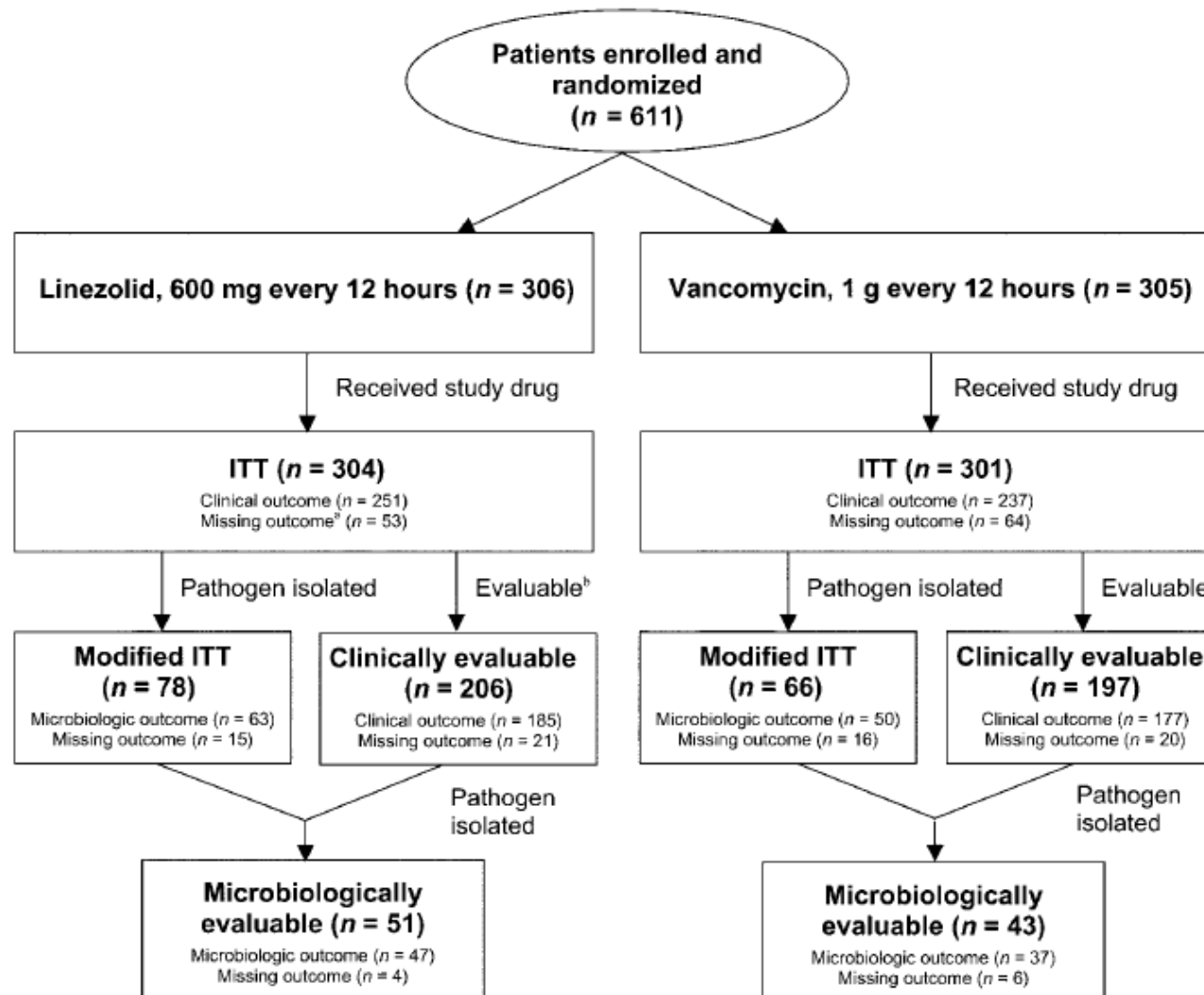


Table 2. Clinical cure rates for the intent-to-treat population, by selected parameters.

Parameter	No. of patients cured/ no. of patients assessed (%) ^a		95% CI	Duration of therapy, mean days ± SD
	Linezolid arm (n = 241)	Aminopenicillin/ β-lactamase inhibitor arms (n = 120)		
Overall	165/203 (81)	77/108 (71)	-0.1 to 20.1	17.0 ± 7.6
Type of infection ^b				
Infected ulcer	131/161 (81)	57/84 (68)	1.9–25.2	17.0 ± 7.5
Cellulitis	68/86 (79)	40/54 (74)	-9.5 to 19.5	17.1 ± 7.9
Deep soft-tissue infection	20/32 (63)	8/14 (57)	-25.5 to 36.2	20.2 ± 7.5
Paronychia	11/12 (92)	9/11 (82)	-17.8 to 37.5	15.1 ± 6.5
Abscess	5/5 (100)	1/1 (100)	...	14.3 ± 6.2
Osteomyelitis ^c	27/44 (61)	11/16 (69)	-34.3 to 19.5	19.0 ± 9.0
Status during initial treatment				
Outpatient	110/134 (82)	57/79 (72)	-1.9 to 21.8	16.0 ± 7.3
Inpatient	55/69 (80)	20/29 (69)	-8.6 to 30.1	19.2 ± 7.8
Route of initial treatment				
Intravenous	41/53 (77)	15/22 (68)	-13.3 to 31.7	20.7 ± 7.6
Oral	124/150 (83)	62/86 (72)	-0.7 to 21.8	15.8 ± 7.2
Presence of ischemia ^c				
Yes	64/79 (81)	29/44 (66)	-1.4 to 31.6	18.2 ± 7.8
No	101/124 (81)	48/64 (75)	-6.2 to 19.1	16.2 ± 7.4

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer



Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Table 1. Baseline demographic and disease characteristics of the intent-to-treat population.

Characteristic	Linezolid recipients (n = 304)	Vancomycin recipients (n = 301)		
Age, years			Absolute neutrophil count ^b	
Mean ± SD	47.2 ± 15.0	48.1 ± 15.7	<100 cells/mm ³	172 (72.0) 175 (72.0)
Range	13–76	15–86	100–500 cells/mm ³	59 (24.7) 63 (25.9)
Sex			>500 cells/mm ³	8 (3.3) 5 (2.1)
Male	179 (58.9)	161 (53.5)	Not reported	65 58
Female	125 (41.1)	140 (46.5)	Duration of neutropenia, days ^c	
Primary malignancy			Mean ± SD	9.3 ± 14.5 9.0 ± 12.0
Leukemia	176 (57.9)	172 (57.1)	Range	–1 to 159 1–168
Lymphoma	86 (28.3)	79 (26.2)	Primary infection	
Myeloma	28 (9.2)	31 (10.3)	Fever of uncertain origin	89 (29.3) 94 (31.2)
Solid tumor or other	14 (4.6)	19 (6.3)	Bacteremia	91 (29.9) 89 (29.6)
Disease status at baseline ^a			Vascular-catheter related	34 (11.2) 31 (10.3)
Progression of disease	185 (61.3)	190 (64.2)	Pneumonia	27 (8.9) 23 (7.6)
Remission	117 (38.7)	106 (35.8)	Skin and soft tissue	27 (8.9) 20 (6.6)
Not reported	2	5	Urinary tract	2 (0.7) 3 (1.0)
			Other	34 (11.2) 41 (13.6)

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Table 3. Clinical outcome at 7 days after the completion of therapy (i.e., at the test of cure assessment).

Population, presentation	No. of successes/no. of patients assessed (%) ^a		95% CI, % ^b	<i>P</i> ^c
	Linezolid group	Vancomycin group		
ITT	219/251 (87.3)	202/237 (85.2)	-4.1 to 8.1	.52
Primary malignancy				
Leukemia	119/143 (83.2)	111/138 (80.4)	-6.2 to 11.8	.55
Lymphoma	63/71 (88.7)	56/62 (90.3)	-12.0 to 8.8	.77
Myeloma	24/24 (100)	23/24 (95.8)	-3.8 to 12.2	.31
Tumor	11/11 (100)	11/12 (91.7)	-7.3 to 24.0	.33
Other	2/2 (100)	1/1 (100.0)	Not calculable	
Type of infection				
Fever of uncertain origin	72/78 (92.3)	66/74 (89.2)	-6.1 to 12.3	.51
Bacteremia of unknown source	59/72 (81.9)	53/67 (79.1)	-10.3 to 16.0	.67
Vascular catheter-related infection	23/27 (85.2)	24/28 (85.7)	-19.2 to 18.1	.96
Skin and soft-tissue infection	19/21 (90.5)	14/17 (82.4)	-13.9 to 30.2	.46
Pneumonia	19/23 (82.6)	13/15 (86.7)	-27.2 to 19.1	.74
Urinary tract infection	2/2 (100)	2/3 (66.7)	-20.0 to 86.7	.36
Other	25/28 (89.3)	30/33 (90.9)	16.7 to 13.5	.83
MITT	55/63 (87.3)	43/50 (86.0)	-11.4 to 14.0	.84
Clinically evaluable	171/185 (92.4)	158/177 (89.3)	-2.8 to 9.1	.30
Microbiologically evaluable	41/47 (87.2)	32/37 (86.5)	-13.8 to 15.3	.92

