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Does frontline use of tigecycline versus meropenem-based regimens for intra-abdominal infection reduce the risk for carbapenem-resistant *Klebsiella pneumoniae* colonization or *Clostridium difficile* infection?

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Background

✓Carbapenem sparing regimens are promoted in many institutions to reduce the potential of selection of carbapenem-resistant Enterobacteriaceae (CRE) and reduce the spread of *Clostridium difficile* infection (CDI)

✓Tigecycline has microbiological activity against *Clostridium difficile* and has been succesfully used as a rescue treatment for CDI

✓Tigecycline was succesfully used for the treatment of CRE infection within a combination regimen

✓A larger use of tigecycline may be associated to a lower rate of CDI and CRE colonization

Tumbarello CID 2012; Wilcox MH CMI 2007; Larson KC Annals Pharmacoterapy 2011

Objectives

Primary objective:

The aim of this study was to evaluate the cumulative 90-day risk for colonization with CRE, or development of CDI in patients receiving tigecycline based regimen compared with patients receiving carbapenem-including regimens for intrabdominal infections (IAI).

Secondary objective:

To compare 30-day mortality in patients treated with meropenem based regimens and tigecycline based regimens

Methods:

✓**Design**: Retrospective, single-centre, cohort study of patients receiving tigecycline, alone or in combination regimens, compared with patients treated with carbapenems, alone or in combination, for intra-abdominal infection (IAI) from October 2011 to October 2015

✓**Setting:** S. Orsola Malpighi Hospital, University of Bologna a 1400-bed tertiary teaching hospital performing over 4000 abdominal surgical interventions per year. The study was approved by Institutional Review Board.

Inclusion Criteria	Exclusion Criteria
✓ age > 18 years	✓ Previous CRE colonization
✓ Receipt of tigecycline alone or in combination	✓ Previous episode of CDI
✓ Diagnosis of IAI	✓ Receipt of gentamycin, colistin or CDI-active therapy (i.e. metronidazole, oral vancomycin)
✓ Minimum follow-up of 3 months	✓ Combination therapy including carbapenems
✓ At least one rectal swab performed within 90 days	

Methods (2)

✓**Matched controls:**

The cohort of patient treated with tigecycline-based regimen (TIG group) were matched (1:1) with a cohort of patients receiving meropenem-based regimen (MER group) for at least 5 days selected with the following criteria

Matching Criteria
✓ age (range ± 5 years);
✓ Admission to the same hospital ward in the same month and year
✓ length of in-hospital stay (range ± 5 days);
✓ duration of antibiotic administration
✓ APACHE II score at time of infection onset (range ± 2);
✓ immune status (we matched patients according with receipt of solid organ transplantation, treatment with steroids at dosage of 0.3 mg/kg prednisone equivalent for < 3 weeks or T cell immunosuppressing medication, or neutropenia [<0.5 x 109 neutrophils/L]).

