# Quadri clinici della infezione da *Klebsiella* produttrice di New Delhi metallo-beta lattamasi

**Dott. Marco Falcone**

Division of Infectious Diseases, Department of Clinical and
Experimental Medicine, University of Pisa (Italy)

# A clinical case



- **Woman of 88 years admitted to ED for fever and altered mental status**

- **Aortic valvulopathy (stenosis) with need of surgical intervention (patient refused)**
- **Ischemic cardiomiopathy**
- **COPD**
- **Obesity**
- **Previous femoral head fracture and necrosis (in the previous year)**

- **Recent hospitalization (in the previous month) for anemia**

# A clinical case

| Vital parameters | Tc 38,7 °C<br>**BP 100/60 mmHg**<br>**HR 100 bpm**<br>RR 20 atm |
|---|---|
| Mental status | Altered (confusion) |
| Laboratory exams | RBC 4,57 x $10^6$<br>Hb 12,5 g7dl<br>**WBC 29,9 x$10^3$ (N91.7%, L 1,6%)**<br>PLT 217 x $10^3$<br><br>PT 1,28<br>AST/ALT 42/45<br>Bilirubin 1,2<br><br>**CRP 19 mg/dl**<br>**PCT 34 ng/ml** |
| Urinary exams | Leucocytes +++ |

Collection blood cultures **Start piperacillin-tazobactam 4.5 g i.v. every 6 h + vancomycin 1 g ev every 12 hours**

# A clinical case

**Source of infection?**

- **Respiratory tract.**    X
- **ABSSSI**    X
- **Intravascular device**    X
- **Urinary tract**    ✔

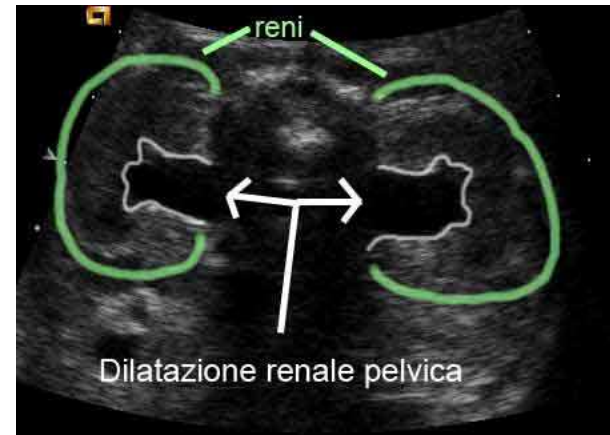**Potential etiology?**

**Risk factors for MDRO**    ✔

**Recent hospitalization: rectal swab**
*not performed during hospitalization*    X

# A clinical case

**Abdomen ultrasound**

...Pathologic **calico**-**pelvic dilation**

- Nephrostomy placement

# A clinical case after 2 days...



| Vital parameters | Tc 40°C<br>BP 60/40 mmHg<br>HR 120 bpm<br>RR 40 atm |
|---|---|
| Mental status | Altered (confusion) |
| Laboratory exams | RBC 4,4 x $10^6$<br>Hb 10,5 g/dl<br>WBC 26 x$10^3$ (N91.7%, L 1,6%)<br>PLT 77 x $10^3$<br><br>PT 2,5<br>AST/ALT 42/45<br>Bilirubin 2<br>CRP 39 mg/dl<br>PCT 68 ng/ml |

Arterial blood gas test

pH 7,46
pCO2 27 mmHg
pO2 73 mmHg (FiO2 35%)

Lactates 2,4

**Septic shock! Transfer to ICU**

# A clinical case after 2 days...

| Esame | | Esito |
|---|---|---|
| 1° microrganismo: *Klebsiella pneumoniae* | | |
| Antibiotico | MIC (µg/ml) | SIR |
| >> BRODODILUIZIONE IN MICROPIASTRA | | << |
| Amikacina | <=4 | S |
| **Amoxicillina/Clavulanato** | >8 | **R** |
| **Ampicillina/sulbactam** | >32 | **R** |
| **Cefepime** | >32 | **R** |
| **Cefotaxime** | >4 | **R** |
| **Ceftazidime** | >128 | **R** |
| **Ciprofloxacina** | >2 | **R** |
| Colistina | <=0.5 | S / R |
| **Doripenem** | >8 | **R** |
| Ertapenem | >1 | - |
| **Fosfomicina** | >64 | **R** |
| **Gentamicina** | 4 | **R** |
| **Imipenem** | >16 | **R** |
| **Levofloxacina** | 4 | **R** |
| **Meropenem** | 64 | **R** |
| Nitrofurantoina | >64 | |
| **Piperacillina/Tazobactam** | >128 | **R** |
| Tigeciclina | 0.5 | S |
| **Trimetoprim-sulfametossazolo** | >4 | **R** |

**Carbapenem resistant**
***Klebsiella pneumoniae***

**Start ceftazidime-avibactam 2,5 g q8 h**

# A clinical case after 2 days...

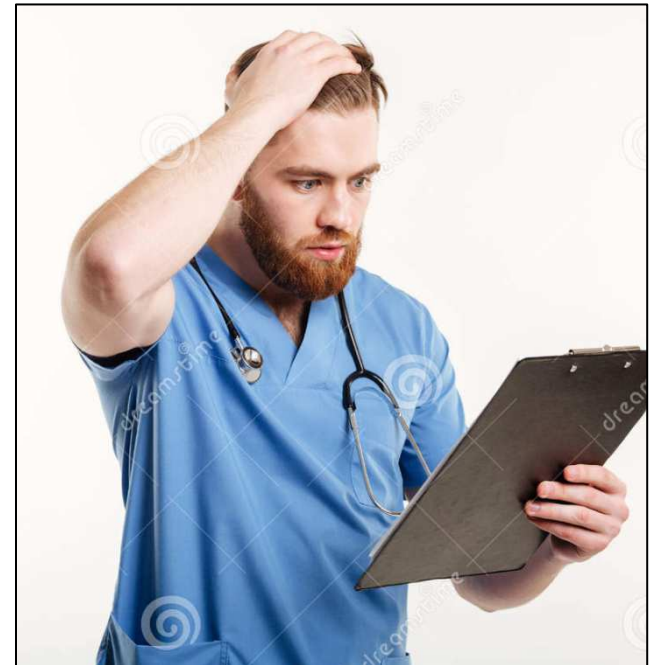Which carbapenemase
Kp produce?

