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Spread of New Delhi-producing Klebsiella Pneumoniae in liver transplant candidates: experience from an Italian border hospital

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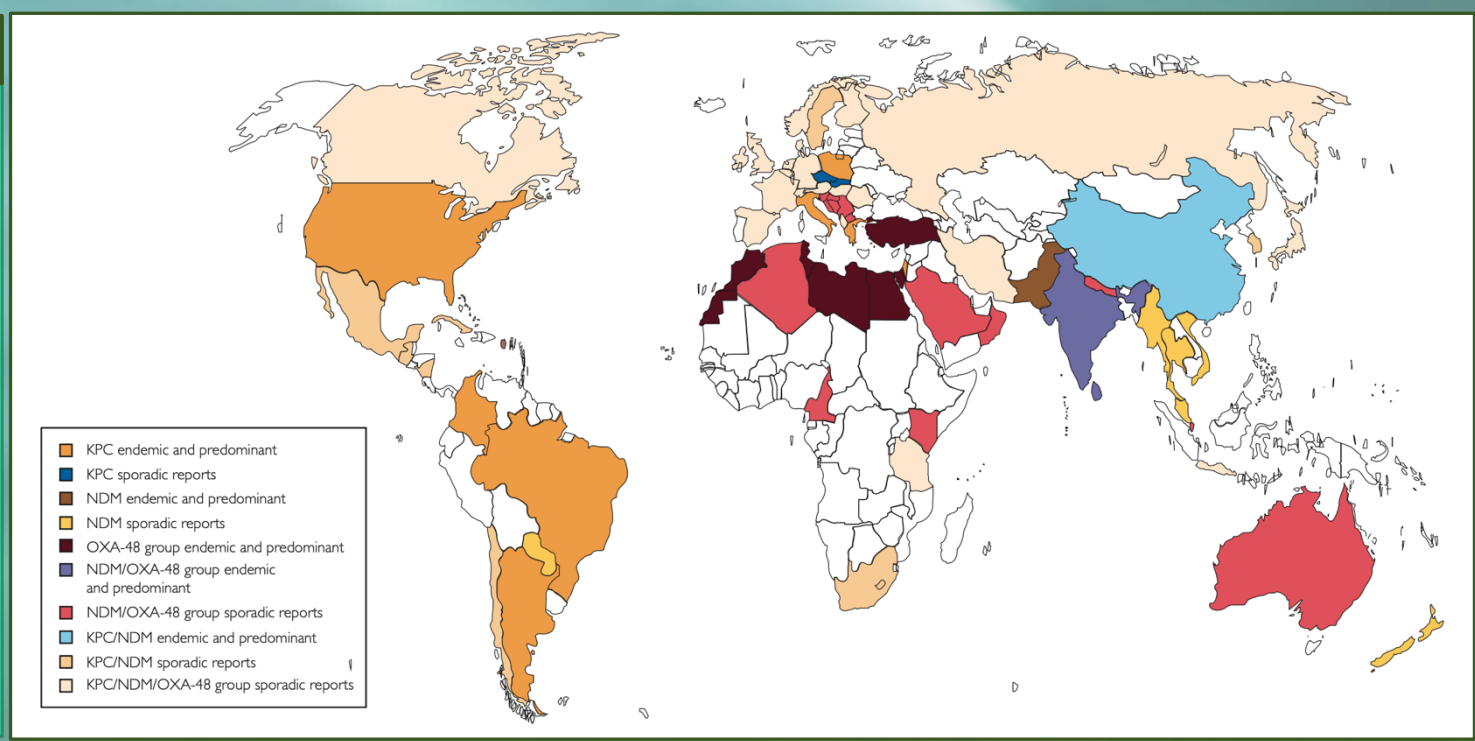
Background

NDM is a recently discovered β-Lactamase and has one of the worst mortality rates, higher than 30% in different studies.
Bacteria bearing this type of enzyme are more prevalent in the Indian subcontinent and Eastern Europe. In the last couple of years there is a growing number of Italian clinical report highlighting the emergence of NDM-bearing pathogens in our country.
The number of antibiotic active against this type of carbapenemases was very low until more recent years.
We report two cases of NDM-producing Klebsiella Pneumoniae (KP) infections in two Serbian patients came from Belgrade to Udine to undergo an orthotopic liver transplant. We successfully treated these infections, employing the latest antibiotic classes that are emerging as the most active therapeutic options against this pathogen.



Case 1

40-year-old male patient with a fulminant hepatitis B came from Belgrade to Udine for liver transplant.

