Tigecycline-based therapy for glycopeptide-resistant Enterococcus faecium infection in a pediatric intensive care unit

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Tigecycline (TGC) is a new semisynthetic glycylcycline, approved in 2005 for the treatment of complicated skin, soft-tissue, and intra-abdominal infections in adults, which exhibits activity against a wide spectrum of bacteria including glycopeptide-resistant *Enterococcus faecium* (GRE) [1].
The first strains of GRE have been reported in France and England in 1986 [2], then worldwide with few available therapeutic options. The safety and efficacy of TGC has not yet been established in children because of the observed increase in mortality associated with TGC in adults and the potential adverse effects in bone and dental enamel.
To the best of our knowledge, only a few studies have reported the use of TGC in children [3-7], especially for management of bacteremia and ventilator-associated pneumonia (VAP).
Herein we report two cases of children with severe infection due to GRE who were successfully treated with TGC in a pediatric intensive care unit (PICU).

Case 1
A two year-old girl with no medical history was admitted to PICU for severe thermal burns following flame injury. UBS score (unit of burned skin) was 75. On the 3rd day of admission, the patient developed a septic shock caused by invasive burn wound infection requiring mechanically ventilation. An empirical broad-spectrum antibiotic including imipenem/cilastatin, teicoplanin and amikacin was started. On the 10th day of care, the wounds got infected again and burn wound swab cultures showed wild-type *Pseudomonas aeroginosa.* Consequently, prior antibiotics were discontinued and the girl was given piperacillin and gentamicin. She slowly improved. On the 18th day, she presented an acute respiratory distress syndrome with fever of 39°C. Laboratory studies revealed biological inflammatory syndrome and high level of procalcitonin related to primary GRE bacteremia. The isolate was resistant to ampicillin, fosfomycin, rifampicin, teicoplanin, vancomycin with high-level aminoglycoside resistance. The only remaining agents to which the isolate was susceptible were TGC, pristinamycin and chloramphenicol. Antibiotics were administered accordingly, including intravenous TGC (1mg/kg/12h) associated with enteral pristinamycin (50mg/kg/day) via a feeding tube. On day 22 post-burn, the girl recovered clinically, procalcitonin became negative and blood cultures were sterilized. She was gradually weaned off ventilator, wound healing improved. The therapy was continued for 14 days. The girl did not experience any TGC-associated side effects during her treatment course. She was discharged after 45 days.

Case 2
A low birth weight neonate boy, born prematurely at 36 gestational weeks with underlying diagnosis of type III esophageal atresia was admitted to our PICU. Surgical repair was performed 38h after his birth via a right thoracotomy. The tracheoesophageal fistula was ligated and a tension-free, primary end-to-end esophageal anastomosis was accomplished. The newborn was ventilated in the postoperative period. Twelve hours after surgery, he developed hypothermia, sclerema, thrombocytopenia and biological inflammatory syndrome with negative bacterial cultures. Therefore he was started on empiric antibiotics including imipenem/cilastatin + amikacin for 10 days. On the 12th day-of-life (DOL) the neonate developed *Chryseobacterium indologenes* mediastinitis relevant to anastomotic leak treated with piperacillin and ciprofloxacin with surgical drainage. On DOL 19, he presented VAP. GRE was isolated from pulmonary protected distal aspiration culture. Antimicrobial susceptibility test revealed sensitivity only to tetracycline and pristinamycin. Owing the lack of other reasonable alternative therapeutic options, a single TGC antibiotic treatment was initiated at a dose of 1mg/kg/12h during 14 days. There were no recorded TGC-associated adverse effects. On follow-up, after the third day of therapy modification, improvement on clinical, biological and radiological parameters was observed. At that time he was extubated and progressively weaned to oxygen. Oral feeding was gradually introduced and the patient was discharged from PICU at 39 days of age.

Conclusion
Our case reports highlight the possibility of use of TGC as an alternative drug in the treatment of GRE healthcare-associated infections in PICU although data regarding its efficacy in pediatric patients are limited according to official guidelines. These cases emphasize the need for pediatric clinical trials to assess not only the safety and efficacy, but also pharmacokinetic and pharmacodynamic features of TGC in PICU that is why it should be reserved for use in situations when alternative treatments are not relevant.

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