~~KPC?~~

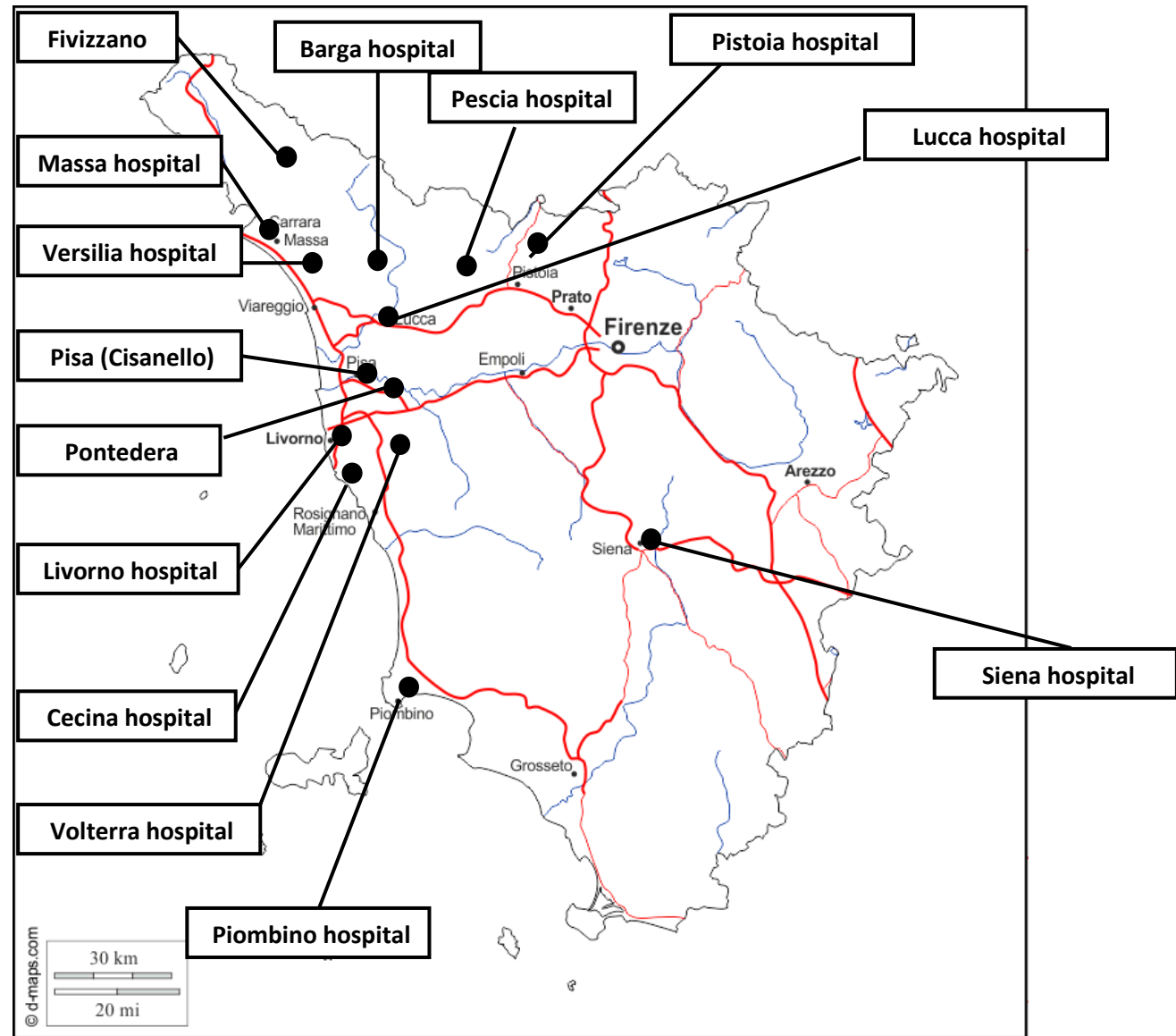- **NDM+**

**Add aztreonam to ceftazidime-avibactam**

# A clinical case after 2 days...

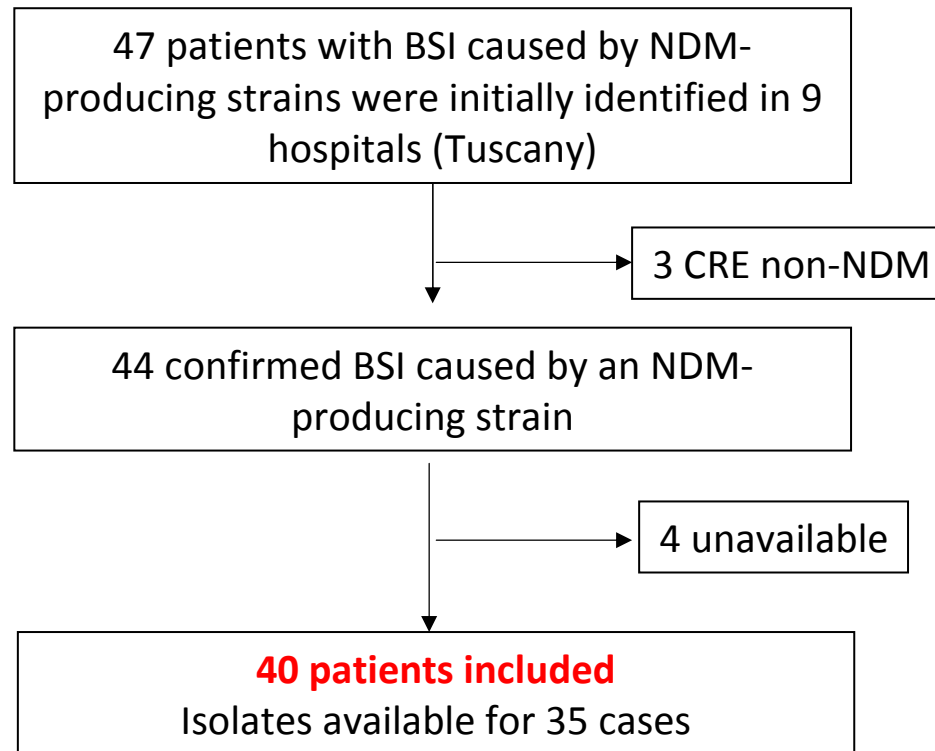| | |
|---|---|
| KPC | negative |
| NDM | positive |
| VIM | negative |
| OXA-48 | negative |
| IMP-1 | negative |



**The patient died after the episode of septic shock**

# Cases of NDM+ *Klebsiella* BSIs in Tuscany

# Clinical features and outcomes of BSIs caused by New Delhi Metallo-β-Lactamase–producing *Enterobacterales* during a regional outbreak



47 patients with BSI caused by NDM-producing strains were initially identified in 9 hospitals (Tuscany)