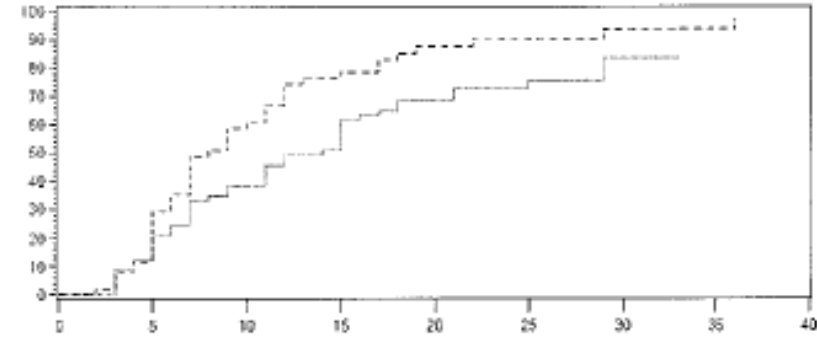
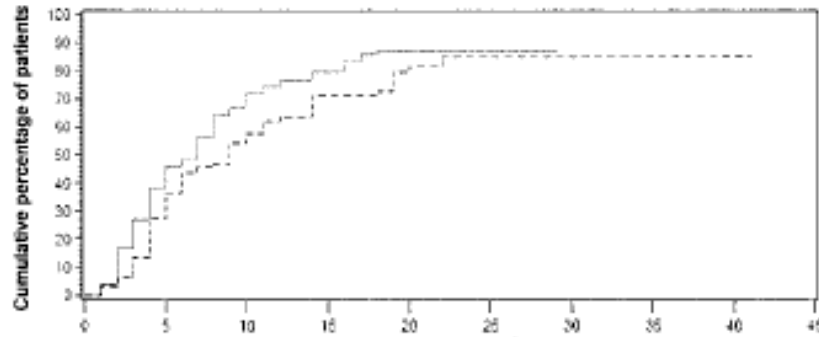
Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer



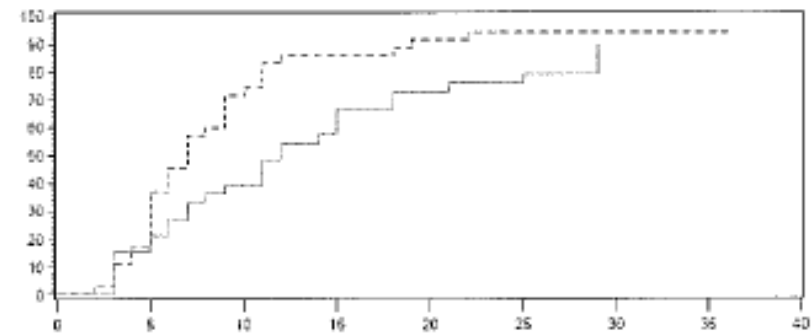
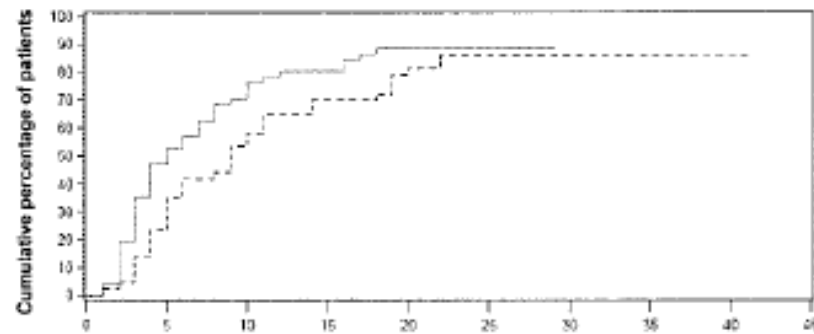
Time to defervescence

Time to ANC >500 cells/mm³

MITT



ME

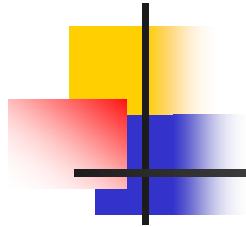


— Linezolid - - - - Vancomycin

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Table 5. Adverse events observed in linezolid and vancomycin recipients.

Type of adverse event	No. (%) of adverse events		P ^b
	Linezolid group ^a (n = 303)	Vancomycin group ^a (n = 300)	
Adverse event			
Any	229 (75.6)	232 (77.3)	.61
Serious event	37 (12.2)	48 (16.0)	.18
Drug-related adverse event ^c			
Any	52 (17.2)	72 (24.0)	.04
Serious event	3 (1.0)	12 (4.0)	
Drug-related adverse event leading to discontinuation	11 (3.6)	15 (5.0)	.41
Drug-related adverse events occurring in ≥5 patients/group			
Nausea	10 (3.3)	8 (2.7)	NS
Rash	6 (2.0)	10 (3.3)	NS
Vomiting	9 (3.0)	6 (2.0)	NS
Diarrhea	3 (1.0)	8 (2.7)	NS
Erythema	4 (1.3)	6 (2.0)	NS
Increased serum creatinine level	1 (0.3)	5 (1.7)	NS
Renal failure ^d	1 (0.3)	7 (2.3)	.04 ^e



- Vous l'avez fait rentrer dans votre hôpital
 - Position?
 - Controlé?
 - Libre?
 - Surveillez vous qq chose?



Dalbavancin



Dalbavancin

- Lipoglycopeptide semi-synthétique
- Profil pharmacocinétique autorisant une injection par semaine
- Activité sur les Gram positifs
- Supérieur à la plupart des autres molécules dont la vanco
- Intérêt dans les infections peau et tissus mous

Randomized, Double-Blind Comparison of Once-Weekly Dalbavancin versus Twice-Daily Linezolid Therapy for the Treatment of Complicated Skin and Skin Structure Infections

Table 2. Selected demographic and baseline characteristics of the overall study population.

Characteristic	Dalbavancin arm (n = 571)	Linezolid arm (n = 283)
SSSI history		
Cause of infection		
Spontaneous	286 (50)	133 (47)
Trauma	141 (25)	77 (27)
Postsurgery infection	57 (10)	31 (11)
Bite	54 (9)	18 (6)
Other	33 (6)	24 (8)
Type of infection		
Major abscess	190 (33)	86 (30)
Cellulitis	157 (27)	84 (30)
Other deep soft-tissue infection	96 (17)	46 (16)
Traumatic wound infection	63 (11)	33 (12)
Surgical wound infection	47 (8)	27 (10)
Infected major burn ^a	18 (3)	7 (2)

Table 4. Evaluation of responses to a late follow-up questionnaire.

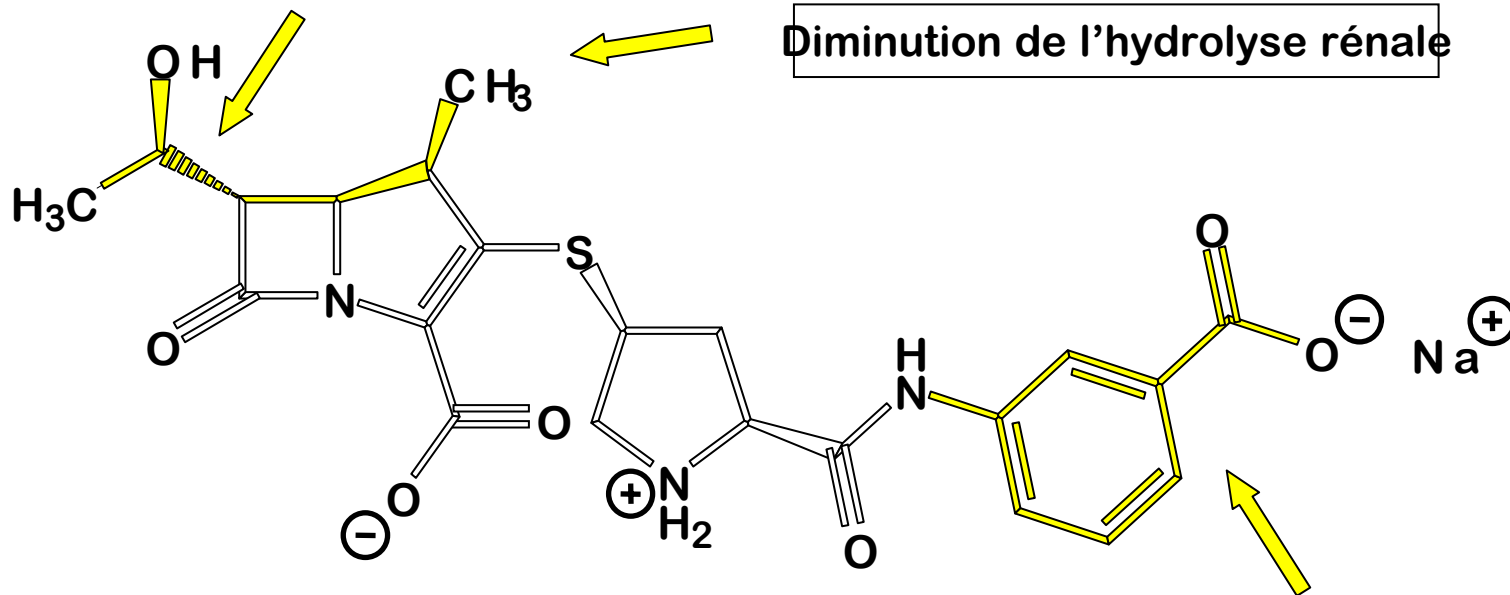
Variable	No. (%) of clinically evaluable patients	
	Dalbavancin arm (n = 434)	Linezolid arm (n = 226)
Patients eligible for late follow-up assessment ^a	316	163
Response		
Success		
All	298 (94)	151 (93)
No visit to health care provider for SSSI after the TOC visit	282 (89)	135 (83)
Contacted health care provider after TOC visit regarding SSSI but did not receive additional antibiotics	16 (5)	16 (10)
Failure ^b	2 (0.6)	1 (0.6)
Unavailable for interview	16 (5)	11 (7)



Ertapénème



Stabilité aux β -lactames



Forte liaison protéique
Augmente la $\frac{1}{2}$ vie

Differentiate within the Class – Carbapenem Classification

Group	Classification
Group 1	Broad-spectrum carbapenems, with limited activity against non-fermentative Gram-negative bacilli (e.g. <i>Pseudomonas, Acinetobacter</i>), that are particularly suitable for community-acquired infections (e.g. ertapenem)
Group 2	Broad-spectrum carbapenems, with activity against non-fermentative Gram-negative bacilli (e.g. <i>Pseudomonas, Acinetobacter</i>), that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem)
Group 3	Carbapenems with clinical activity against Methicillin-Resistant <i>Staphylococcus</i> (e.g. In development)



