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Between a rock and a hard place: Novel solutions when resistance and renal failure meet

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Case 1: Mrs W

- Mrs W: 77 year old lady
- Background:
 - Hypertension, lifelong smoker, RA
- Admitted with SOB and chest pain- diagnosed with MI and acute AF
- Symptomatic severe aortic stenosis and L main stem coronary artery stenosis
- Aortic valve replacement (AVR) and coronary artery bypass graft (CABG)



Case 1: Post operative period

- Complicated post-operative recovery in CITU
 - Significant bleeding from surgical site-Team attempt to manage this conservatively
 - PEA and respiratory arrest
- Surgical exploration D11 post op:
 - Blood/clot evacuated and washed out from L pleural space and retrosternally
- Further surgical exploration and washout of mediastinal haematomas D24 post op
- Intra-pleural thrombolysis, haematoma evacuated D30 post-op



Case 1: Antibiotic history

Multiple courses of antibiotics despite no clear evidence of infection - Not discussed with Microbiology

- 4th of Feb-14th of Feb: Piperacillin/tazobactam
- 11th of Feb-15th of Feb: Gentamicin
- 9th of Feb-17th of Feb: Fluconazole
- 18th of Feb-1st of March: Meropenem
- 18th of Feb-21st of Feb: Teicoplanin
- 4th of March-18th of March: Linezolid
- 11th of March-14th of March: Piperacillin/tazobactam



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Case 1: Continual decline

- Day 46 post-op:
 - New deterioration: Increasing WCC, CRP, lactate, FiO₂, fever
 - Increased respiratory secretions
 - Bronchial breathing L lung midzone
 - Deteriorating renal function but not on dialysis- **Cr 123, Ur 27 , eGFR 37**
 - Re-do thoractomy, **large collection of pus in chest cavity**

Case 1: Microbiology

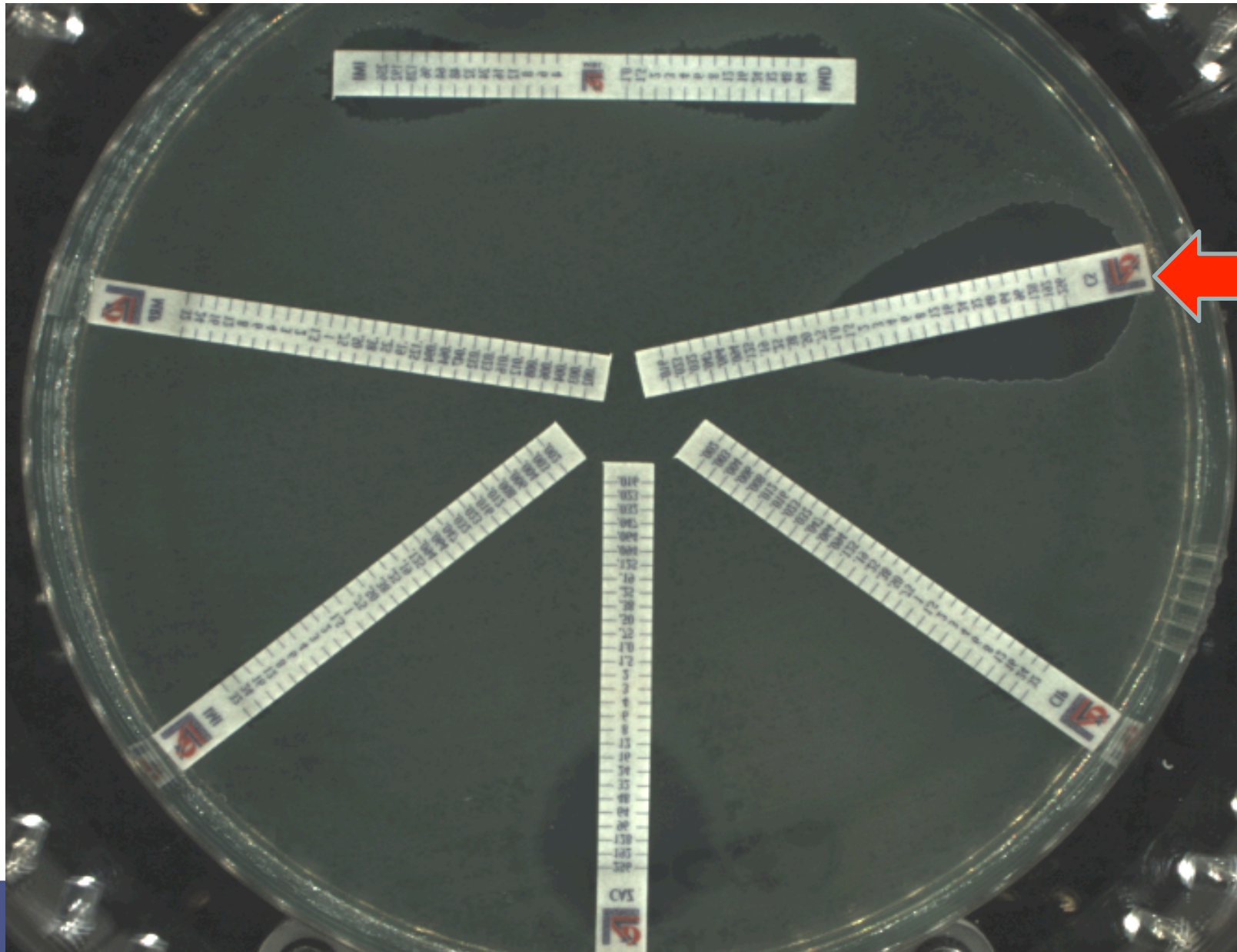
| Date | Sample | Organism | Susceptibilities |
|---------|------------------|-------------------------------|--|
| 4/2/17 | Urine | <i>Candida sp.</i> | |
| 18/2/17 | Sputum | <i>Klebsiella oxytoca</i> | Ampicillin R only |
| 25/2/17 | L pleural tissue | <i>E. Faecium (VRE)</i> | Vanc R, Teic R, Amp R, Linezolid S, Tigecycline S |
| 10/3/17 | Skin swab | <i>Pseudomonas aeruginosa</i> | No susceptibilities performed |
| 10/3/17 | Line Tip | <i>Pseudomonas aeruginosa</i> | Ceftaz R, Cipro R, Gent S, Mero R, Pip/Taz R, Amikacin S |
| 11/3/17 | Sputum | <i>Pseudomonas aeruginosa</i> | As above |
| 13/3/17 | BC | <i>Pseudomonas aeruginosa</i> | As above |