3 CRE non-NDM

44 confirmed BSI caused by an NDM-producing strain

4 unavailable

**40 patients included**
Isolates available for 35 cases

# Clinical features and outcomes of BSIs caused by New Delhi Metallo-β-Lactamase–producing *Enterobacterales* during a regional outbreak

| | All patients N= 40 | Survivors N=23 | Non-survivors N=17 | p |
|---|---|---|---|---|
| Age, years, median (IQRs) | 70.5 (55.25-77.75) | 63 (48-76) | 74 (67-82.5) | *0.018* |
| **Ward of hospitalization** | | | | 0.687 |
| Medical wards | 20 (50%) | 12 (52.2%) | 8 (47.1%) | |
| ICU wards | 13 (32.5%) | 8 (34.8%) | 5 (29.4%) | |
| Surgery | 7 (17.5%) | 3 (13%) | 4 (23.5%) | |
| **Comorbidities** | | | | |
| Cardiovascular disease | 20 (50%) | 9 (39.1%) | 11 (64.7%) | 0.110 |
| Malignancy | 19 (47.5%) | 9 (39.1%) | 10 (58.8%) | 0.218 |
| COPD | 12 (30%) | 5 (21.7%) | 7 (41.2%) | 0.185 |
| Diabetes | 12 (30%) | 8 (34.8%) | 4 (23.5%) | 0.443 |
| Chronic renal diseases | 7 (17.5%) | 4 (17.4%) | 3 (17.6%) | 0.983 |
| **Charlson Comorbidity Index** - median | 4 (2-7) | 3 (0-5) | 6 (3-8.5) | *0.010* |
| **Source of infection** | | | | 0.067 |
| Unknown | 10 (25%) | 3 (13%) | 7 (41.2%) | |
| Urinary tract | 10 (25%) | 7 (30.4%) | 3 (17.6%) | |
| Intravascular device | 9 (22.5%) | 8 (34.8%) | 1 (5.9%) | |
| ABSSSI | 6 (15%) | 3 (13%) | 3 (17.6%) | |
| Respiratory tract | 3 (7.5%) | 2 (8.7%) | 1 (5.9%) | |
| Intra-abdominal | 2 (5%) | 0 | 2 (11.8%) | |
| **NDM rectal colonization** | 27 (67.5%) | 17 (89.5%) | 10 (62.5%) | 0.058 |

# Clinical features and outcomes of BSIs caused by New Delhi Metallo-β-Lactamase–producing *Enterobacterales* during a regional outbreak

| Bacterial species and antimicrobial agent tested | MIC (mg/L) | Susceptibility rates (%) | | |
|---|---|---|---|---|
| | Range | S | I | R |
| ***Klebsiella pneumoniae (N=31)*** | | | | |
| Ceftriaxone | >4 | - | - | 100 |
| Ceftazidime | >64 | - | - | 100 |
| Cefepime | >16 | - | - | 100 |
| PIP-TAZ | >128/4 | - | - | 100 |
| Ciprofloxacin | >1 | - | - | 100 |
| Levofloxacin | >8 | - | - | 100 |
| Amikacin | >32 | - | - | 100 |
| Gentamycin | ≤0.5 to >8 | 3.2 | - | 96.8 |
| Meropenem | 4 to 64 | - | 3.2 | 96.8 |
| Ertapenem | 1 to >2 | - | - | 100 |
| TMP-SMX | ≤1/19 to >8/152 | 3.2 | - | 96.8 |
| Tigecycline | ≤0.25 to >4 | 80.6 | - | 19.4 |
| Colistin | ≤0.5 to >8 | 90.3 | - | 9.7 |
| Aztreonam | >32 | - | - | 100 |
| Fosfomycin* | 4 to 64 | 80.6 | - | 19.4 |
| CLZ-TAZ | >64/4 | - | - | 100 |
| CAZ-AVI | >32 | - | - | 100 |
| MER-VAB | 4 to >64 | 3.2 | - | 96.8 |
| AZT-AVI | ≤0.25 to 1 | 100 | - | - |

# Clinical features and outcomes of BSIs caused by New Delhi Metallo-β-Lactamase–producing *Enterobacterales* during a regional outbreak

| | All patients N= 40 | Survivors N=23 | Non-survivors N=17 | p |
|---|---|---|---|---|
| **Antibiotic regimens** | | | | 0.054 |
| No *in vitro* active antibiotic therapy | 14 (35%) | 5 (21.7%) | 9 (52.9%) | |
| CAZ-AVI + ATM | 12 (30%) | 10 (43.5%) | 2 (11.8%) | |
| Colistin based regimen** | 9 (22.5%) | 4 (17.4%) | 5 (29.4%) | |
| Others*** | 5 (12.5%) | 4 (17.4%) | 1 (5.9%) | |

*Colistin was used in combination with meropenem (4 cases), fosfomycin (3 cases), tigecycline (1 case), AZT + piperacillin-tazobactam (1 case).

**Other therapies include: 1 patient treated with fosfomycin + tigecycline + amikacin (death); 1 patient treated with meropenem + tigecycline + fosfomycin; 1 patient treated with fosfomycin alone; 1 patient treated with tigecycline + meropenem; 1 patient treated with tigecycline alone.

# Ceftazidime-Avibactam and Aztreonam, an interesting strategy to overcome beta-Lactam resistance conferred by metallo-beta-lactamases in Enterobacteriaceae and *P. aeruginosa*
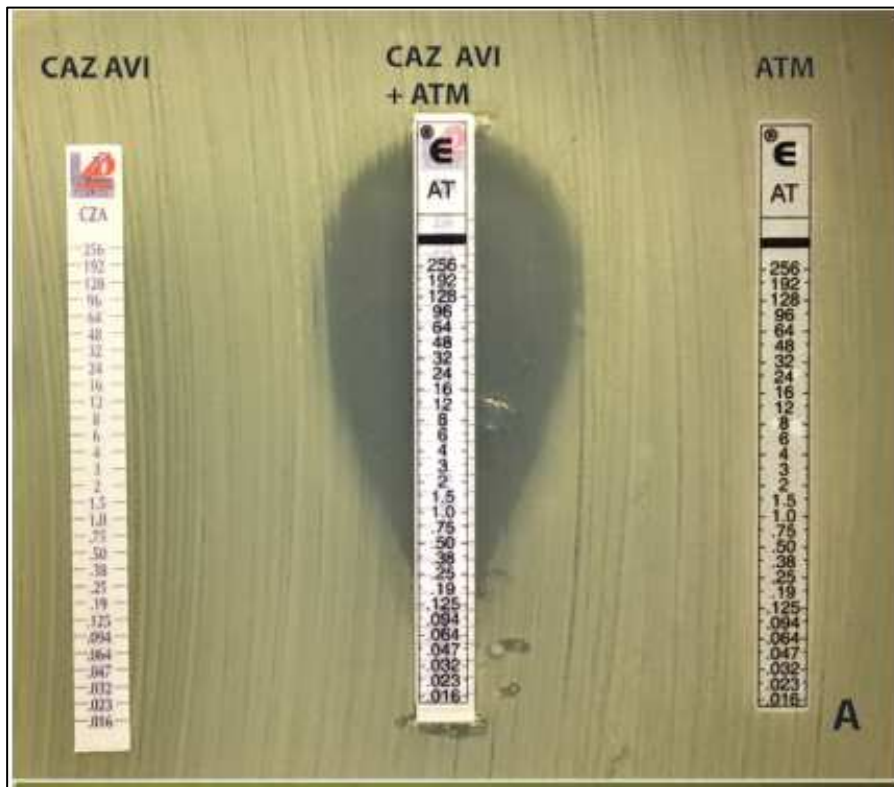