Antimicrobial spectrum

- Covers common pathogens
 - Gram(+) aerobes - *S. aureus*, *S. pneumoniae*, *Group A & B Streptococci*
 - Gram(-) aerobes - *Enterobacteriaceae*, *H. influenzae*, *M. catharralis*
 - Anaerobes - *B. fragilis*, *Clostridium sp.*, *Eubacterium sp.*, *Peptrostreptococcus sp.*, *Porphyromonas asaccharolytica*, *Prevotella sp.*
- **Poor activity** against MRSA, *enterococci*, *Pseudomonas spp*, and *Acinetobacter sp.*



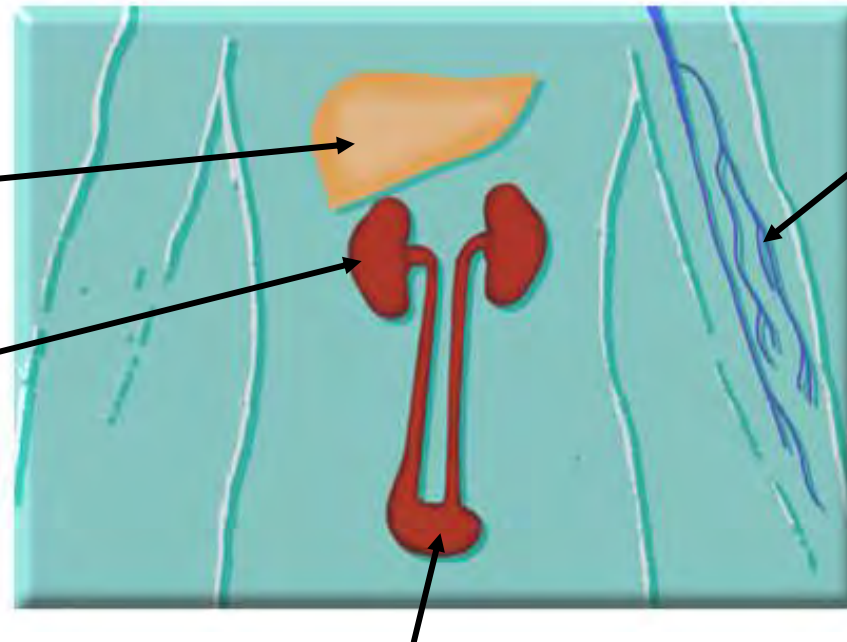
Antimicrobial Spectrum

Aerobes, Gram-positive	No. of isolates	MIC ₉₀ (µg/mL)
<i>Staphylococcus aureus</i> (MSSA)	883	0.25
<i>Streptococcus agalactiae</i>	306	0.06
<i>Streptococcus pneumoniae</i> (PRSP and PSSP)	1096	1
<i>Streptococcus pyogenes</i>	411	0.016
<hr/>		
Aerobes, Gram-negative		
<i>Escherichia coli</i>	1596	0.016
<i>Haemophilus influenzae</i>	726	0.06
<i>Klebsiella pneumoniae</i>	904	0.06
<i>Moraxella catarrhalis</i>	255	0.016
<i>Proteus mirabilis</i>	323	0.03
<hr/>		
Anaerobes		
<i>Bacteroides fragilis</i> and group:	390	1
Clostridia	51	1
Eubacteria	47	1
<i>Peptostreptococcus spp</i>	12	0.5
<i>Porphyromonas asaccharolytica</i>	57	0.03
<i>Prevotella spp</i>	61	0.25

Metabolism and excretion

No hepatic metabolism, minimizing drug-drug interactions

Requires no dose adjustment in the majority of patients *



92% to 95% protein binding

Achieves high concentrations in urine

*Severe renal insufficiency (creatinine clearance < 30 mL/min/1.73 m²): 500 mg daily. Patients on hemodialysis may also require a supplemental dose.



Five Indications for ertapenem

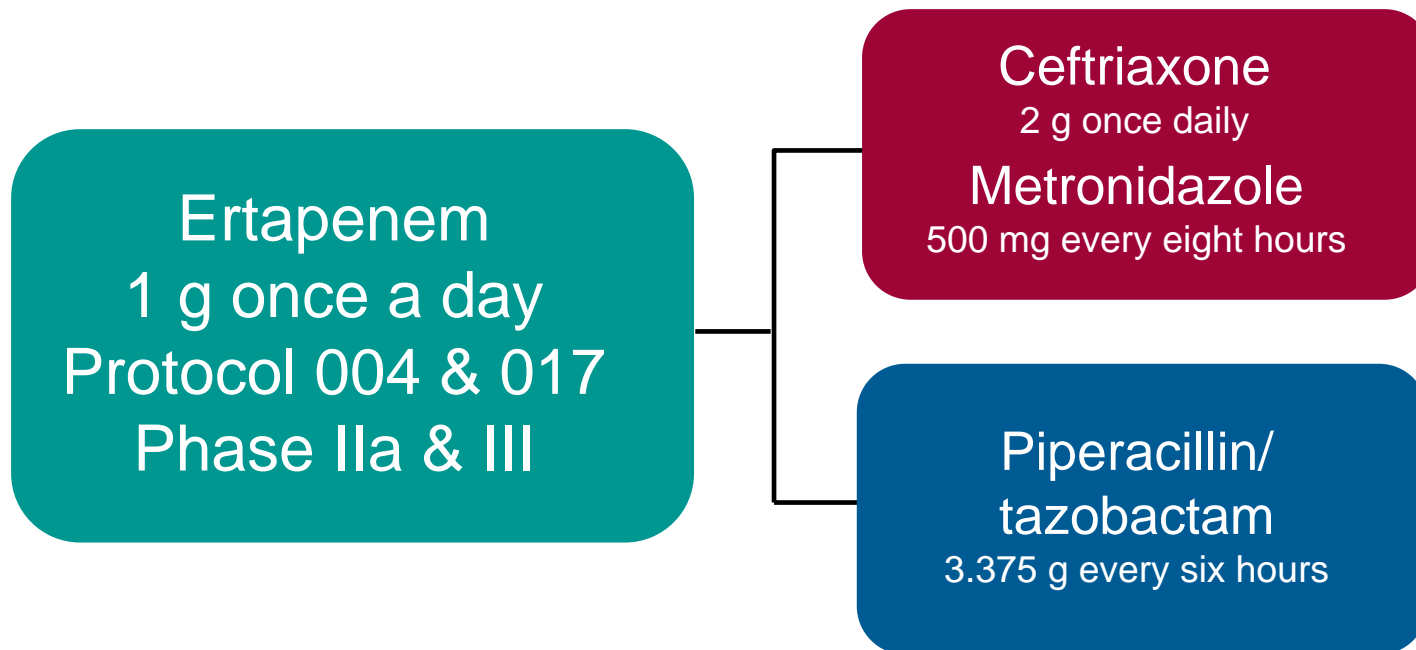
- Intra-abdominal infection
- Skin and skin structure infection
- Acute gynaecological infection
- Community-acquired pneumonia
- Complicated urinary tract infection