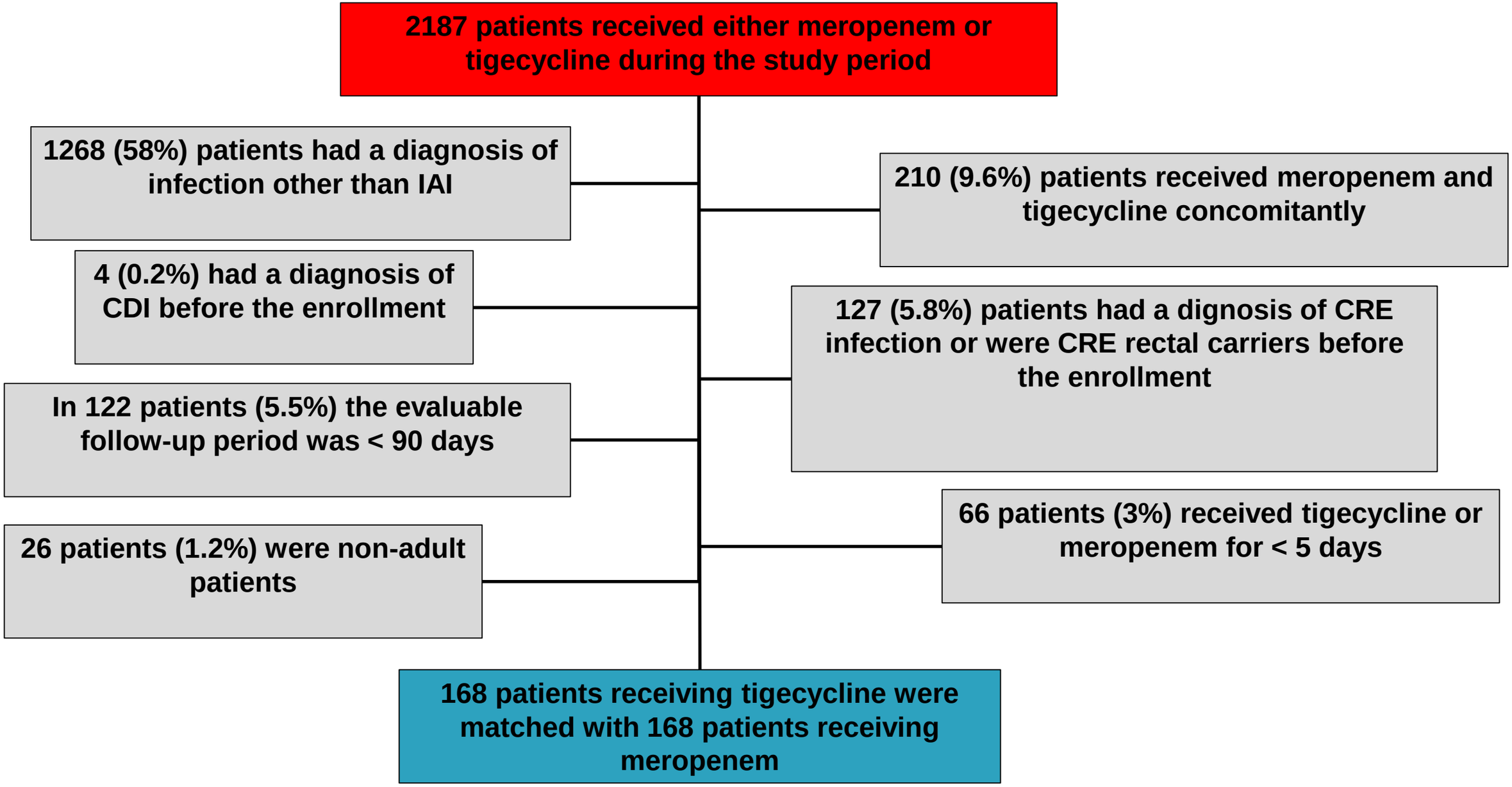
Endopints

Primary endpoints:

1. Positive rectal swab for CRE within 90 days
2. Positive *Clostridium difficile* glutamate dehydrogenase (GHD) antigen plus positive toxin A/B (in a patient with unformed stools) within 90 days

Secondary endpoint:

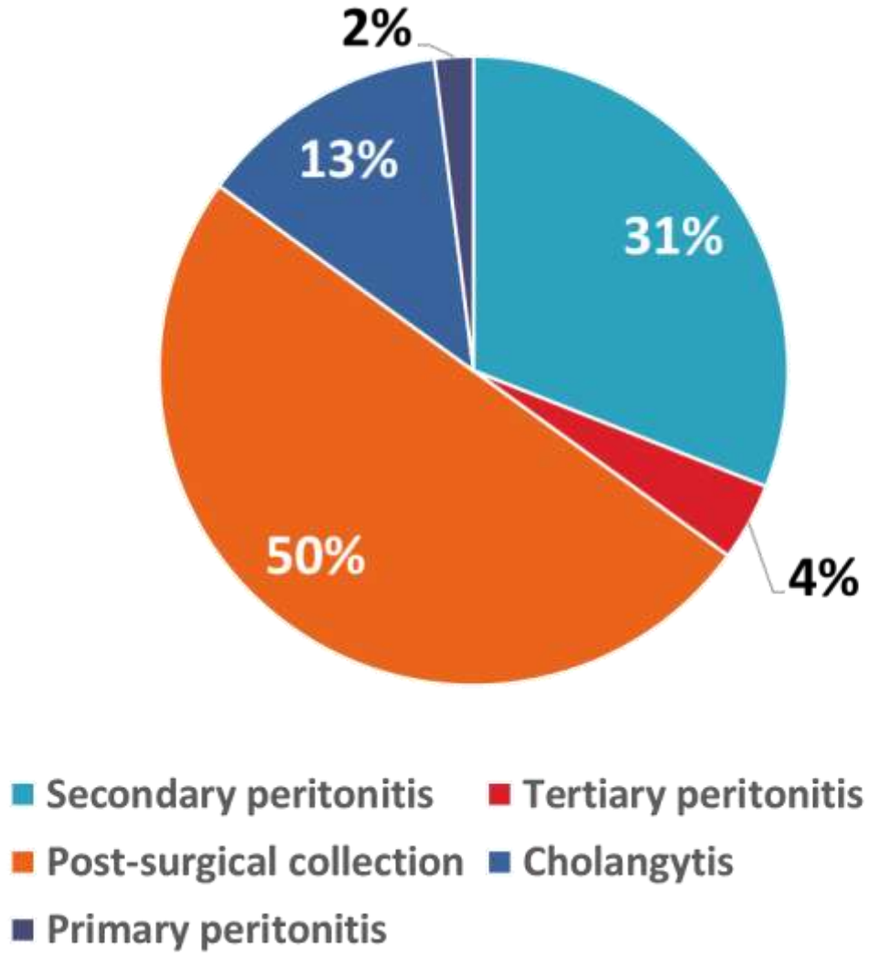
Mortality within 30 days form diagnosis of IAI