*K. pneumoniae* NDM-1/OXA-48 from patient 1
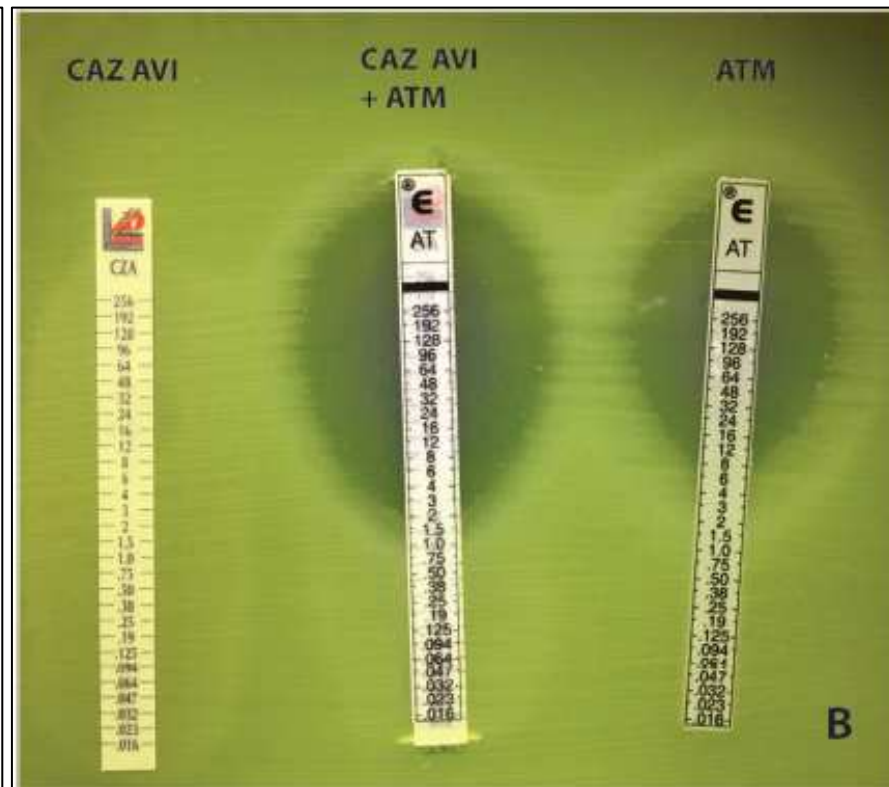
*Pseudomonas aeruginosa* NDM-1/AmpC from patient 2

# Can Ceftazidime-Avibactam and Aztreonam Overcome beta–Lactam Resistance Conferred by Metallo-beta-Lactamases in Enterobacteriaceae?

| Isolate | Known *bla* gene(s) | Disk diffusion assay inhibition zone diam (mm) | | | |
|---|---|---|---|---|---|
| | | 30 μg CAZ (CLSI S ≥ 21, I = 18–20, R ≤ 17 mm) | 30 μg ATM (CLSI S ≥ 21, I = 18–20, R ≤ 17 mm) | 30 μg CAZ–20 μg AVI (FDA S ≥ 21, R ≤ 20 mm) | CAZ-AVI with ATM[b] |
| *E. coli* DH10B | None | 33 | 35 | 35 | 40 (5) |
| *E. cloacae* 6.31 | NDM-1, CTX-M-15, ACT/MIR, OXA-48 | 6 | 6 | 14 | 26 (12) |
| *E. cloacae* 6.43 | NDM-1, CTX-M-15, ACT/MIR | 6 | 6 | 17 | 25 (8) |
| *E. cloacae* joint infection | NDM-1, CTX-M, TEM-1, AmpC[c] | 6 | 6 | 18 | 28 (10) |
| *E. coli* 8.68 | NDM-1, CTX-M-15, CMY-2, TEM | 6 | 6 | 19 | 21 (2) |
| *E. coli* 8.69 | NDM-1, CTX-M-15, CMY-2, SHV-5 | 6 | 6 | 17 | 24 (7) |
| *E. coli* 8.70 | NDM-1, CTX-M-15, CMY-2, TEM, SHV-5 | 6 | 6 | 20 | 22 (2) |
| *E. coli* 8.71 | NDM-1, CTX-M-15, CMY-2, TEM | 6 | 6 | 17 | 20 (3) |
| *E. coli* 8.72 | NDM-1, CTX-M-15, CMY-2, TEM | 6 | 6 | 18 | 23 (5) |
| *E. coli* 8.73 | NDM-1, CTX-M-15, CMY-2, TEM | 6 | 6 | 17 | 20 (3) |
| *E. coli* 8.74 | NDM-1, TEM | 6 | 6 | 20 | 27 (7) |
| *E. coli* 6728 | NDM-1 | 6 | 15 | 18 | 18 (0) |
| *K. pneumoniae* 1.41 | NDM-1, CTX-M-15, DHA, SHV, TEM | 6 | 6 | 17 | 32 (15) |
| *K. pneumoniae* 1.42 | NDM-1, CTX-M-15, SHV-12 | 6 | 6 | 17 | 27 (10) |
| *K. pneumoniae* 1.44 | NDM-1, CTX-M-15, CMY-2, DHA, SHV, TEM | 6 | 6 | 15 | 25 (10) |
| *K. pneumoniae* 1.50 | NDM-1, CTX-M-15, SHV | 6 | 6 | 20 | 30 (10) |
| *K. pneumoniae* 1.63 | NDM-1, CTX-M-15, CMY-2, SHV, TEM | 6 | 6 | 15 | 30 (15) |
| *K. pneumoniae* 6913 | IMP, SHV | 6 | 28 | 17 | 28 (0) |
| *K. pneumoniae* 11-01-13 | NDM-1, CTX-M-15, SHV | 6 | 6 | 17 | 30 (13) |
| *Providencia rettgeri* 6384 | NDM-1, SHV | 6 | 37 | 6 | 34 (−3) |
| *P. rettgeri* 1.27 | NDM-1, CMY-2, DHA | 6 | 14 | 10 | 20 (6) |
| *Morganella morganii* 1.39 | NDM-1, CTX-M-15, DHA | 6 | 12 | 10 | 25 (13) |
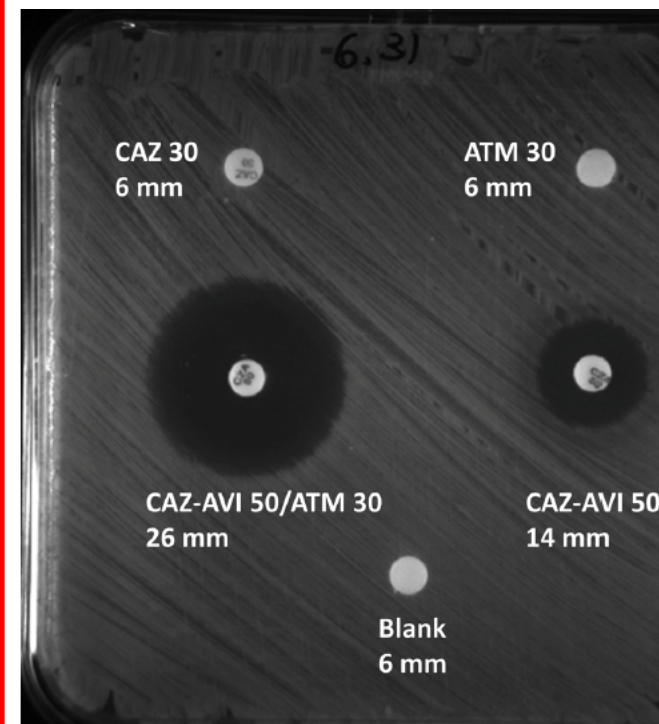