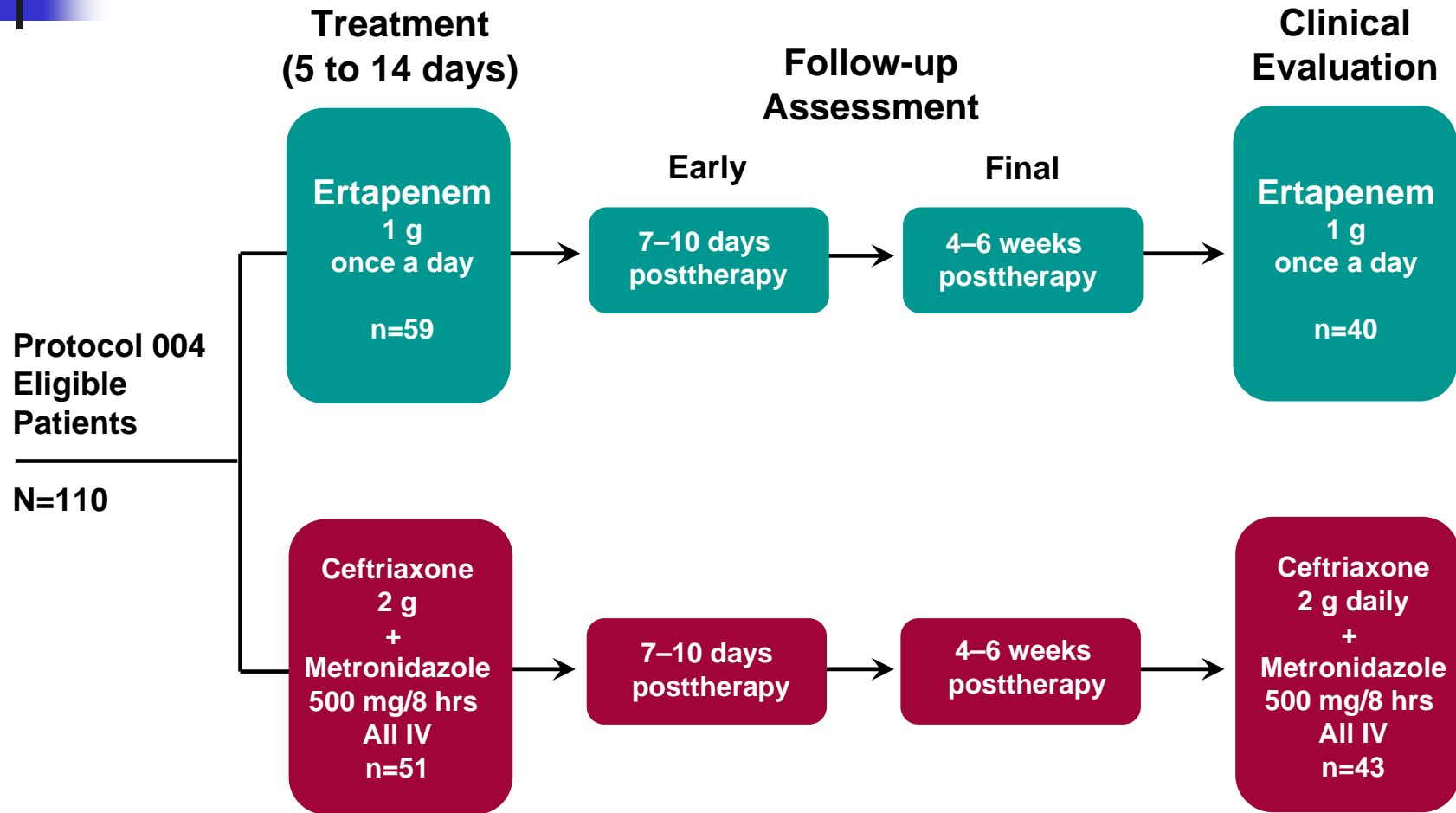
Intra-abdominal Infections

Summary of Clinical Studies

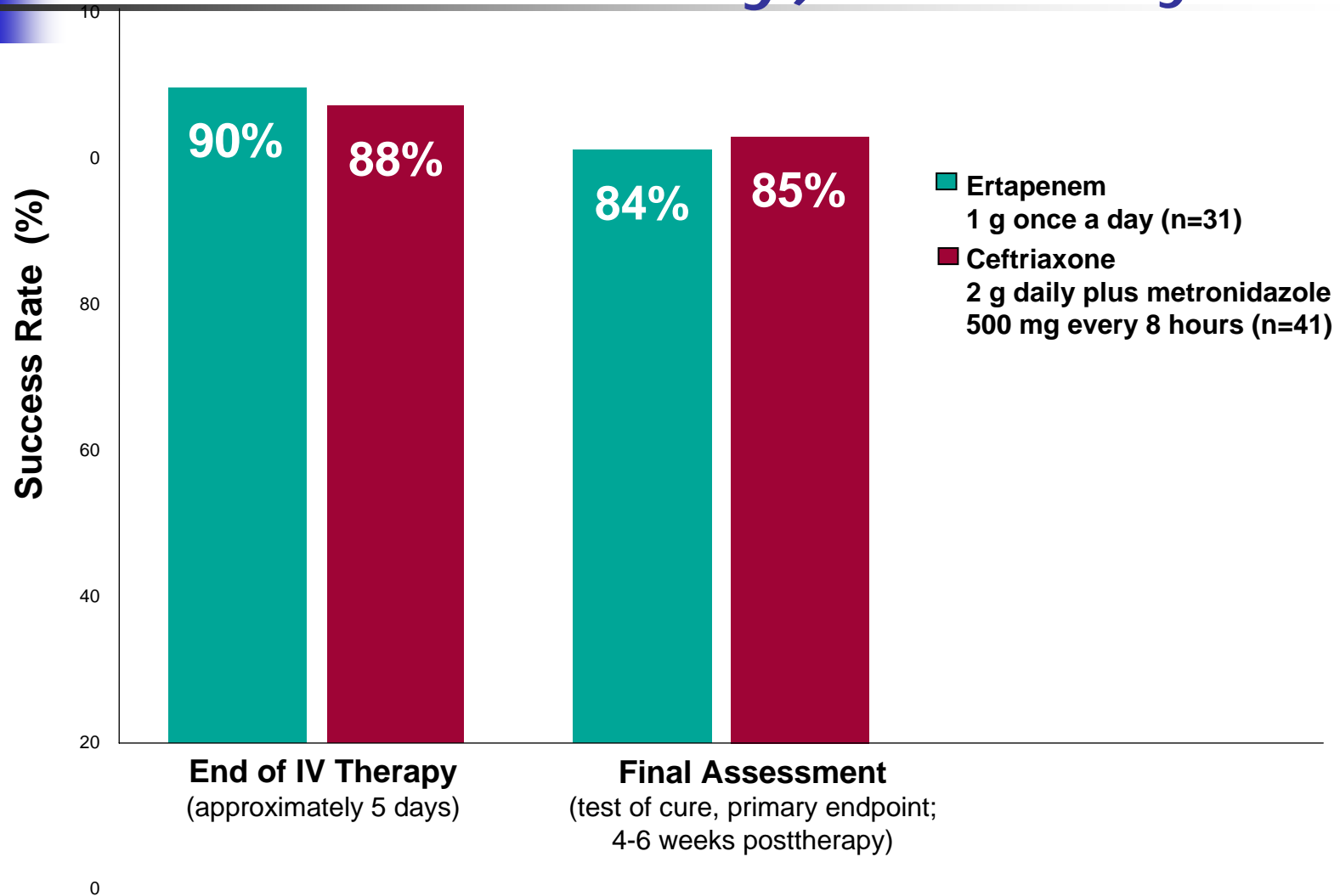
775 Patients Studied Worldwide



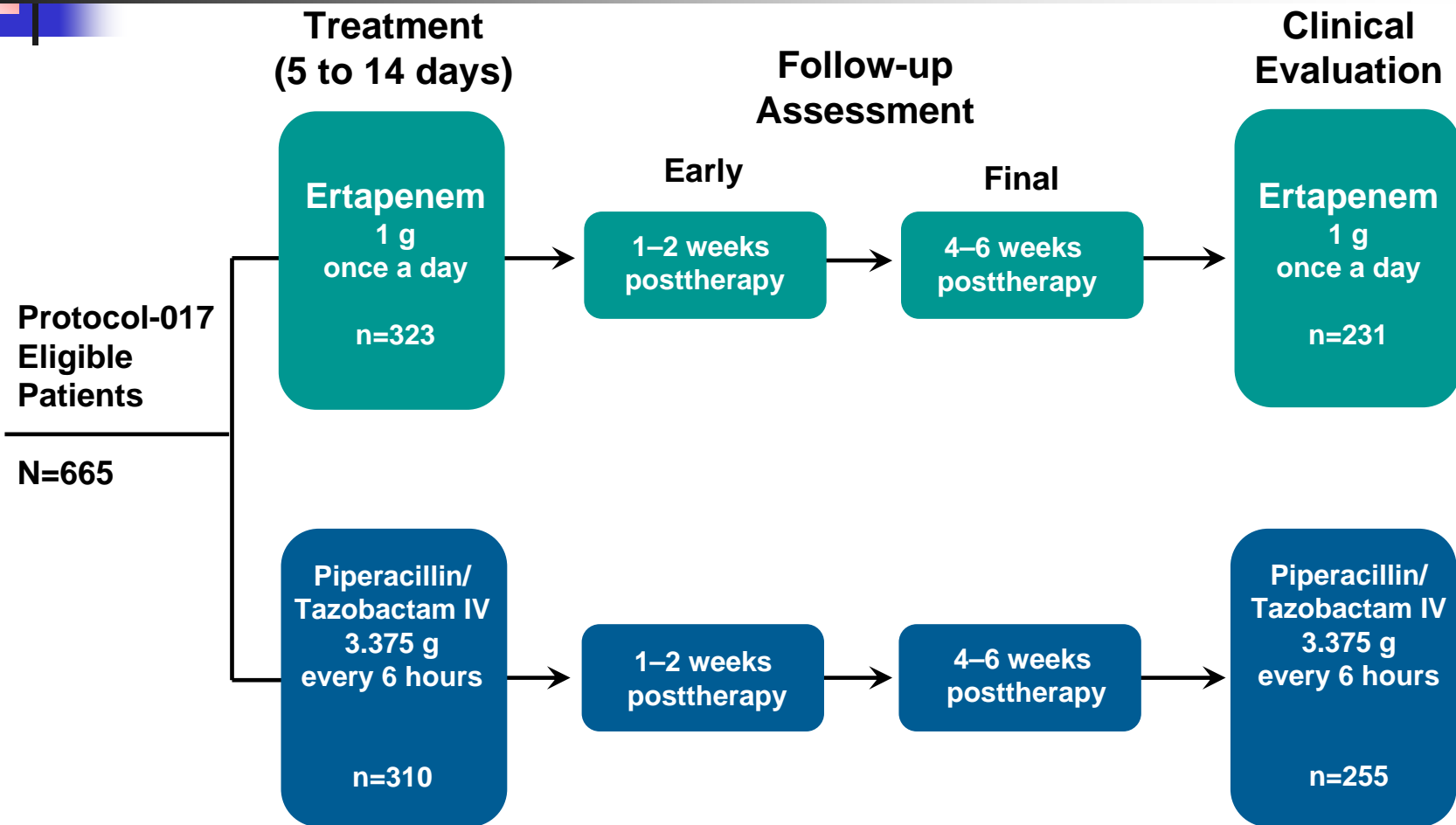
Protocol 004: Phase IIa Intra-Abdominal Study