2187 patients received either meropenem or tigecycline during the study period
1268 (58%) patients had a diagnosis of infection other than IAI
4 (0.2%) had a diagnosis of CDI before the enrollment
In 122 patients (5.5%) the evaluable follow-up period was < 90 days
26 patients (1.2%) were non-adult patients
210 (9.6%) patients received meropenem and tigecycline concomitantly
127 (5.8%) patients had a dignosis of CRE infection or were CRE rectal carriers before the enrollment
66 patients (3%) received tigecycline or meropenem for < 5 days
168 patients receiving tigecycline were matched with 168 patients receiving meropenem

	Total, n=336 (%)	Patients treated with tigecycline, n=168	Patients treated with meropenem, n=168	P value
Demographic data				
Age, years [median (IQR)]	60 (46-73)	62 (47-73)	58 (44-73)	0.38
Sex, male	196 (53)	94 (56)	102 (60)	0.37
Comorbidities				
Charlson score [median (IQR)]	5 (3-8)	6 (3-8)	5 (3-7)	0.15
Immunosuppression	59 (17)	25 (15)	34 (20)	0.19
Length of hospital stay	27 (17-41)	25 (14-42)	28 (20-41)	0.38
Concomitant treatments				
Proton-pump inhibitors	298 (89)	152 (90)	146 (87)	0.30
Steroids	43 (13)	21 (12)	22 (13)	0.87
IAI characteristics				
Healthcare associated	264 (79)	132 (79)	132 (79)	1
Previous surgery (< 30 days)	196 (55)	109 (65)	87 (51)	**0.03**
Previous hospital admission (<90 days)	231 (68)	115 (68)	105 (62)	0.25
Medical Unit at the time of IAI onset				
ICU	34 (10)	17 (10)	17 (10)	1
Surgery	185 (55)	93 (55)	92 (55)	0.91
Medicine	117 (35)	58 (34)	59 (35)	0.90