Marshall S, Antimicrob Agents Chemother. 2017;61(4).

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*
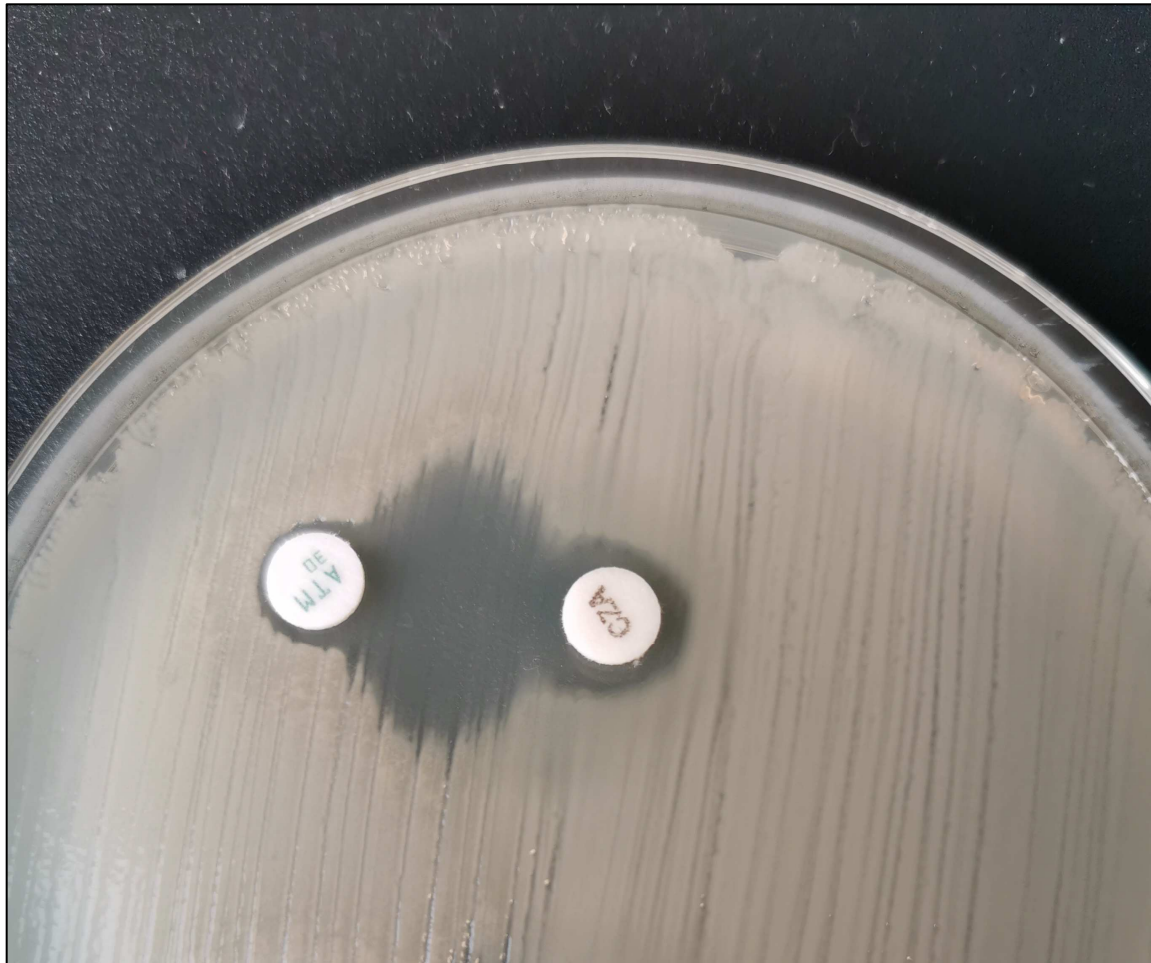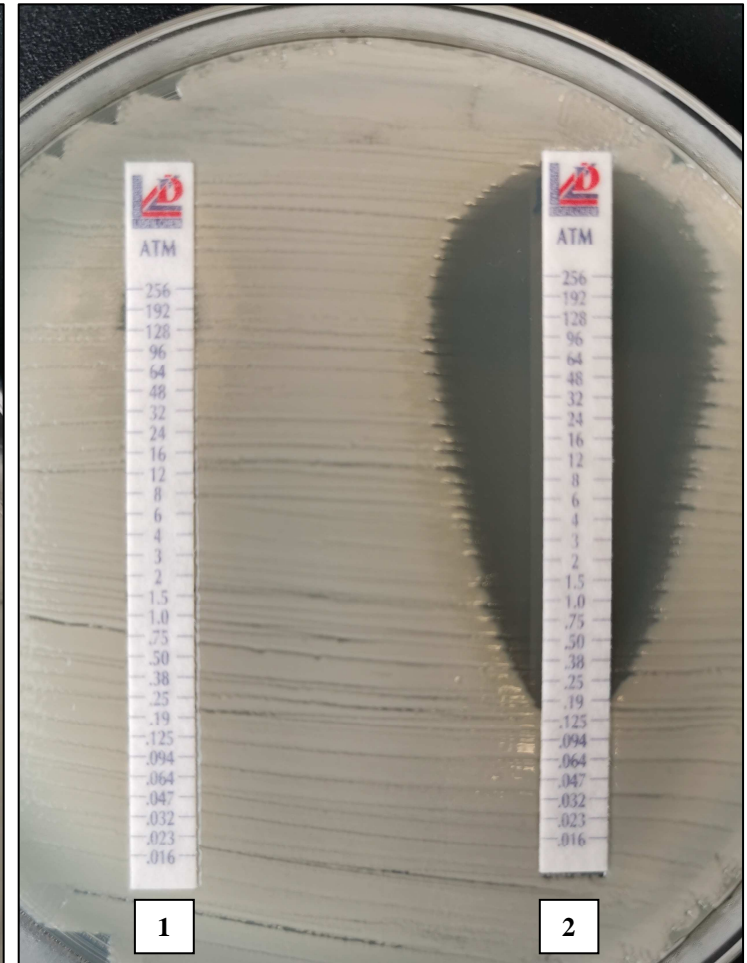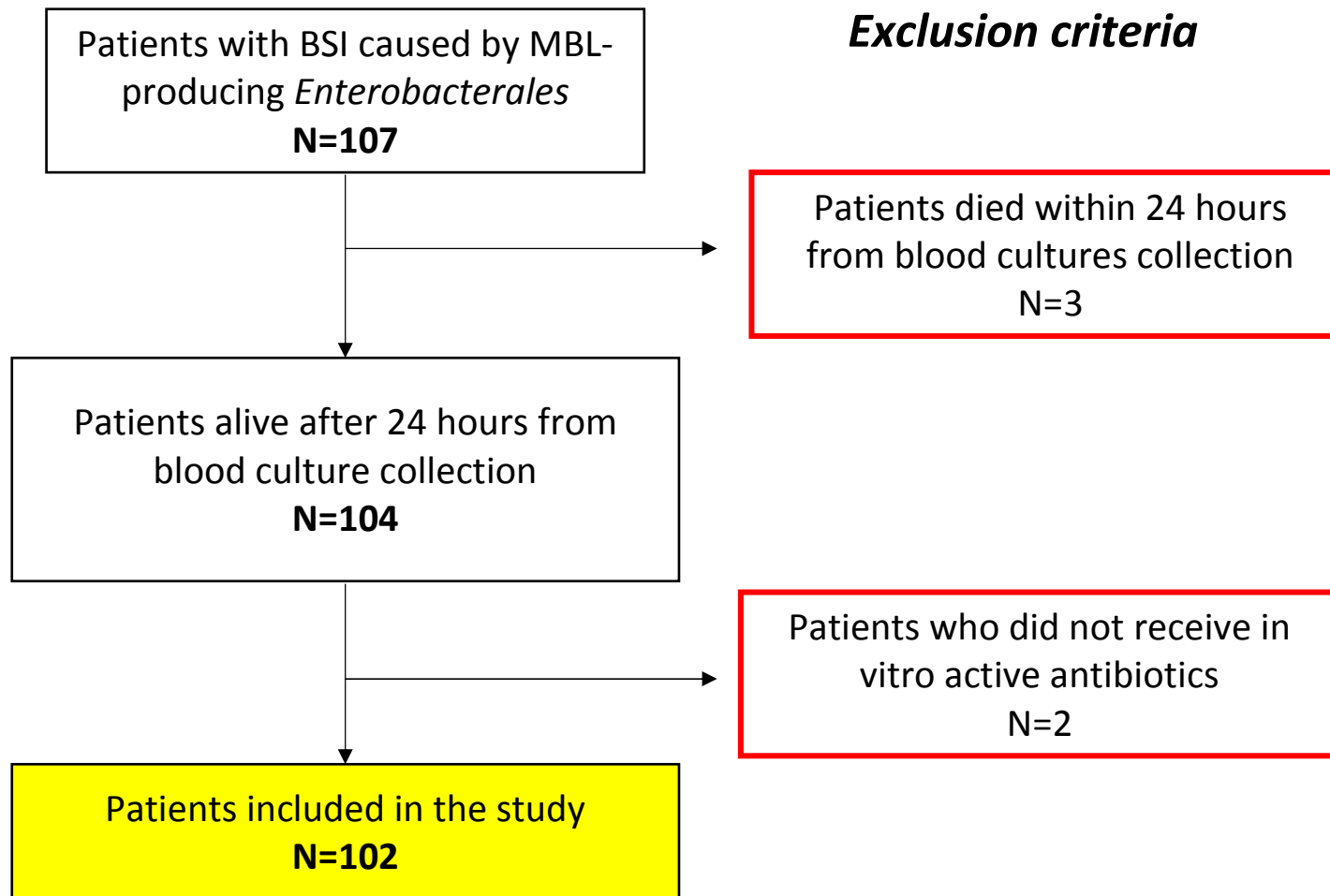


**Panel A**

**Panel B**

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*

➢ Prospective observational study (3 hospitals Italy and Greece).

➢ Aim of the study: to evaluate the impact of the combination CAZ-AVI *plus* ATM compared to other targeted active antibiotic regimens on the outcome of patients with BSI due to MBL-producing *Enterobacterales*.

➢ The **primary outcome measure** was the 30-day all-cause mortality.

➢ **Secondary outcomes measures** were clinical failure at day 14 and length of stay (LOS) after BSI diagnosis.