Protocol 004 (Phase IIa Intra-abdominal Study): Efficacy



Protocol 017: Pivotal Intra-abdominal Study



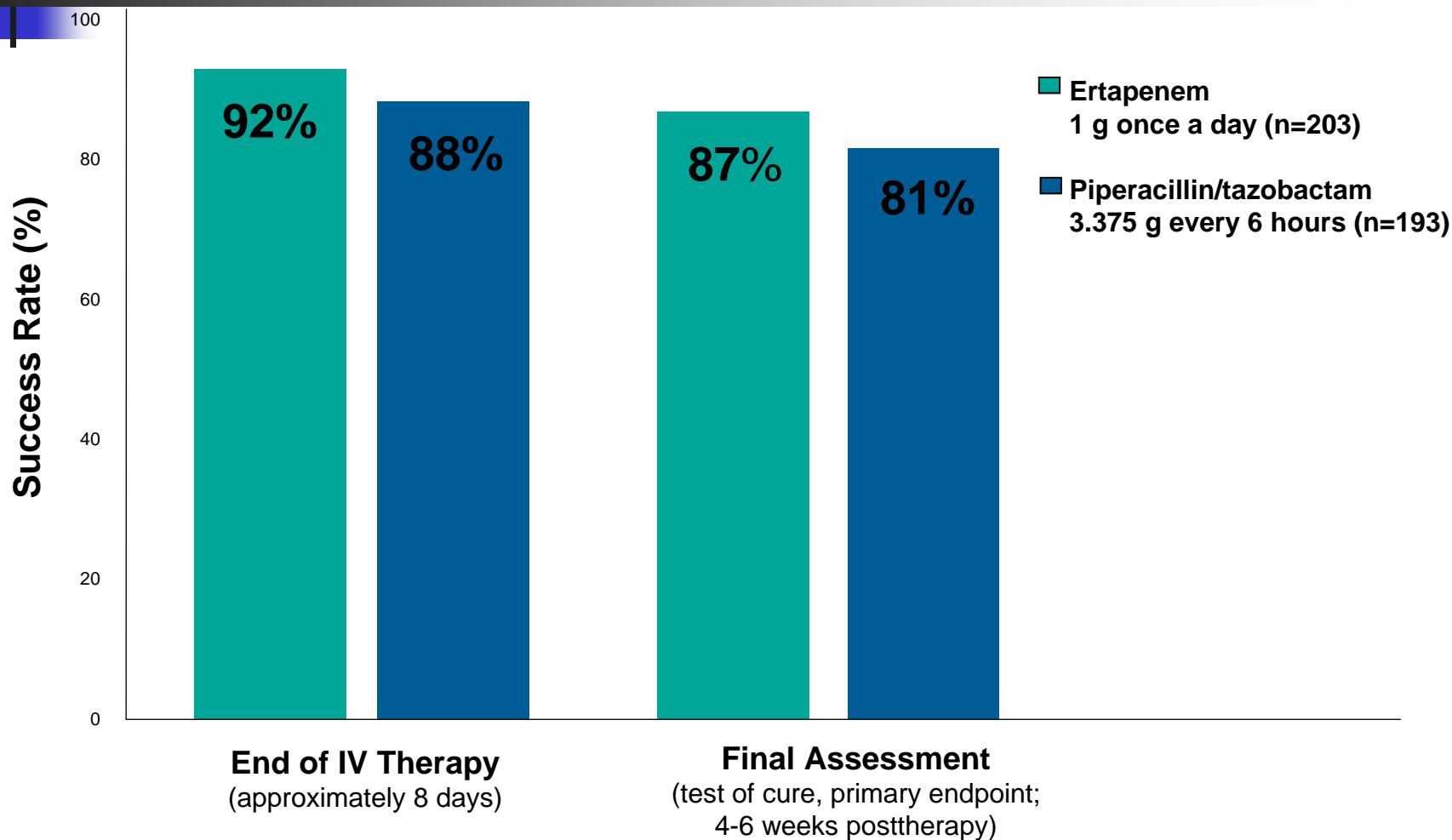


Pivotal Intra-abdominal Study

- 59.5% microbiologically evaluable of 665 randomized patients
- Demographics of microbiological evaluable population

	Ertapenem N=203	Pip/Tazo N=193
Age: Mean	44.9	43.1
Range	17-89	17-86
Appendicitis	60.6%	58.5%
Other diagnoses	39.4%	41.5%
Generalized peritonitis	29.6%	27.5%
APACHE II ≤ 15	94.6%	92.8%

Pivotal Intra-abdominal Study: Efficacy





Pivotal Intra-abdominal Study: Consistent Success Rate Across a Variety of Infection Processes

Generalized
peritonitis
Multiple
abscesses
Single abscess
Localized
disease

**Ertapenem
1 g once a day
% (n/N)**

83%
(50/60)
89%
(8/9)
90%
(53/59)
87%
(65/75)

**Piperacillin/
tazobactam
3.375 g every 6
hours % (n/N)**

74%
(39/53)
50%
(2/4)
82%
(55/67)
88%
(61/69)

Pivotal Intra-abdominal Study: Consistent Success Rate Across a Variety of Infection Sites

	Ertapenem 1 g once a day % (n/N)	Piperacillin/ tazobactam 3.375 g every 6 hours % (n/N)
Appendix	89% (109/123)	90% (102/113)
Colon	78% (28/36)	69% (25/36)
Small bowel; stomach/duodenum	91% (20/22)	79% (15/19)
Cholangitis; cholecystitis	92% (12/13)	83% (10/12)

Acquisition of Resistant Bowel Flora during a Double-Blind
Randomized Clinical Trial of Ertapenem versus
Piperacillin-Tazobactam Therapy for
Intraabdominal Infections

132 Patients traités par Ertapenem
132 Patients traités par Pip-Taz

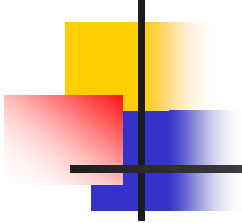
TABLE 2. Frequency of assessable patients with resistant gram-negative bacilli isolated from rectal swabs at different time points during the study by treatment group^a

Isolate	No. of assessable patients in treatment group and at time point indicated (%) ^b			
	Ertapenem		Piperacillin-tazobactam	
	Baseline	End of therapy	Baseline	End of therapy
Piperacillin-tazobactam-resistant <i>Enterobacteriaceae</i>	1 (0.8)	2 (1.6)	1 (0.8)	9 (7.4)
Ertapenem-resistant <i>Enterobacteriaceae</i>	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
ESBL-producing <i>E. coli</i> or <i>Klebsiella</i> species	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imipenem-resistant <i>P. aeruginosa</i>	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Piperacillin-tazobactam-resistant <i>P. aeruginosa</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Ertapenem once a day versus piperacillin–tazobactam every 6 hours for treatment of acute pelvic infections: a prospective, multicenter, randomized, double-blind study

Table 1 Baseline characteristics and therapy of randomized and clinically evaluable patients with acute pelvic infection, by treatment group

Characteristic	Randomized ^a		Clinically evaluable	
	Ertapenem (n = 216)	Pip–Taz (n = 196)	Ertapenem (n = 163)	Pip–Taz (n = 153)
<i>Diagnosis at entry (percent)</i>				
Endomyometritis	164 (75.9)	148 (75.5)	120 (73.6)	115 (75.2)
Septic abortion	22 (10.2)	23 (11.7)	20 (12.3)	19 (12.4)
Pelvic cellulitis	7 (3.2)	10 (5.1)	6 (3.7)	9 (5.9)
Pelvic abscess	8 (3.7)	7 (3.6)	4 (2.5)	5 (3.3)
Parametritis	7 (3.2)	6 (3.1)	6 (3.7)	4 (2.6)
Other	7 (3.2)	2 (1.0)	7 (4.3)	1 (0.7)



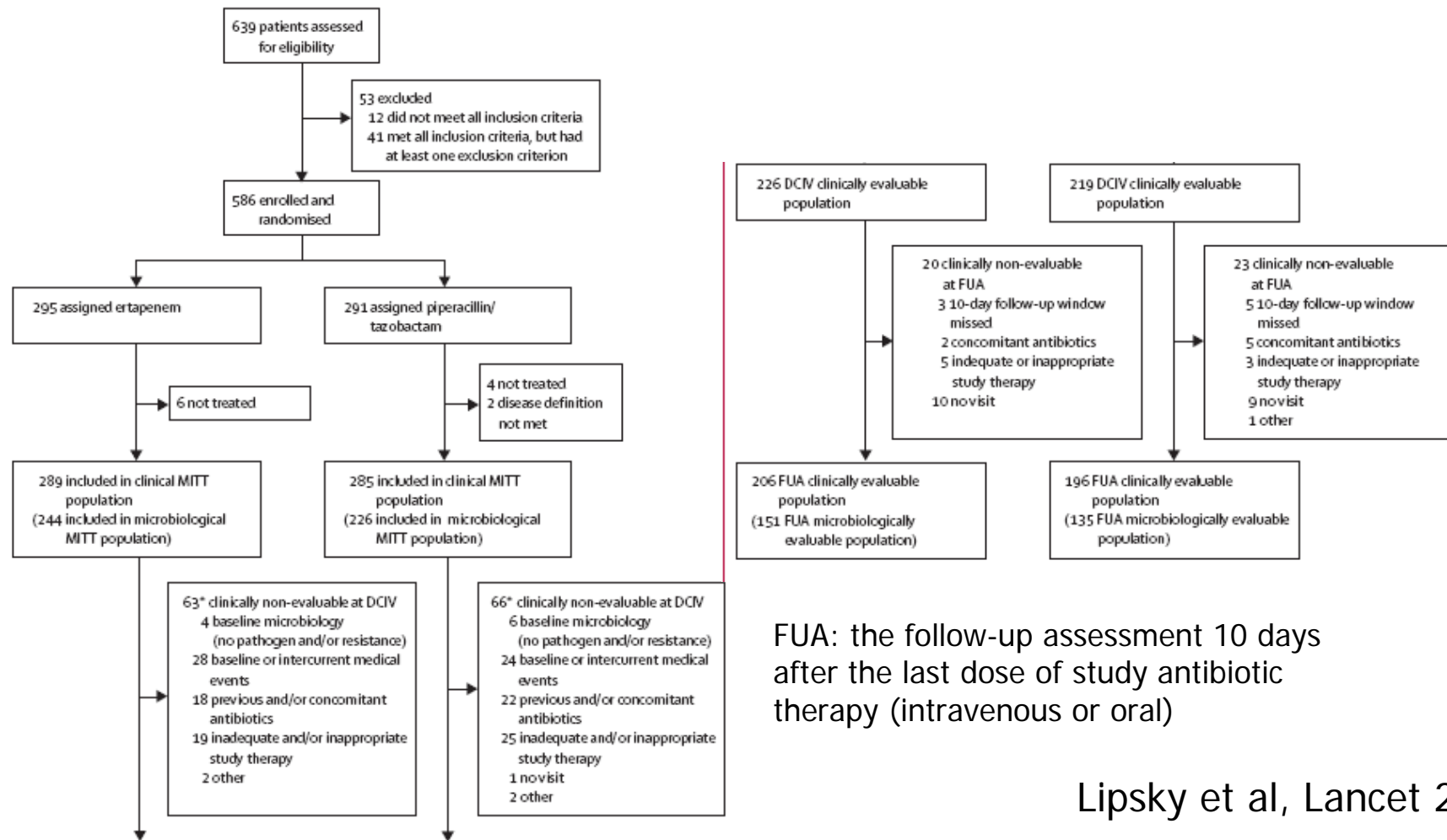
Ertapenem once a day versus piperacillin–tazobactam every 6 hours for treatment of acute pelvic infections: a prospective, multicenter, randomized, double-blind study