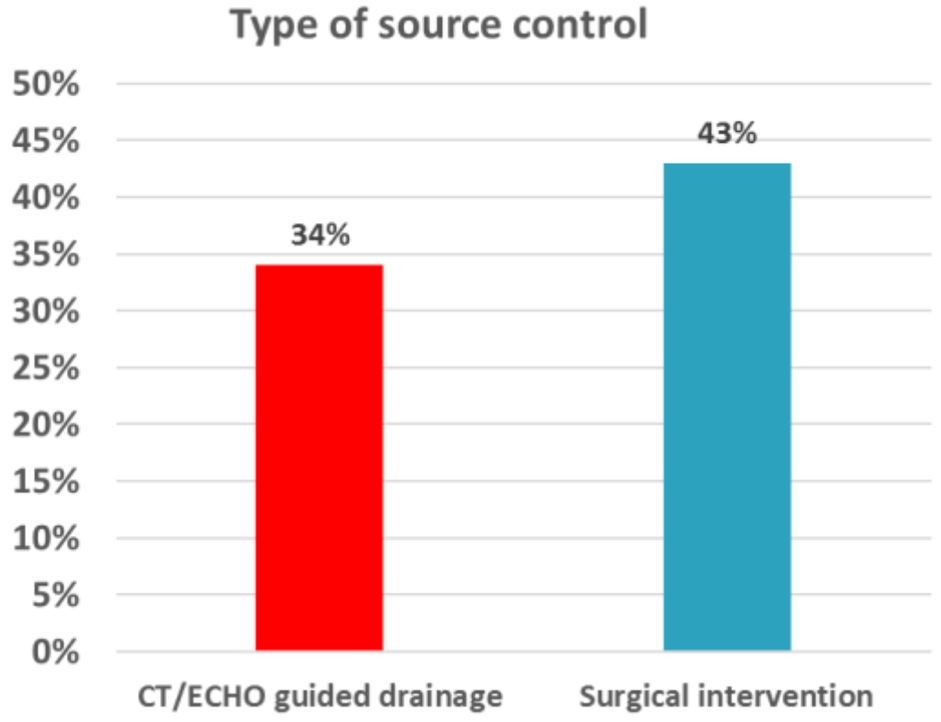
Abbreviations: IQR interquartile range, IAI intraabdominal infection, CR, ICU intensive care unit

Results:
Kind of IAI

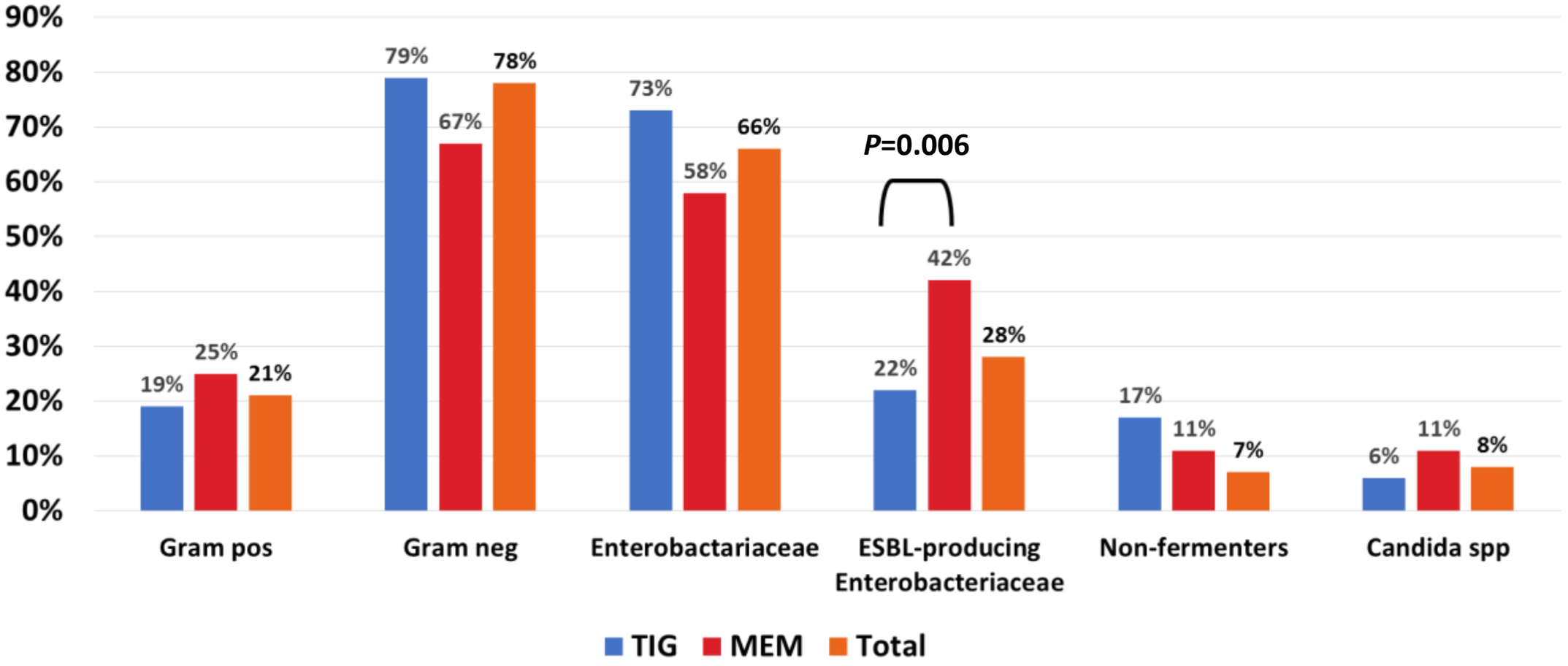


Source control

- **Performed in 77 % of cases**
- **Not performed mainly in cholangytis**



Results
IAI: etiology
(176 cases with at least 1 isolate among 336 episodes)