➢ **Analysis**: Cox regression analysis including a propensity score (PS) for receiving CAZ-AVI *plus* ATM was performed to evaluate primary and secondary outcomes. A PS-based matched analysis was also performed

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*

| | Overall N=102 | CAZ-AVI plus ATM N=52 | OAAs N=50 | p |
|---|---|---|---|---|
| Age, years, median | 70 (55-78) | 69 (49.75-77) | 70.5 (57.5-78) | 0.247 |
| Comorbidities | | | | |
|    Cardiovascular disease | 41 (40.2%) | 22 (42.3%) | 19 (38%) | 0.657 |
|    Solid cancer | 35 (34.3%) | 16 (30.8%) | 19 (38%) | 0.442 |
|    COPD | 20 (19.6%) | 6 (11.5%) | 14 (28%) | 0.036 |
|    Diabetes | 34 (33.3%) | 20 (38.5%) | 14 (28%) | 0.263 |
|    Chronic renal diseases | 15 (14.7%) | 8 (15.4%) | 7 (14%) | 0.844 |
|    Chronic liver failure | 10 (9.8%) | 3 (5.8%) | 7 (14%) | 0.162 |
|    Solid organ transplantation | 8 (7.8%) | 2 (3.8%) | 6 (12%) | 0.126 |
| Charlson Comorbidity Index | 4 (2-6.25) | 4 (1-6) | 4.5 (2-7) | 0.339 |
| Source control | 58 (56.9%) | 34 (65.4%) | 24 (48%) | 0.076 |
| Drug-induced AKI | 11 (10.8%) | 1 (1.9%) | 10 (20%) | ***0.003*** |
| Primary Outcome | | | | |
|    30-day mortality | 32 (31.4%) | 10 (19.2%) | 22 (44%) | ***0.007*** |
| Secondary outcome measures | | | | |
|    Clinical failure at day 14 | 39 (38.2%) | 13 (25%) | 26 (52%) | ***0.005*** |
|    Median LOS after BSI** | 16.5 (10-31.5) | 14 (10-20.25) | 23 (9.5-42.75) | 0.135 |

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*

**Cox regression analysis of factors independently associated with 30-day mortality**

|  | HR (95% CI) | p value |
|---|---|---|
| **Cardiovascular disease** | 6.62 (2.78-15.79) | *<0.001* |
| **Solid organ transplantation** | 3.52 (1.42-8.69) | *0.006* |
| **SOFA score (1-point increment)** | 1.21 (1.1-1.32) | *<0.001* |
| **CAZ-AVI plus ATM (vs OAAs)** | 0.17 (0.07-0.42) | *<0.001* |

PS-adjusted analysis: CAZ-AVI *plus* ATM : HR 0.4, 95% CI 0.18-0.91, p=0.03

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*
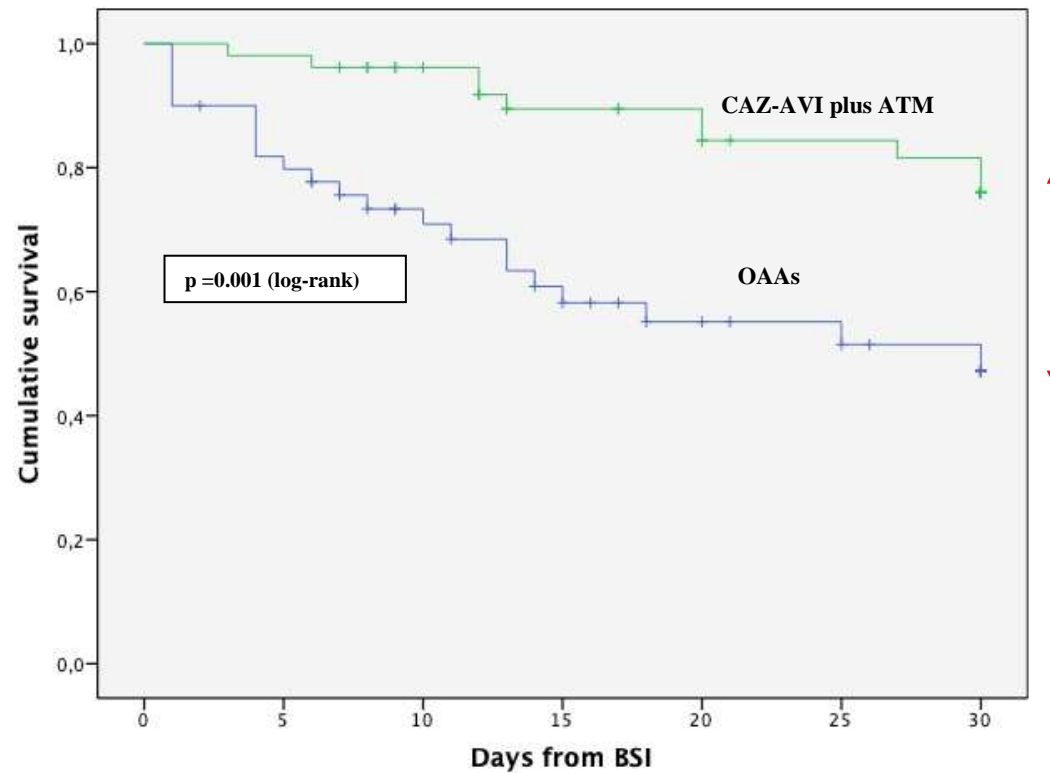
## Secondary endpoints: clinical failure and LOS

**PS-adjusted analysis for secondary study endpoints**

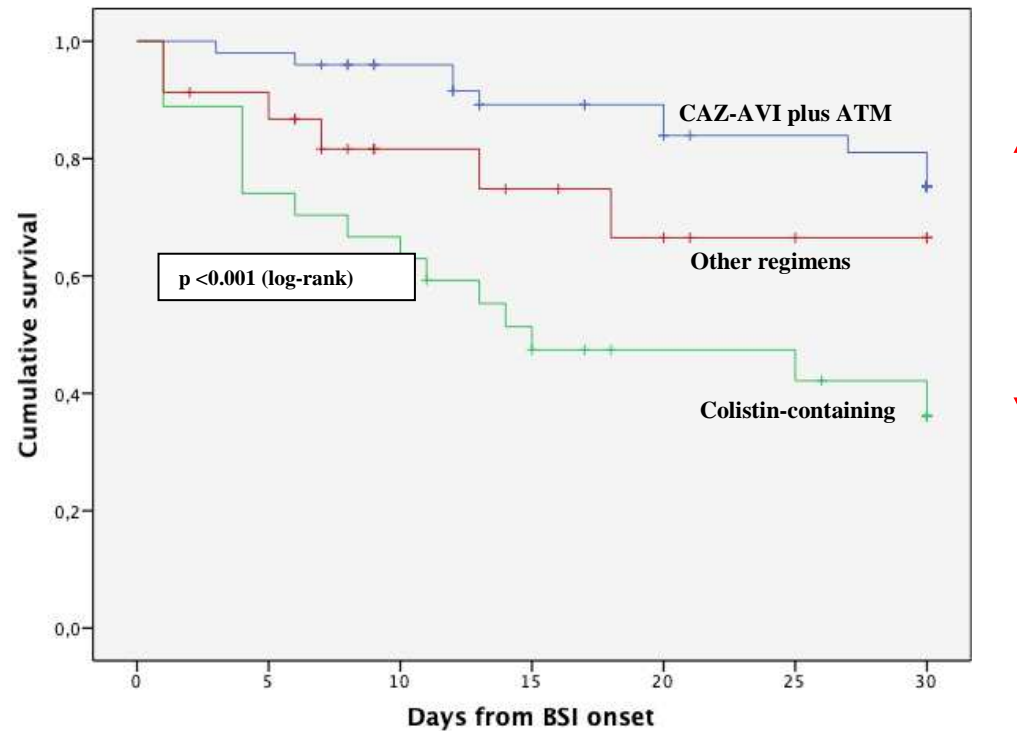|  |  | HR (95% CI) | sHR (95% CI) | P value |
|---|---|---|---|---|
| **Clinical failure at day 14** | CAZ-AVI *plus* ATM | 0.30 (0.14 -0.65) | - | *0.002* |
| **Length of hospital stay from BSI onset \*** | CAZ-AVI *plus* ATM | - | 0.49 (0.30-0.82) | *0.007* |