Table 2 Cure rates in clinically evaluable patients, by stratum or subgroup

<i>Stratum/subgroup</i>	<i>Ertapenem</i>		<i>Piperacillin–tazobactam</i>	
	<i>n/m</i>	<i>% response (95% CI)</i>	<i>n/m</i>	<i>% response (95% CI)</i>
<i>At DCIV</i>				
<i>Stratum</i>				
Obstetric/postpartum infection	130/137	94.9 (91.2, 98.6)	122/132	92.4 (87.9, 97.0)
Gynecological/postoperative infection	25/26	96.2 (88.6, 100)	19/21	90.5 (77.6, 100)
Overall	155/163	95.1 (91.8, 98.4)	141/153	92.2 (87.9, 96.4)

n/m, ratio of number of patients cured/number of patients with assessment; CI, confidence interval; DCIV, discontinuation of IV therapy

Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial



FUA: the follow-up assessment 10 days after the last dose of study antibiotic therapy (intravenous or oral)

Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial

	Ertapenem (n=206)	Piperacillin/tazobactam (n=196)	Observed differences (95% CI)*
Moderate	127/142 (89.4%)	119/135 (88.1%)	1.3 (-6.3 to 9.1)
Severe	53/64 (82.8%)	43/61 (70.5%)	12.3 (-2.6 to 27.1)
Grade 0	2/2 (100.0%)	5/5 (100.0%)	0
Grade 1	125/140 (89.3%)	114/130 (87.7%)	1.6 (-6.2 to 9.6)
Grade 2	43/51 (84.3%)	33/48 (68.8%)	15.6 (-1.2 to 32.1)
Grade 3	10/13 (76.9%)	10/13 (76.9%)	0.0 (-33.3 to 33.3)
Stage B	172/195 (88.2%)	156/187 (83.4%)	4.8 (-2.3 to 12.0)
Stage D	8/11 (72.7%)	6/9 (66.7%)	6.1

Data are number of FUA clinically evaluable patients with favourable assessment/number of FUA clinically evaluable patients assessed (observed response) unless otherwise indicated. * CIs not calculated for categories in which there were <10 patients in at least one treatment group. Moderate infections include: grade 0 or 1 stage B or D. Severe infections include: grade 2 or 3 stage B or D.

Table 3: Rate of favourable clinical response at 10-day FUA, by baseline stratum and wound classification

Ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults: combined analysis of two multicentre randomized, double-blind studies

Guillermo Ortiz-Ruiz¹, Norbert Vetter², Robin Isaacs^{3*}, Alexandra Carides³, Gail L. Woods^{3†} and Ian Friedland^{3‡}

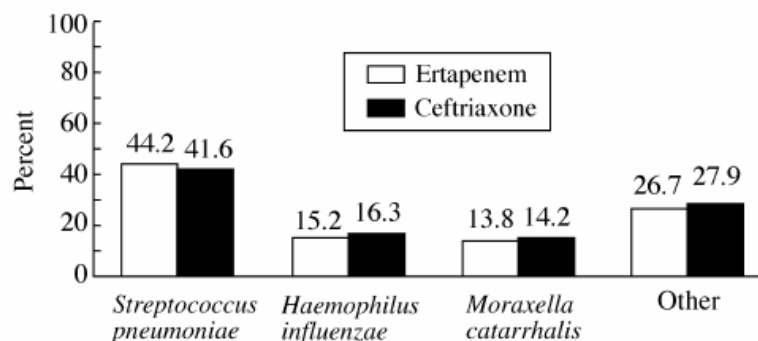


Table 3. Clinical cure rates, by stratum, in clinically evaluable patients with community-acquired pneumonia at the TOC visit

Stratum	Ertapenem		Ceftriaxone	
	<i>n/m</i>	% response (95% CI ^a)	<i>n/m</i>	% response (95% CI ^a)
Age ≤ 65 years	203/223	91.0 (87.3–94.8)	165/179	92.2 (88.2–96.1)
Age > 65 years	132/141	93.6 (89.6–97.7)	105/115	91.3 (86.1–96.5)
PSI ≤ 3	254/274	92.7 (89.6–95.8)	196/209	93.8 (90.5–97.1)
PSI > 3	81/90	90.0 (83.8–96.2)	74/85	87.1 (79.9–94.2)
Overall	335/364	92.0 (89.2–94.8)	270/294	91.8 (88.7–95.0)



Alors?

- Intra-abdominal infection
- Skin and skin structure infection
- Acute gynaecological infection
- Community-acquired pneumonia
- Complicated urinary tract infection

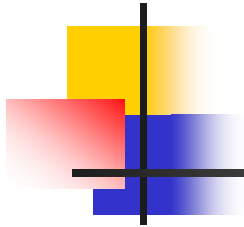


Daptomycine



Daptomycine

- Lipopeptide cyclique
- Rapidement bactéricide in vitro contre la plupart des Gram positifs
- Indiqué pour les infections compliquées de la peau et des tissus mous
- Dose 4 mg/kg BW IV par jour



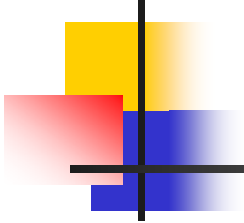
MAJOR ARTICLE

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

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CID 2004

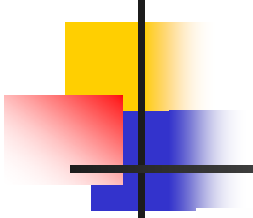


The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

- Etude internationale multicentrique
- Peni anti-staph ou vanco vs dapto
- Ratio 1/1
- Durée 7-14j

Table 1. Demographic and baseline clinical characteristics of the intent-to-treat population.

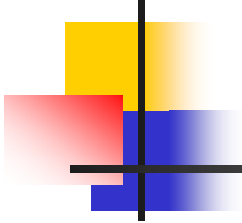
Characteristic	Daptomycin group (n = 534)	Comparator group ^a (n = 558)
Comorbid conditions		
Diabetes mellitus	160 (30)	194 (35)
Peripheral vascular disease	103 (19)	128 (23)
Immunocompromise	18 (3)	19 (3)
Baseline diagnosis ^b		
Wound infection	224 (42)	254 (46)
Major abscess	138 (26)	124 (22)
Infected diabetic ulcer	61 (11)	72 (13)
Infected ulcer, not diabetic	70 (13)	75 (13)
Other infection	41 (8)	33 (6)
Bacteremia ^c	14 (3)	12 (2)
SIRS ^d	190 (36)	213 (38)



The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Table 3. Infecting gram-positive organism at baseline for the modified intent-to-treat (MITT) population.

Organism	No. (%) of patients	
	Daptomycin group (n = 428)	Comparator group ^a (n = 471)
<i>Staphylococcus aureus</i>		
All	305 (71.3)	323 (68.6)
Methicillin-susceptible <i>S. aureus</i> ^b	231 (54.0)	239 (50.7)
Methicillin-resistant <i>S. aureus</i> ^b	40 (9.3)	47 (10.0)
<i>Streptococcus pyogenes</i>	92 (21.5)	103 (21.9)
<i>Streptococcus agalactiae</i>	30 (7.0)	41 (8.7)
<i>Streptococcus dysgalactiae equisimilis</i>	12 (2.8)	15 (3.2)
Viridans streptococci group	26 (6.1)	38 (8.1)
<i>Enterococcus faecalis</i>	45 (10.5)	61 (13.0)



The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Table 4. Combinations of multiple infecting gram-positive organisms at baseline in the modified intent-to-treat population.

Organism	No. (%) of patients	
	Daptomycin group (n = 428)	Comparator group ^a (n = 471)
<i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>	48 (11.2)	50 (10.6) ^b
<i>Streptococcus agalactiae</i>	14 (3.3)	25 (5.3) ^c
<i>Streptococcus dysgalactiae equisimilis</i>	5 (1.2) ^b	8 (1.7)
Viridans streptococci group	5 (1.2) ^d	1 (0.2)
<i>Enterococcus faecalis</i>	11 (2.6)	20 (4.2)
<i>S. pyogenes</i> and <i>E. faecalis</i>	1 (0.2)	0 (0)
<i>S. agalactiae</i> and <i>S. dysgalactiae equisimilis</i>	0 (0)	1 (0.2)
<i>E. faecalis</i>	3 (0.7)	1 (0.2)
<i>S. dysgalactiae equisimilis</i> and Viridans streptococci group	1 (0.2)	0 (0)
<i>E. faecalis</i>	1 (0.2)	0 (0)
Viridans streptococci group and Second Viridans streptococci group species	2 (0.5)	4 (0.8)
<i>E. faecalis</i>	1 (0.2)	7 (1.5)

Table 5. Clinical success rates, by study population.

Population	Daptomycin group		Comparator group ^a		95% CI ^b
	No. of patients	Success rate, %	No. of patients	Success rate, %	
Intent-to-treat	534	71.5	558	71.1	-5.8 to 5.0
Modified intent-to-treat	428	74.5	471	74.7	-5.5 to 5.9
Clinically evaluable	446	83.4	456	84.2	-4.0 to 5.6
Microbiologically evaluable	365	84.7	396	85.9	-3.8 to 6.3

^a Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

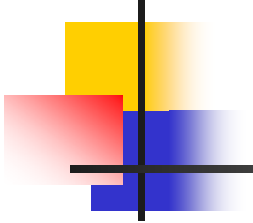
^b The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).