- Surveillance swabs and blood cultures were positive for NDM/OXA-48 KP (**Antibiogram n°1**). A therapy with cefiderocol, tigecycline, fosfomycin was set up.
- These antibiotics were stopped after 30 days, after clinical improvement.
- Few days later, a new clinical worsening and blood culture again positive for KP NDM.
- This time KP was **resistant to cefiderocol** (MIC >256) too (**Antibiogram n°2**). Antibiotic therapy was switched to ceftazidime/avibactam, aztreonam, tigecycline for 50 days, due to persistence of K. pneumoniae NDM in peritoneal fluid.
- During this long period of antibiotic treatment, the patient also developed an acute organ rejection and hepatic artery thrombosis, requiring retransplantation.
- After 2 months, all the antibiotic therapy was stopped but, soon later, blood culture and cultures from the peritoneal fluid revealed positive for Enterococcus faecium VRE, KP NDM/OXA-48, and Acinetobacter baumannii XDR, requiring new antibiotic therapy with ampicillin/sulbactam and daptomycin for Enterococcus; cefiderocol for Acinetobacter and ceftazidime-avibactam plus aztreonam for KP.
- After 14 days of therapy the cultures became negative for KP and Acinetobacter, but positive for Enterococcus requiring therapeutic shift to tedizolid and oritavancin.
- At the transfer in Belgrade, after 6 months of hospital stay, the patient was awake, spontaneous breathing and hemodynamically stable, had started FKT, cultures were negative, but surveillance swabs continued to be positive for VRE and CPE.

Antibiogram KP NDM/OXA-48 n°1

ANTIBIOTIC		*MIC*
Amikacin	R	>16
Amoxicillin-clavulanic acid	R	>64
Cefepime	R	>16
Ceftazidime	R	>64
Ceftazidime-avibactam	R	>64
Ceftolozane-tazobactam	R	>64
Ceftriaxone	R	>4
Ciprofloxacin	R	>1
Colistin	R	>4
Ertapenem	R	>2
Gentamycin	R	>8
Meropenem	R	>64
Piperacillin-tazobactam	R	>128
Trimetoprim-sulfametoxazolo	R	>8
Cefiderocol	S	8

Antibiogram KP NDM, OXA-48 n°2

ANTIBIOTIC		*MIC*
Amikacin	R	>16
Amoxicillin-clavulanic acid	R	>64
Cefepime	R	>16
Ceftazidime	R	>64
Ceftazidime-avibactam	R	>64
Ceftolozane-tazobactam	R	>64
Ceftriaxone	R	>4
Ciprofloxacin	R	>1
Colistin	S	<0,5
Ertapenem	R	>2
Gentamycin	R	>8
Meropenem	I	8
Piperacillin-tazobactam	R	>128
Trimetoprim-sulfametoxazolo	R	>8
Cefiderocol	R	>256
Fosfomycin	R	64
Tigecycline	R	2
Aztreonam	R	>1024

Case 2

A 22-year-old female patient came from Belgrade with an acute liver failure due to Wilson's disease to undergo a liver transplantation.

- Upon arrival in intensive care unit in Udine, culture and serological tests were performed. They tested positive for a totisensitive Klebsiella pneumoniae and Proteus spp MDR. A therapy with cefepime was started. On the same day, the patient had the liver transplant.
- Next day she was positive on the surveillance rectal swab for NDM KP strain. Because of rising fever and rectal colonization by K. pneumoniae NDM, therapy was escalated to **cefiderocol**, tigecycline and anidulafungin.
- After 14 days of targeted therapy, cefiderocol and tigecycline were suspended because of clinical improvement. Nonetheless persistent CPE positivity on the rectal swab.
- Twenty days after stopping the above antibiotic therapy, the patient was discharged.

Discussion

NDMs, like other MBLs, can inactivate all beta-lactams **except aztreonam**. Furthermore, the plasmid containing the blaNDM gene often hosts several **other genes responsible for resistance to other antibiotics** (aminoglycosides, quinolones, and other β -lactamases that neutralize the action of aztreonam).

Antibiotics against Metallo-β-lactamases

- Double or triple combination therapies were the only clinical chances, combining different classes of older antibiotics: **tigecycline**, **fosfomycin** and **colistin**.
- **Aztreonam** is the only beta-lactam that is not inactivated by NDM and, more generally, by MBL. For this reason, combination therapy has recently been proposed that utilizes **aztreonam and ceftazidime-avibactam**. Even the simple combination of aztreonam and avibactam proved an effective solution.
- **Cefiderocol**, the first of the siderophores group, resists the action of beta-lactamases of all four classes of Ambler and has excellent activity against MDR pathogens. It is not active against Gram-positive and anaerobes.

NDM in patients undergoing OLTx

To date, we are not aware of any studies or reports that have specifically assessed treatment and outcomes in infections by NDM-producing pathogens in OLTx patients. Numerous reports of infections in OLTx patients by KP producing KPC and VIM, which underline an increased risk of recurrent infection, morbidity and mortality.

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