| Antibiotic | MIC | Interpretation |
|-------------------------------|------------|----------------|
| Ceftazidime | 16 | R |
| Imipenem | >32 | R |
| Meropenem | >32 | R |
| Colistin | 1 | S |
| Ciprofloxacin | >32 | R |
| Fosfomycin | >256 | No breakpoints |
| Tobramycin | 1.5 | S |
| Piperacillin/tazobactam | >256 | R |
| Gentamicin | 2 | S |
| Amikacin | 6 | S |
| Ceftolozane/tazobactam | 1.5 | S |
| Ceftazidime/avibactam | 6 | S |



Phenotypic results



Colistin
MIC

Case 1: Outcome

- Received 7 days of ceftolozane/tazobactam and 5 days of fosfomycin
- Continued to deteriorate:
 - Renal and respiratory failure, septic shock
- *Pseudomonas aeruginosa*:
 - Carbapenem resistance due to ampC β -lactamase, porin loss and efflux mechanisms
- Decision made for comfort care and patient passed away



Case 2: Ms A

- Ms A: 42 year old lady
- Background:
 - **Cystic Fibrosis**
 - Recurrent haemoptysis
 - 3x bronchial embolisations last 10 years
 - Pancreatic insufficiency
 - CF-related DM
 - ABPA
 - Osteopenia
 - Chronic sinusitis
- On waiting list for lung transplant

**Cystic
Fibrosis**
a fight we
must win



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Case 2: Microbiology

- Microbiology
 - Chronic Pseudomonas colonisation (mucoid and non-mucoid phenotypes)
 - Candida
 - Exophiala dermatitidis x1
 - Acid Fast Bacilli-negative
- Antibiotics
 - Last inpatient stay (5 months previously) had 2 weeks IV abx
 - Meropenem 2g tds
 - Tobramycin
 - Fosfomycin 4g qds



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Case 2: Clinical deterioration

- Clinical progression
 - Recent increase in number of exacerbations
 - 1x inpatient admission for exacerbation
 - 7x clinic appointments
 - 7x courses of home IV abx
 - 10% decline in FEV₁ since last years AR
 - Excellent compliance, motivated patient



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Case 2: Outcome

- Day 14 of current treatment:
 - Switched from meropenem to **ceftolozane/tazobactam**
 - Continued on aminoglycoside
 - And....