Table 6. Clinical success rates, by investigator baseline diagnosis, for the clinically evaluable population.

Investigator diagnosis	Daptomycin group		Comparator group ^a		95% CI ^b
	No. of patients	Success rate, %	No. of patients	Success rate, %	
Wound infection	169	84	180	87	-4.8 to 10.1
Major abscess	102	92	92	88	-12.6 to 4.3
Infected ulcer, diabetic	47	66	56	70	-14.4 to 21.8
Infected ulcer, nondiabetic	47	79	58	83	-11.2 to 19.3

^a Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

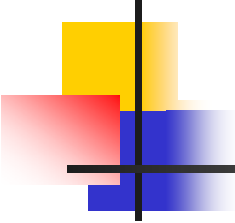
^b The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).



The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

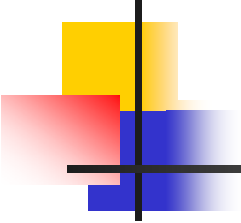
Table 7. Clinical success rates, by infecting gram-positive organism, at baseline for the microbiologically evaluable population.

Treatment arm	Daptomycin group	Comparator group	95% CI
<i>Staphylococcus aureus</i> ^b			
Methicillin-susceptible	170/198 (85.9)	180/207 (87.0)	−5.6 to 7.8
Methicillin-resistant	21/28 (75.0)	25/36 (69.4)	−28.5 to 17.4
<i>Streptococcus pyogenes</i>	79/84 (94.0)	80/88 (90.9)	−11.1 to 4.9
<i>Streptococcus agalactiae</i>	23/27 (85.2)	22/29 (75.9)	−30.9 to 12.2
<i>Streptococcus dysgalactiae</i>	8/8 (100)	9/11 (81.8)	−48.6 to 12.2
<i>Enterococcus faecalis</i>	27/37 (73.0)	40/53 (75.5)	−16.3 to 21.3



Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

- Uncomplicated right-sided endocarditis
 - definite or possible MSSA endocarditis in the absence of predisposing abnormalities or active infection of the mitral or aortic valve
 - serum creatinine level < 2.5 mg/dL
 - no evidence of extrapulmonary sites of infection.
 - medication for a minimum of 14 to 28 days.
- Complicated right-sided endocarditis
 - definite or possible endocarditis in the absence of predisposing abnormalities or active infection of the mitral or aortic valve, with extrapulmonary sites of infection,
 - serum creatinine level of at least 2.5 mg/dL
 - MRSA bacteremia, or the absence of injection-drug use.
 - medication for a minimum of 28 to 42 days.



Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

- Etude ouverte randomisée 1/1
- Daptomycin 6 mg/kg/j vs vanco (1g/12h) ou peni anti-staph (2g/4h)
- Si Tt standard ou endocardite gauche, genta (1 mg/kg/8h)

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Table 1. (Continued.)

Characteristic	Daptomycin (N= 120)	Standard Therapy (N= 115)
Baseline pathogen — no. (%)		
Infection with MRSA	45 (37.5)	44 (38.3)
Diagnosis according to adjudication committee — no. (%)		
Baseline diagnosis		
Definite endocarditis	17 (14.2)	20 (17.4)
Possible endocarditis	73 (60.8)	71 (61.7)
Not endocarditis	30 (25.0)	24 (20.9)
Final diagnosis		
Uncomplicated bacteremia	32 (26.7)	29 (25.2)
Complicated bacteremia	60 (50.0)	61 (53.0)
Uncomplicated right-sided endocarditis	6 (5.0)	4 (3.5)
Complicated right-sided endocarditis	13 (10.8)	12 (10.4)
Left-sided endocarditis	9 (7.5)	9 (7.8)

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

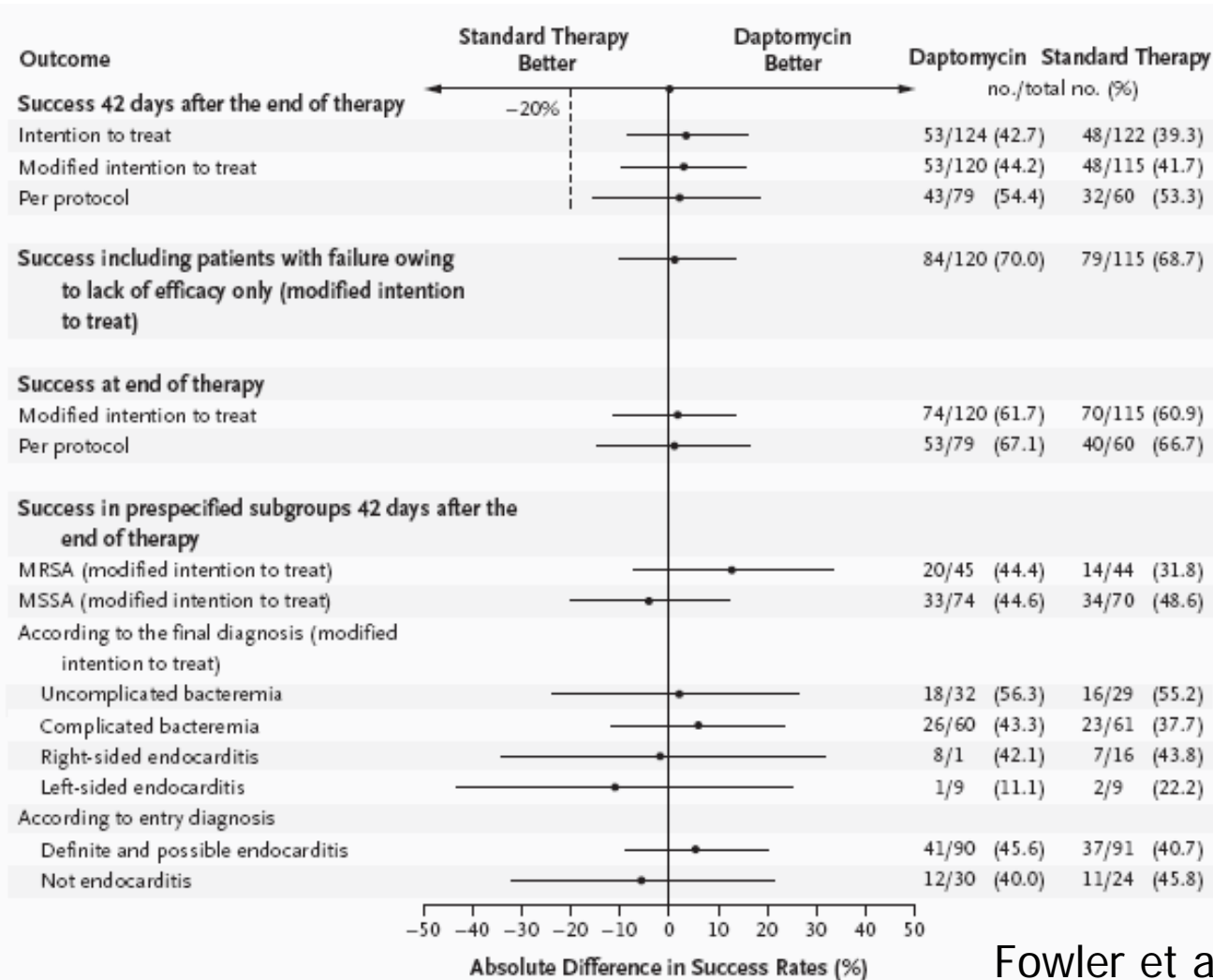
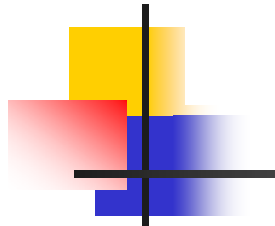
Criteria	Daptomycin	Standard Therapy	Absolute Difference in Success Rates
	<i>no. of patients/total no. (%)</i>		<i>% (95% CI)*</i>
Overall success (intention to treat)	53/124 (42.7)	48/122 (39.3)	3.4 (-8.9 to 15.7)
Overall success (modified intention to treat)	53/120 (44.2)	48/115 (41.7)†	2.4 (-10.2 to 15.1)
Success according to methicillin susceptibility of <i>Staphylococcus aureus</i> ‡			
MSSA	33/74 (44.6)	34/70 (48.6)	-4.0 (-20.3 to 12.3)
MRSA	20/45 (44.4)	14/44 (31.8)	12.6 (-7.4 to 32.6)
Success according to final diagnosis			
Uncomplicated bacteremia	18/32 (56.2)	16/29 (55.2)	1.1 (-23.9 to 26.0)
Complicated bacteremia	26/60 (43.3)	23/61 (37.7)	5.6 (-11.8 to 23.1)
Uncomplicated right-sided endocarditis	3/6 (50.0)	1/4 (25.0)	25.0 (-33.3 to 83.3)
Complicated right-sided endocarditis§	5/13 (38.5)	6/12 (50.0)	-11.5 (-50.3 to 27.2)
Left-sided endocarditis¶	1/9 (11.1)	2/9 (22.2)	-11.1 (-45.2 to 22.9)

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Success in predefined strata

Baseline diagnosis: definite plus possible endocarditis			
Overall	41/90 (45.6)	37/91 (40.7)	4.9 (-9.5 to 19.3)
MSSA	26/54 (48.1)	26/53 (49.1)	-0.9 (-19.8 to 18.0)
MRSA	15/36 (41.7)	11/38 (28.9)	12.7 (-8.9 to 34.3)
Final diagnosis: right-sided endocarditis plus complicated bacteremia			
Overall	34/79 (43.0)	30/77 (39.0)	4.1 (-11.3 to 19.5)
MSSA	20/49 (40.8)	21/48 (43.8)	-2.9 (-22.6 to 16.7)
MRSA	14/30 (46.7)	9/29 (31.0)	15.6 (-8.9 to 40.2)
Final diagnosis: uncomplicated bacteremia‡			
Overall	18/32 (56.2)	16/29 (55.2)	1.1 (-23.9 to 26.0)
MSSA	12/21 (57.1)	11/17 (64.7)	-7.6 (-38.6 to 23.5)
MRSA	6/10 (60.0)	5/11 (45.5)	14.5 (-27.7 to 56.8)
Overall per-protocol success	43/79 (54.4)	32/60 (53.3)	1.1 (-15.6 to 17.8)