Polymicrobial infections were diagnosed in 51/176 (29%) of culture-positive IAI

	Total, n=336 (%)	Patients treated with tigecycline n=168	Patients treated with meropenem, n=168	P value
Infection severity				
Septic shock	35 (10)	18 (11)	17 (10)	0.85
APACHE II score [median (IQR)]	8 (5-12)	9 (5-11)	8 (5-11)	0.19
Treatments received for IAI				
Glycopeptides	104 (37)	24 (14)	80 (48)	**<0.001**
Piperacillin/tazobactam	174 (51)	135 (80)	39 (23)	**<0.001**
Fluoroquinolones	30 (9)	17 (10)	13 (7)	0.44
Length of treatment, days [median (IQR)]	11 (8-18)	11 (7-17)	11 (8-19)	0.38
Source control				
Relaparotomy	143 (43)	69 (41)	64 (38)	0.57
Imaging-guided drainage	114 (34)	59 (35)	47 (28)	0.16
Median length of hospital stay (IQR)	27 (17-41)	25 (14-42)	28 (20-41)	0.38

Abbreviationa: IQR interquartile range, IAI intraabdominal infection, ICU intensive care unit, CDI Clostridium difficile infection, CR-KP carbapenem resistant Klebsiella pneumoniae

	Total, n=336 (%)	Patients treated with tigecycline n=168	Patients treated with meropenem, n=168	P value
ICU admission	153 (45)	89 (50)	68 (40)	0.06
Mechanical ventilation (> 48 h)	40 (12)	22 (13)	18 (11)	0.50
In-hospital mortality	35 (10)	16 (9)	19 (11)	0.59
Diarrhoea experienced	34 (10)	14 (8)	20 (12)	0.27
CDI	11 (3)	1 (1)	10 (6)	**0.006**
CRE carriage acquisition	30 (9)	17 (10)	13 (7)	0.44

CDI incidence density

- hospital-wide 3.3/10000 patient-days
- TIG group 1.8/10000 patient-days
- MER group 18/10000 patient-days

CRE new rectal acquisition incidence density

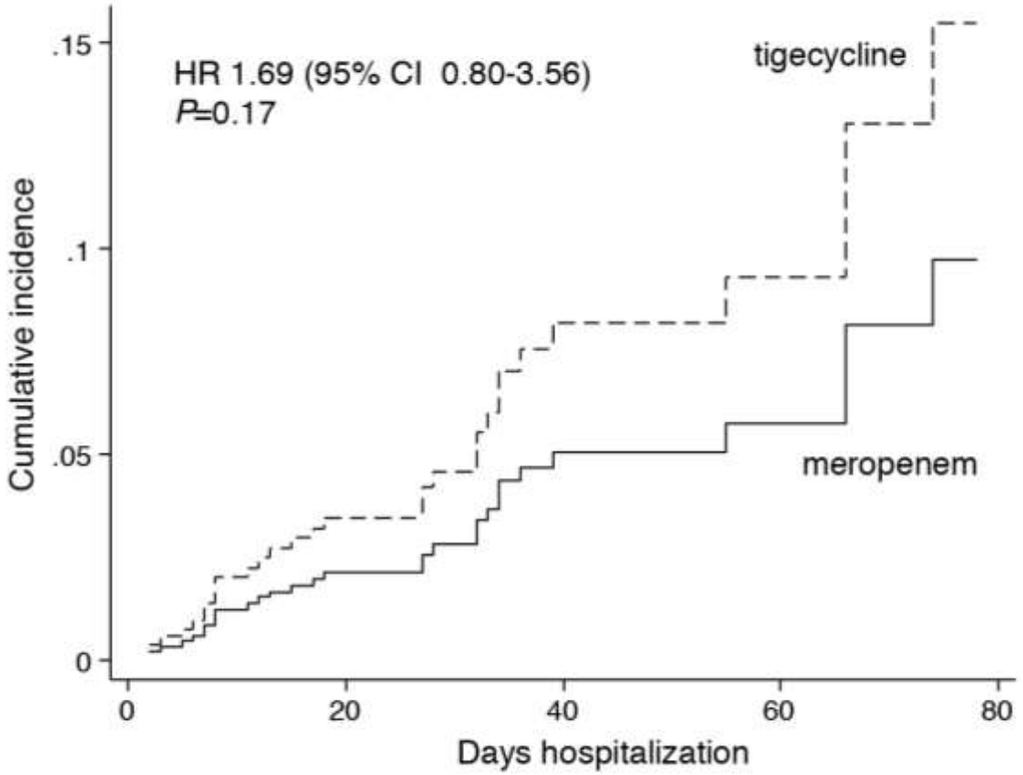
- hospital-wide 12.3/10000 patient-days
- TIG group 31.2/10000 patient-days
- MER group 23.7/10000 patient-days