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*



Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAZ-AVI *plus* ATM | 52 | 51 | 50 | 47 | 45 | 45 | 42 |
| OAAs | 50 | 40 | 36 | 31 | 30 | 29 | 28 |

Falcone M, Daikos GL, et al, Clin Infect Dis, 2020

# Efficacy of ceftazidime-avibactam plus aztreonam in patients with BSI caused by MBL- producing *Enterobacterales*
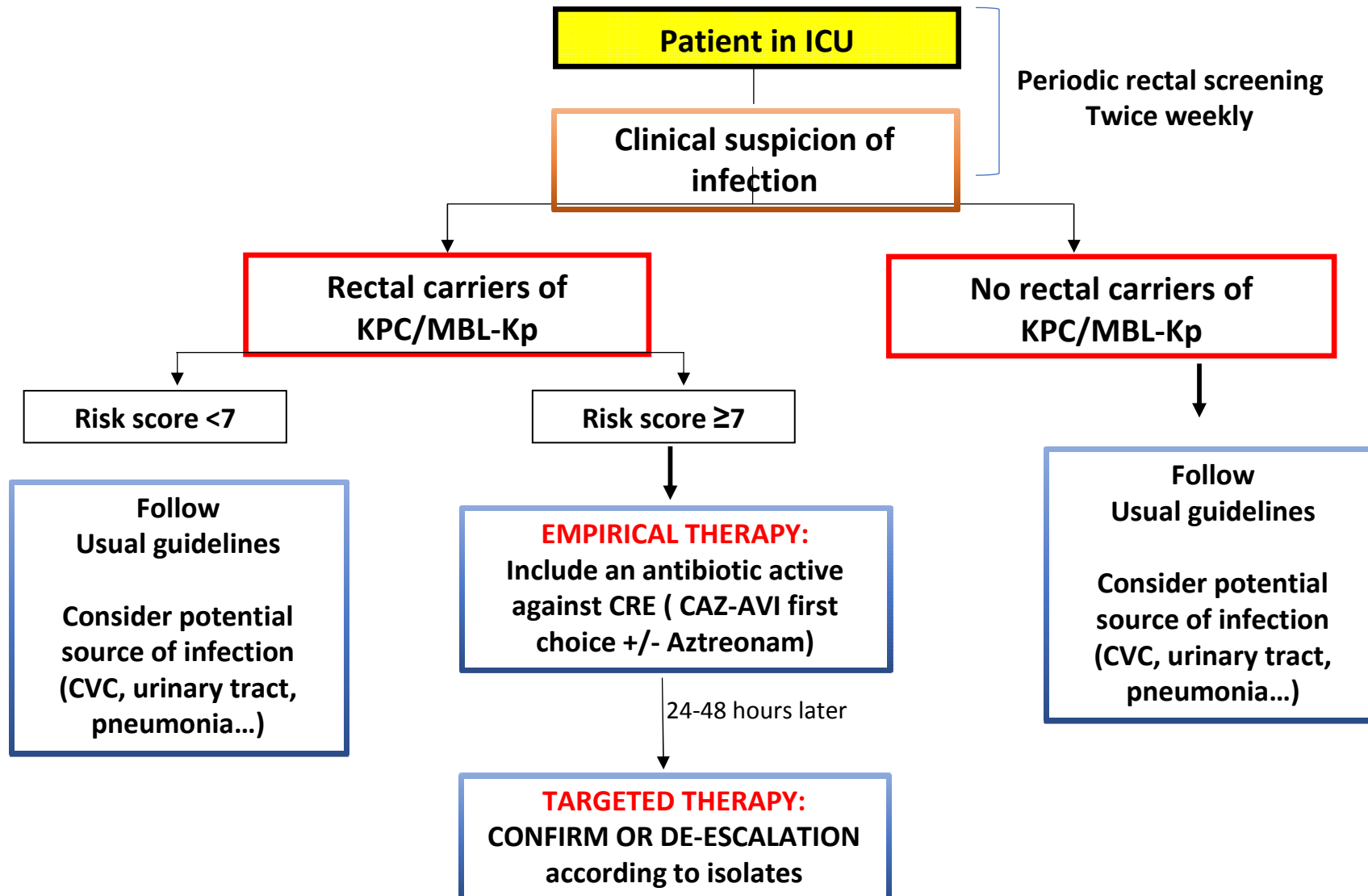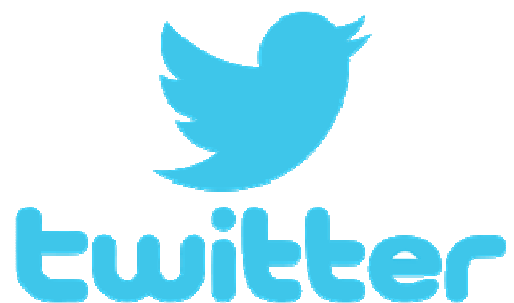
# KPC/MBL Kp rectal carriers: proposed algorithm
## (PISA University Hospital)



**Patient in ICU**

**Clinical suspicion of infection**

Periodic rectal screening
Twice weekly

**Rectal carriers of KPC/MBL-Kp**

**No rectal carriers of KPC/MBL-Kp**

Risk score <7

Risk score ≥7

Follow
Usual guidelines

Consider potential source of infection (CVC, urinary tract, pneumonia…)

**EMPIRICAL THERAPY:**
Include an antibiotic active against CRE ( CAZ-AVI first choice +/- Aztreonam)

24-48 hours later

**TARGETED THERAPY:**
CONFIRM OR DE-ESCALATION according to isolates

Follow
Usual guidelines

Consider potential source of infection (CVC, urinary tract, pneumonia…)

**David van Duin**
@davidvanduin

**2,595**
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**Shane Cross**
@shane6cross

RT @TheIDApprentice: If you didn't know, now you know. CAZ-AVI-ATM is the way to go. #siccrhymes https://t.co/TowaxtB6QD