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

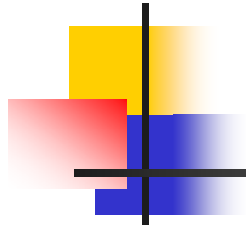


Fowler et al, NEJM 2006

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Table 3. Reasons for Treatment Failure According to the Adjudication Committee.*

Reason for Failure	Daptomycin (N=120)	Standard Therapy (N=115)	P Value†
	no. (%)		
Overall	67 (55.8)	67 (58.3)	
Microbiologic failure, clinical failure, or both	23 (19.2)	15 (13.0)	0.22
Microbiologic failure‡	19 (15.8)	11 (9.6)	0.17
Clinical failure without microbiologic failure§	4 (3.3)	4 (3.5)	1.00
Adverse event	8 (6.7)	17 (14.8)	0.06
Receipt of nonstudy antibiotics that could have influenced outcome	20 (16.7)¶	16 (13.9)‖	0.59
Death	13 (10.8)	13 (11.3)	1.00
No blood obtained for culture**	9 (7.5)	12 (10.4)	0.50
Patient could not be evaluated (e.g., withdrew consent, left hospital against medical advice)	9 (7.5)	14 (12.2)	0.27



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JAC

Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections

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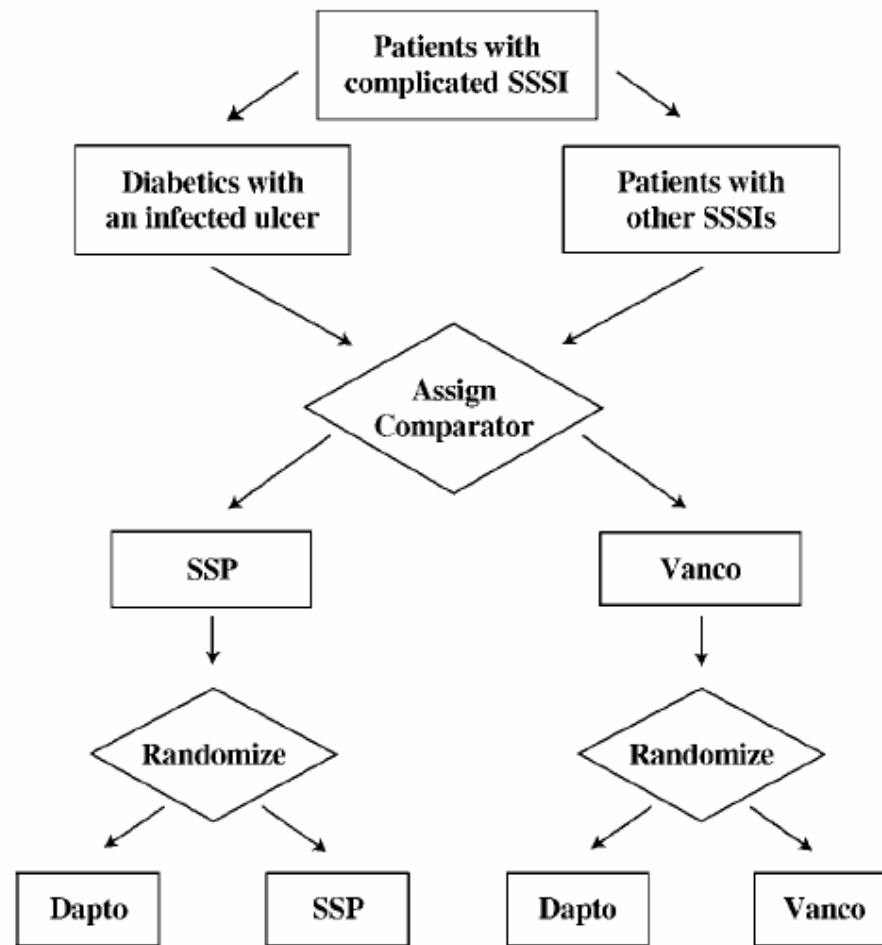
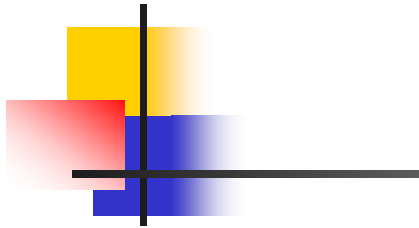
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²*Cubist Pharmaceuticals, Inc, Lexington, MA, USA*



Patient eligibility

- diabetes between the ages of 18 and 85 years who required hospitalization for an infected ulcer that was known or suspected (based on a Gram-stained smear) to be caused by a Gram-positive organism.
- Infection was defined as the presence of at least three of the following:
 - elevated body temperature (greater than 38.8°C);
 - leucocytosis (white blood cell count greater than 12.010⁹/L) or a left-shifted leucocyte differential (10% or more band forms);
 - local pain
 - tenderness to palpation
 - erythema
 - induration
 - purulent secretions



Dapto = daptomycin
SSP = semi-synthetic penicillin
SSSI = skin and skin-structure infection
Vanco = vancomycin

Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections

Table 1. Clinical success rates for patients with infected diabetic ulcers by antibiotic treatment group (clinically evaluable population)

Comparator group	Daptomycin ^a (<i>n</i> = 47) [% (<i>n</i> / <i>N</i>)]	Comparator (<i>n</i> = 56) [% (<i>n</i> / <i>N</i>)]	95% CI
Pooled	66.0 (31/47)	70.0 (39/56)	−14.4–21.8
Semi-synthetic penicillin	64.0 (16/25)	70.4 (19/27)	–
Vancomycin	71.4 (10/14)	69.0 (20/29)	–

^aPre-randomization assignment unavailable in 8 subjects.

Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections

Table 2. Gram-positive pathogens isolated from infected diabetic ulcers at baseline in the clinically evaluable population

	Daptomycin (n = 47)	Comparator (n = 56)
Monomicrobial culture	32	32
<i>Staphylococcus aureus</i>		
susceptibility unspecified	2	5
methicillin-susceptible	11	9
<i>S. aureus</i> (MSSA)		
methicillin-resistant	1	4
<i>S. aureus</i> (MRSA)		
<i>Staphylococcus lugdunensis</i>	0	1
<i>Streptococcus agalactiae</i>	3	5
<i>Streptococcus anginosus</i>	0	1
<i>Streptococcus dysgalactiae</i>	1	2
subsp. <i>equisimilis</i>		
<i>Streptococcus oralis</i>	1	0
<i>Streptococcus pyogenes</i>	0	1
other <i>Streptococcus</i> spp.	1	1
<i>Enterococcus faecalis</i>	10	3
<i>Enterococcus faecium</i>	1	0
<i>Enterococcus avium</i>	1	0

Table 2. Gram-positive pathogens isolated from infected diabetic ulcers at baseline in the clinically evaluable population

	Daptomycin (n = 47)	Comparator (n = 56)
Polymicrobial cultures	11	18
MSSA + <i>E. faecalis</i>	3	1
MSSA + <i>S. agalactiae</i>	3	6
MSSA + <i>Streptococcus</i> spp.	2	1
MSSA + <i>S. pyogenes</i>	0	1
MRSA + <i>E. faecalis</i>	0	2
MRSA + <i>S. agalactiae</i>	0	3
<i>E. faecalis</i> + <i>Streptococcus</i> spp.	3	2
<i>E. avium</i> + <i>S. dysgalactiae</i>	0	1
subsp. <i>equisimilis</i>		
MSSA + <i>S. agalactiae</i> + <i>E. faecalis</i>	0	1
No pathogen	4	6

Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections

Table 3. Clinical and microbiological success rates by infecting pathogen^a

Baseline pathogen	Clinical success [n/N (%)]		Pathogen eradication [n/N (%)]	
	daptomycin	comparator	daptomycin	comparator
<i>Staphylococcus aureus</i> (methicillin-susceptible)	15/19 (79)	15/19 (79)	12/19 (63)	13/19 (68)
<i>S. aureus</i> (methicillin-resistant)	0/1 (0)	6/9 (67)	0/1 (0)	3/9 (33)
<i>Streptococcus pyogenes</i>	0/0	2/2 (100)	0/0	0/2 (0)
<i>Streptococcus agalactiae</i>	5/7 (71)	12/16 (75)	5/7 (71)	9/16 (56)
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	2/2 (100)	3/3 (100)	2/2 (100)	3/3 (100)
<i>Enterococcus faecalis</i>	10/16 (63)	6/9 (67)	10/16 (63)	5/9 (56)

^a Microbiologically evaluable population.

Conclusions: The clinical and microbiological efficacy and safety of daptomycin were similar to those of commonly used comparator antibiotics for treating infected diabetic foot ulcers caused by Gram-positive pathogens. Daptomycin should be considered for treating these infections, especially those caused by resistant Gram-positive pathogens.



A venir

- Ceftobiprole:
 - CSP
 - Large spectre
 - Activité contre le SARM
- RO49084634
 - Carbapénème
 - Actif Pyo et SARM
- Doripenem
 - PSDP
 - Pyo (CMI 2-4x plus basses que imipenem)
 - 2 x moins de résistances induites
- SMP 601
 - GP, GN, ERV, VISA,.... , Pnp nosoc, ISTM, inf abdo....
 - Ne fait pas la vaisselle



A venir

- Oritavancin
 - GP semi synthétique
 - Gram + résistants à la méthi et la vanco
 - Activité dans le biofilm
 - Tps et conc dep
- DC-159a
 - FQ
 - Staph, strepto, PSDP
 - Steno malt, Pyo, Acineto
 - Moins de mutants
 - Sup LVF MXF
-