 - Improvement in FEV1 and clinical symptoms
 - Improvement in CRP, WCC
 - Significant patient satisfaction



Case 2: *Pseudomonas aeruginosa* susceptibilities to ceftolozane/tazobactam

| Date | Organism | MIC | Interpretation |
|----------|--|------|----------------|
| 18/01/17 | <i>Pseudomonas aeruginosa</i> 1 | >24 | R |
| | <i>Pseudomonas aeruginosa</i> 2 | >256 | R |
| | <i>Pseudomonas aeruginosa</i> 3 (mucoid) | >64 | R |



In-vitro susceptibility

Table 2. Overall susceptibilities of Enterobacteriaceae and *P. aeruginosa* referred to AMRHAI

| | Enterobacteriaceae (n = 3249) | | | <i>P. aeruginosa</i> (n = 1414) | | |
|-------------------------|-------------------------------|-------|------|---------------------------------|-------|------|
| | BP (mg/L) | no. S | %S | BP (mg/L) | no. S | %S |
| Colistin | S ≤ 2 | 2951 | 90.8 | S ≤ 2 | 1351 | 95.5 |
| | | | | S ≤ 4 | 1369 | 96.8 |
| Amikacin | S ≤ 8 | 2729 | 84.0 | S ≤ 8 | 1033 | 73.1 |
| Tigecycline | S ≤ 1 | 2449 | 75.4 | — | — | — |
| Imipenem | S ≤ 2 | 2365 | 72.8 | S ≤ 4 | 235 | 16.6 |
| Gentamicin | S ≤ 2 | 2062 | 63.5 | S ≤ 4 | 991 | 70.1 |
| Meropenem | S ≤ 2 | 2300 | 70.8 | S ≤ 2 | 149 | 10.5 |
| | | | | S ≤ 4 | 245 | 17.3 |
| Tobramycin | S ≤ 2 | 1748 | 53.8 | S ≤ 4 | 1031 | 72.9 |
| Ciprofloxacin | S ≤ 0.5 | 1465 | 45.1 | S < 0.5 | 535 | 37.8 |
| Ceftolozane/tazobactam | S ≤ 1+4 | 1048 | 32.3 | S ≤ 4+4 | 1193 | 84.4 |
| Cefepime | S ≤ 1 | 947 | 29.1 | S ≤ 8 | 744 | 52.6 |
| Temocillin | S ≤ 8 | 880 | 27.1 | — | — | — |
| Ertapenem | S ≤ 0.5 | 731 | 22.5 | — | — | — |
| Aztreonam | S ≤ 1 | 678 | 20.9 | — | — | — |
| Piperacillin/tazobactam | S ≤ 8+4 | 531 | 16.3 | S ≤ 16+4 | 661 | 46.7 |
| Ceftazidime | S ≤ 1 | 505 | 15.5 | S ≤ 8 | 802 | 56.7 |
| Cefotaxime | S ≤ 1 | 432 | 13.3 | — | — | — |
| Amoxicillin/clavulanate | S ≤ 8 | 118 | 3.6 | — | — | — |
| Ampicillin | S ≤ 8 | 18 | 0.6 | — | — | — |
| Carbenicillin | — | — | — | S ≤ 128 | 555 | 39.3 |

BP, breakpoint; no. S, number susceptible; %S, percentage susceptible.



