Ceftazidime/avibactam and ceftolozane/tazobactam in treatment of pulmonary infections by Imipenem resistant *Pseudomonas aeruginosa*.

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INTRODUCTION

- **Recently, ceftolozane/tazobactam and ceftazadime/avibactam became available to clinicians to meet the rising need for therapeutics to treat multidrug resistant (MDR) organisms.**
- **Phase 3 clinical trials investigating efficacy of these agents compared to carbapenems in nosocomial pneumonia are currently in progress.**
- **However, data regarding their role in treatment of pulmonary infections caused by Imipenem resistant *Pseudomonas* (*Psa*) is still lacking.**
- **This report summarizes our early institutional expereince.**

METHODS

- **We identified patients with Imipenem resistant *Psa* pneumonia. Each was treated with ceftolozane/tazobactam or ceftazadime/avibactam.**
- **Genetic analyses of *Psa* isolates were performed to understand the molecular basis for the emergence of this resistance phenotype in our institution.**
- **Patients' characteristics, severity of illness and outcomes were reviewed.**
- **Multilocus sequence typing (MLST) was performed to evaluate *Psa* strain relatedness.**
- **PCR was done to screen for presence of *blaKPC* and metallo-beta-lactamase (MBL) genes. *OprD* genes was sequenced and analyzed. Expasy Swiss modeling server was used to construct models of OprD porin.**

STRAIN	INFXN	DRUG	CCI*	APACHEII	F/u cultures	Clinical Resolution	Death
1	HCAP	Ceftolozane/tazobactam+ tobramycin	1	13	CLEARED	YES	NO
2	HCAP	Ceftolozane/tazobactam	3	N/A	CLEARED	YES	NO
3	HCAP+bacteremia	Ceftazadime/avibactam	10	17	CLEARED	NO	YES

*CCI Charlson comorbidity Index

TABLE 1: PATIENT'S CHARACTERISTICS AND OUTCOMES

	STRAIN 1	STRAIN 2	STRAIN 3
Cipro	R	R	S
Gent	I	S	S
Imipenem	R	R	R
Cefepime	R	S	I
Pip/Tazo	R	S	R
Tol/Tazo		S	S
Taz/Avi			S

TABLE2: ISOLATE SUSCEPTIBILITES

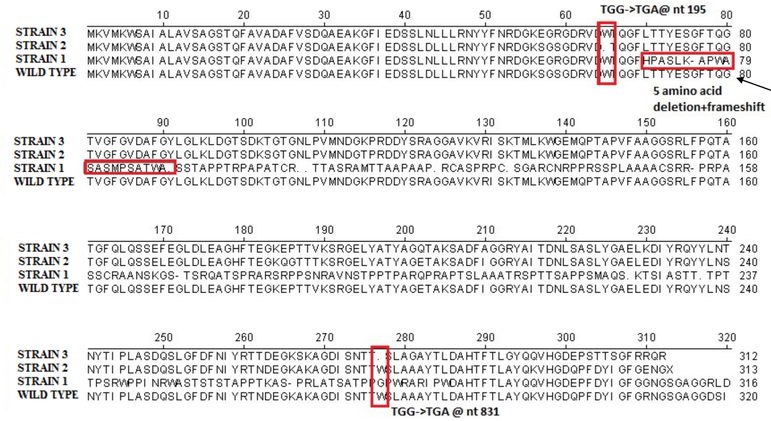

FIGURE 1: OprD PROTEIN SEQUENCES

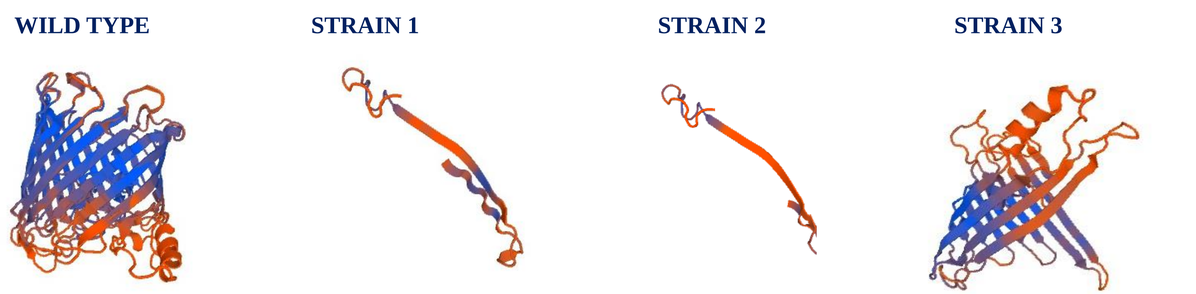

FIGURE 2: OprD PROTEIN MODELS

RESULTS

- **Patient characteristics, treatment, and outcomes are summarized in Table 1. In all three cases microbiologic eradication was achieved. Two out of three patients survived.**
- ***Psa* isolates were not related by MLST typing and did not possess *blaKPC* or MBL genes. All isolates had mutations in the o*prD* gene resulting in early stop codons. Modelling of these OprD channels showed significantly truncated proteins.**

CONCLUSION

- **Our early experience demonstrates ceftazidime/avibactam and ceftolozane/tazobactam are promising therapeutic options for the treatment of Imipenem resistant non carbapenemase producing *Psa* pulmonary infections.**
- **Our genetic analysis indicates that Imipenem resistance in these isolates was partly mediated by OprD porin mutations, causing truncated, likely non-functional protein.**
- **Analysis of additional cases is needed to delineate the role of these novel cephalosporin/beta-lactamase inhibitor combinations in treatment of MDR *Psa* infections. As importantly, understanding the impact of mutations in OprD porins may lead to deeper insights o the mechanisms responsible for imipenem transport into *Psa*.**