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Cystic Fibrosis and Piperacillin/Tazobactam: Adverse Reactions[☆]



Fibrosis quística y piperacilina tazobactam: reacciones adversas

To the Editor,

Cystic fibrosis (CF) patients commonly have chronic lung infections and frequent exacerbations caused by a range of bacteria, including *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Achromobacter xylosoxidans*, requiring multiple cycles of antibiotics such as piperacillin/tazobactam. This combination has been associated in the literature with increased bone marrow toxicity, and it should be used with caution.¹

We report 2 cases of CF patients, presenting with fever and myelotoxicity caused by piperacillin/tazobactam administered for *P. aeruginosa* infection, who required a switch to another antibiotic.

The first patient was a 20-year-old man with CF genotype F508del/F508, colonized with methicillin-resistant *Staphylococcus aureus* and *P. aeruginosa*. He was admitted for a respiratory exacerbation, with increased cough, greenish expectoration, weight loss, and worsening lung function, manifesting as forced vital capacity (FVC) 2950 ml (53%), forced expiratory volume in 1 second (FEV₁) 1885 ml (42%), and FEV₁/FVC 63.90. Treatment was started with intravenous piperacillin/tazobactam 4/0.5 g every 8 hours, and tobramycin 400 mg/24 h. The patient was discharged after 10 days to complete treatment at home. He was readmitted 7 days later with fever, myalgia, and epigastralgia. Clinical laboratory tests showed anemia (hemoglobin 11.3 g/dl) and leukopenia

(2940/mm³), with a normal blood smear. Piperacillin/tazobactam was switched to ceftazidime, while the aminoglycoside was maintained, leading to an improvement in laboratory parameters.

Our second case was a 23-year-old man with CF genotype F508del/unknown mutation with the following lung function status: FVC 2950 ml (60%); FEV₁: 1670 ml (42%); and FEV₁/FVC (56.56%); along with chronic *P. aeruginosa* bronchial infection. In view of symptoms of respiratory infection and functional decline, treatment was started with piperacillin/tazobactam 4/0.5 g/8 h and tobramycin 400 mg/24 h. On day 17 of treatment, he developed fever (39.5 °C) with no other accompanying signs. Clinical laboratory tests revealed anemia (hemoglobin 12.5 g/dl), thrombocytopenia (96,000/mm³) (Table 1), coagulation changes (prothrombin activity 56% and cephalin time 41.6 s), and hepatic involvement (GOT 170 U/l, GPT 51 U/l, GGT 24 U/l, and LDH 1462 U/l). Piperacillin/tazobactam was switched to levofloxacin. On day 4 after admission, the patient's platelet count (165,000/mm³), coagulation parameters (prothrombin activity 102% and cephalin time 29.6 s), and liver function (GOT 18 U/l, GPT 27 U/l, GGT 19 U/l, LDH 285 U/l) improved.

Several papers have been published on the adverse effects of piperacillin/tazobactam in CF patients. For reasons that are still unclear, these events seem to be more common in CF than in the general population.³ Risk factors include a high accumulative dose of antibiotics in a short period of time and prolonged treatments (>10 days).^{1–3} Haptene-induced hemolytic anemia⁴ has been reported to respond well to intravenous immunoglobulin.² Leukopenia, thrombocytopenia, fever, and hypersensitivity reactions that range from pruritis and skin rash to anaphylactic shock⁵

Table 1
Adverse Reactions Associated With Piperacillin/Tazobactam in Cystic Fibrosis.

Reference	Year	Number of Patients	Age/Sex	Dose	Onset of Symptoms (day)	Adverse Effects (%)	Treatment
Reichardt P. ¹	1996–1998	32	NR	Accumulated dose over 14 days 4.9 g/kg	11	Fever, general malaise, and headache Leukopenia and thrombocytopenia	PTZ discontinuation
Bandara M. ³	2010	1	39/F	4.5 g iv every 6 h	7	Hemolytic anemia	Transfusion, steroids, iv immunoglobulin, PTZ discontinuation
Zanetti R.C. ²	2013	1	19/F	NR	13	Hemolytic anemia	Transfusion, immunoglobulina iv, PTZ discontinuation
Marik P.E. ⁴	2013	1	24/M	NR	15	Hemolytic anemia	Transfusion, steroids, immunoglobulina iv, PTZ discontinuation

F: female; iv: intravenous; M: male; NR: not reported; PTZ: piperacillin/tazobactam.

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have also been reported, but no cases of coagulation changes or liver toxicity have been published.

In our experience, CF patients show increased adverse effects to piperacillin/tazobactam, so they should be used with caution in this population. One of our patients, who was a frequent exacerbator (requiring ≥ 2 intravenous antibiotics/year),⁶ received piperacillin/tazobactam in an attempt to improve results obtained with previous antibiotic combinations. We conclude that this drug may be considered for use in second-line treatment, but it is inadvisable to use it for periods longer than 14 days. High doses should also be avoided, even for short periods of time.

Conflict of Interests

The authors state that they have no conflict of interests.

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