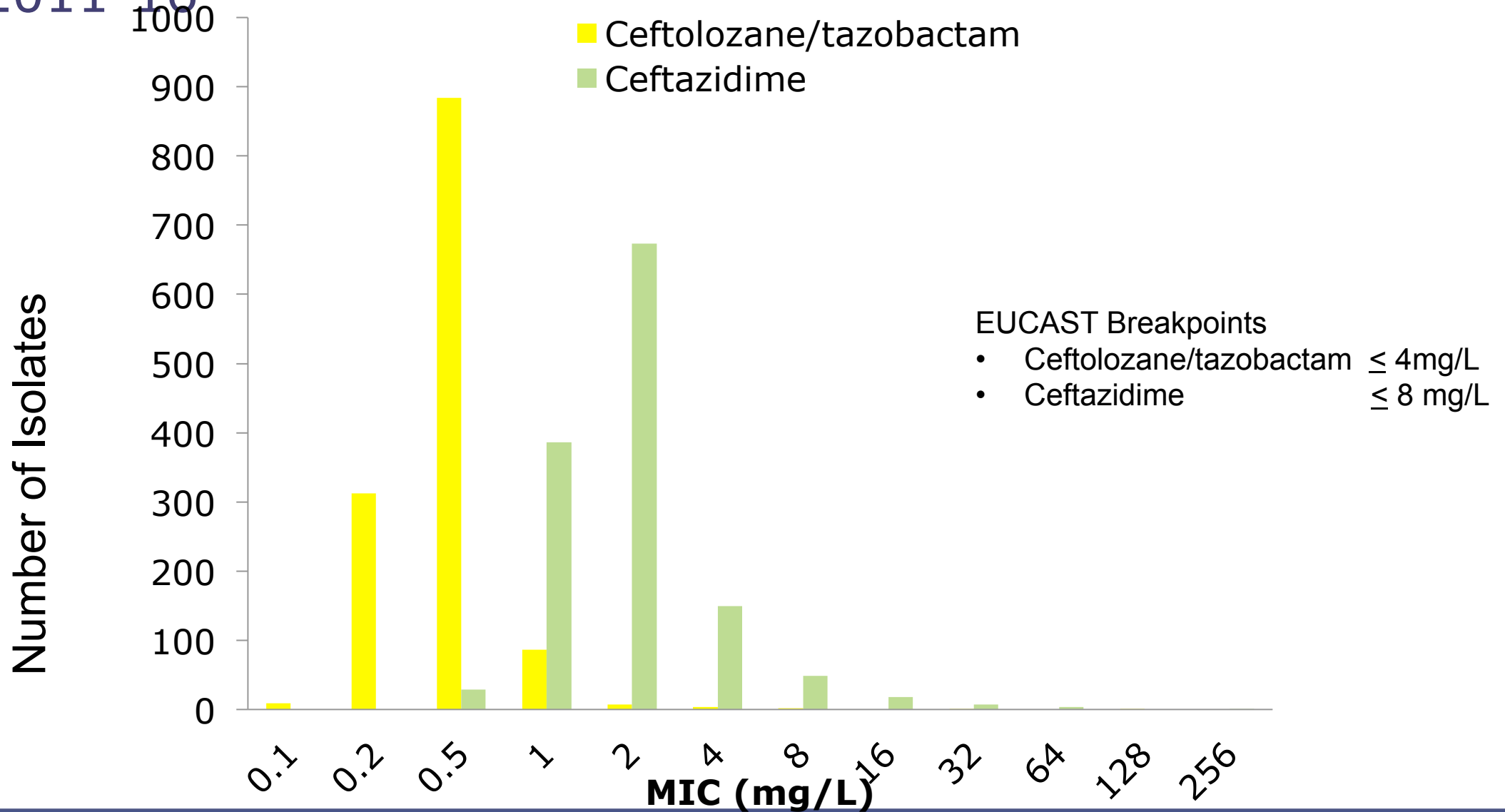
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Ceftolozane-tazobactam and ceftazidime vs. *P. aeruginosa*

BSAC Resistance Surveillance Bacteraemia Program

2011-16



Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

Ghady Haidar,¹ Nathan J. Philips,² Ryan K. Shields,^{1,3,4} Daniel Snyder,² Shaoji Cheng,⁴ Brian A. Potoski,^{1,3,5} Yohei Doi,¹ Binghua Hao,⁴ Ellen G. Press,¹ Vaughn S. Cooper,² Cornelius J. Clancy,^{1,4,6a} and M. Hong Nguyen^{1,3,4a}

- Conclusions: Ceftolozane-tazobactam (C/T)* was successful in treating 71% of patients with MDR-*P.aeruginosa* infections, most of whom had pneumonia. The emergence of C/T resistance in 3 patients is worrisome and may be mediated in part by AmpC-related mechanisms

*C/T=ceftolozane-tazobactam

Haider *et al.* CID 2017; 65(1):110-20



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Multicenter Evaluation of Ceftolozane/Tazobactam for Serious Infections Caused by Carbapenem Resistant *Pseudomonas aeruginosa*.