Results:

Multivariate analysis.
Factors associated to CRE colonisation

CRE colonisation risk factor	Hazard ratio (95% CI)	P value
Receipt of tigecycline regimen	1.69 (0.80-3.56)	0.17
Hospital-acquired IAI	10.46 (1.37-79.43)	0.02
Pancreatic surgery	4.59 (1.60-13.14)	0.004
Upper GI surgery	6.18 (2.03-18.82)	0.001
Other surgery[a]	3.23 (1.07-9.76)	0.04

Model predicted cumulative incidence of CRE colonisation

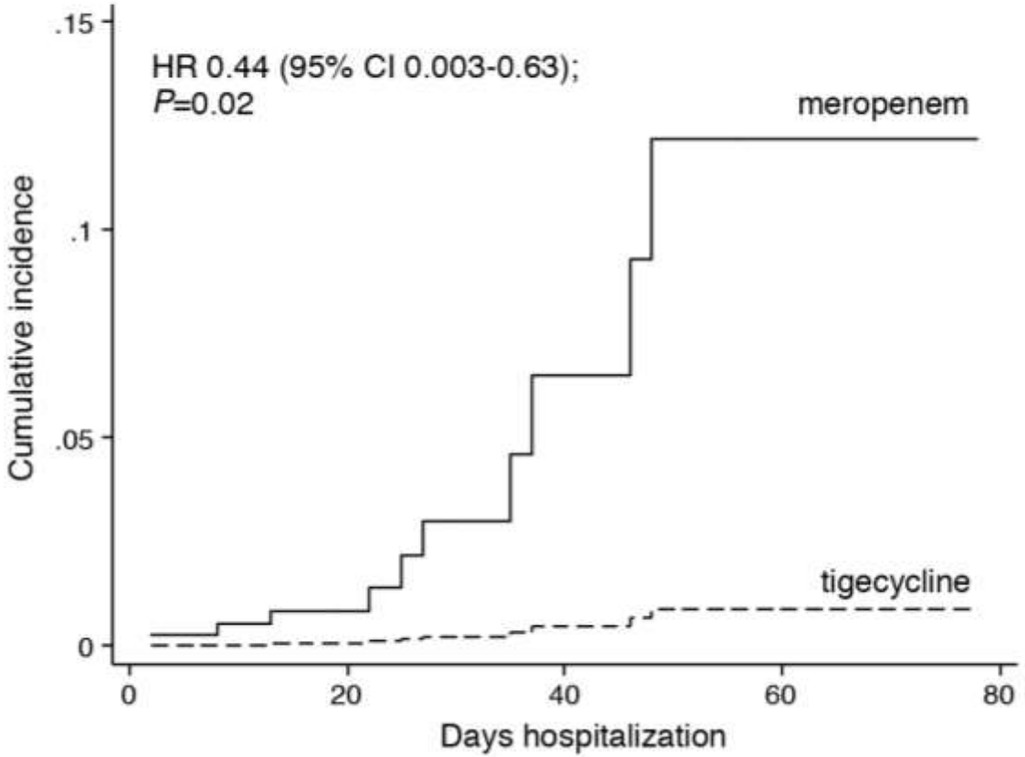


Results:

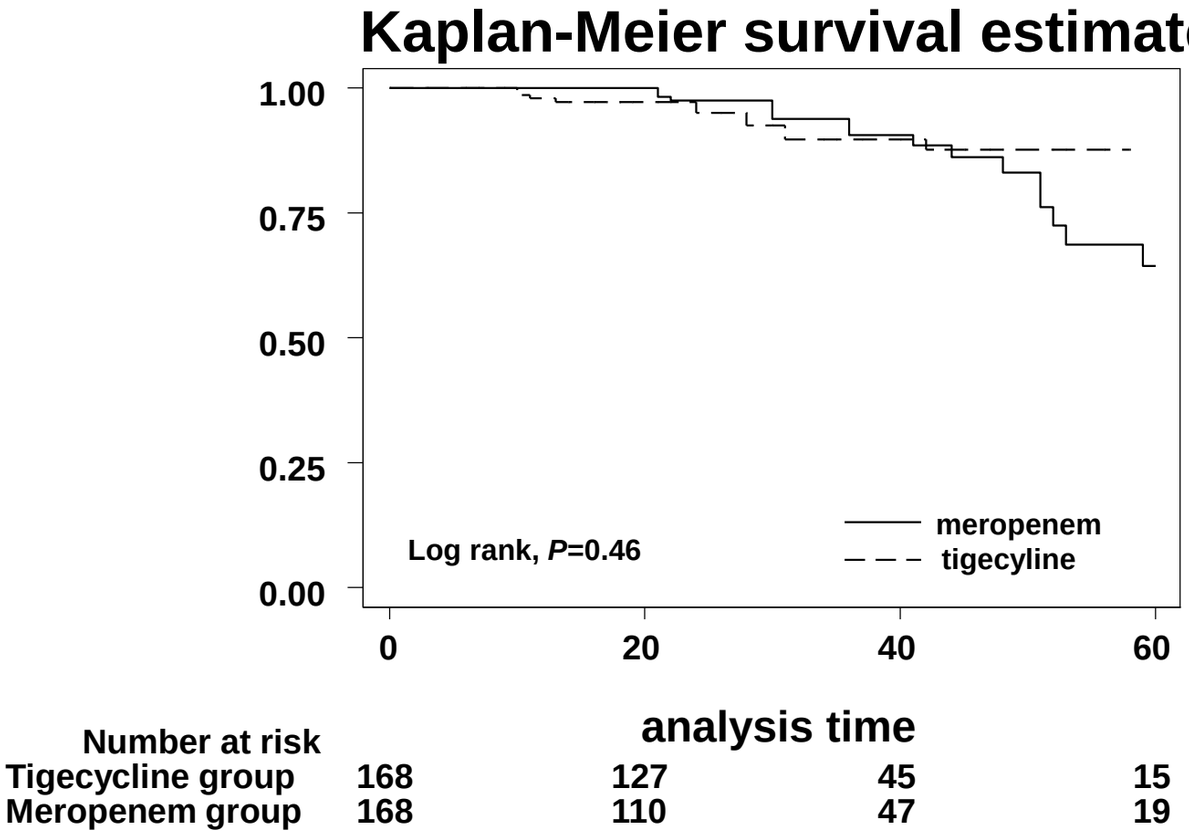
Multivariate analysis. Factors associated to CDI

CDI Risk factors	Hazard ratio (95% CI)	P value
Receipt of tigecycline regimen	0.44 (0.003-0.63)	0.02
Abdominal fluid collection	4.85 (1.13-20.82)	0.03
Neutropenia	24.01 (3.82-150.67)	0.001

Model predicted cumulative incidence CDI



Results:
Comparison of mortality rate among patients treated with tigecycline vs meropemem based regimen



Similar results were obtained analysing separately patients with infection caused by

- ✓ ESBL producing strains (log rank, *P*=0.31)
- ✓ Non-fermenters (log rank, *P*=0.55)

Conclusions

✓ Compared to MER-containing treatment regimens, TIG-based antimicrobial treatment for IAI was associated with a 10-fold lower incidence of CDI

✓No apparent effect on the incidence of CRE colonisation.

✓Further prospective studies are needed to confirm the potential benefits of carbapenem sparing strategies for reducing CDI and CRE spread.

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