Munita JM^{1,2,3}, Aitken SL^{1,4}, Miller WR^{1,2}, Perez F⁵, Rosa R^{6,7}, Shimose LA^{6,7}, Lichtenberger PN⁷, Abbo LM^{6,7}, Jain R⁸, Niqo M², Wanqer A⁹, Araos R³, Tran TT^{1,2}, Adachi J¹⁰, Rakita R¹¹, Shelburne S¹⁰, Bonomo RA⁵, Arias CA^{1,2,12}.

- Retrospective, multicenter, ‘real-world’ study from USA
- 35 patients with MDR* *P.aeruginosa*
- Pneumonia in 51%
- Other indications: Osteomyelitis, bacteraemia, surgical site infection, pyelonephritis
- Outcomes with C/T
 - Treatment success: 74% overall
 - Treatment failure: 26% (9 patients)
- Adverse effects
- Limitations: small study, retrospective, C/T used at physicians discretion rather than pre-specified in a protocol

*MDR= Multi-drug resistant

Munita *et al.* *CID* 2017; 65 (1):158-61

Salvage Therapy with Ceftolozane-Tazobactam for Multidrug-Resistant *Pseudomonas aeruginosa* Infections

Juan José Castón^{a,b}, Álvaro De la Torre^c, Isabel Ruiz-Camps^d, María Luisa Sorlí^e, Vicente Torres^f and Julián Torre-Cisneros^{a,b,g}

- Retrospective, multicenter study from Spain
- 12 patients with MDR *P.aeruginosa* who received C/T as salvage therapy
- Most patients had significant co-morbidities (9/12)
- 50% treated for pneumonia, 42% had a bacteraemia
- 10/12 patients (83.3%) experienced septic shock and 2/12 (16.7%) had a diagnosis of sepsis
- 3 of 12 patients (25%) died during the follow up period
- **Microbiological cure: 58.3% patients**

| | Comorbidities | Primary focus | Bacte raemia | Presentation | CT days/ (g/8h) | Clinical outcome | Microb outcome |
|----|--|------------------------|-------------------------|---------------------|--------------------------------|-----------------------------|---------------------------------|
| 1 | DM | Abdominal | Yes | Septic shock | 14/1.5 | Cure | Eradication |
| 2 | None | Respiratory | Yes | Septic shock | 10/3 | Cure | Eradication |
| 3 | Bronchomalacia | Respiratory | No | Severe sepsis | 10/3 | Cure | Eradication |
| 4 | None | Abdominal | No | Septic shock | 21/1.5 | Cure | Eradication |
| 5 | Burkitt lymphoma, severe neutropenia | Otitis, mastoiditis | No | Sepsis | 21/3 | Cure, late recurrence | Eradication, late recurrence |
| 6 | Lung cancer, DM, COPD, acute RF | Respiratory | Yes | Septic shock | 15/3 | Death | Eradication |
| 7 | HepC | Abdominal | No | Septic shock | 11/1.5 | Death | Persistence |
| 8 | DM, COPD | Biliary | No | Septic shock | 9/1.5 | Cure | Eradication, late recurrence |
| 9 | DM, COPD, RF | VCC | Yes | Septic shock | 14/1.5 | Cure | Eradication |
| 10 | None | Respiratory | No | Septic shock | 14/1.5 | Cure | No data |
| 11 | Immunosuppression | Respiratory | Yes | Septic shock | 3/1.5 | Death | Persistence |
| 12 | Lung transplant, acute RF, immunosup, mediastinitis | Respiratory | No | Septic shock | 21/1.5 | Cure | Persistence |



Learning Points

- Ceftolozane/tazobactam is a useful novel therapeutic agent to consider in complex clinical cases where therapeutic options are limited
- Case 1 highlights the importance of timely source control and emphasises the need for judicious antimicrobial prescribing
- Case 2 demonstrates that ceftolozane/tazobactam can be used to treat infective exacerbations of CF in patients colonised with MDR *Pseudomonas aeruginosa*



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