

therapy in antibody-mediated autoimmune diseases such as autoimmune thrombocytopenic purpura, autoimmune haemolytic anaemia, systemic lupus erythematosus and rheumatoid arthritis. [2–4] The production of antibody depends on the antigenically driven clonal expansion of B cells into antibody-producing effector plasma cells. Plasma cells are short-lived cells, and survival of the populations depends on differentiation from their progenitor B cells [5]. B-cell ablation with rituximab could prevent further plasma cell and subsequent antibody formation, extinguishing the inflammatory anti-GBM response.

In our case, the anti-GBM titre did not decrease below reference level even though 51 L of plasma volume had been exchanged, suggesting a high rate of antibody formation. The rapid decline of antibody titre and proteinuria could very well have been due to a late effect of simultaneous earlier therapy, but the theory behind the use of rituximab does not rule out that the rituximab might have had beneficial effect on antibody formation.

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Interaction between tacrolimus and clindamycin

Sir,

Tacrolimus is widely used in organ transplantation to prevent allograft rejection. Its hepatic metabolism via cytochrome P450 (CYP) 3A4 represents the major eliminating process. In addition, its bioavailability depends on intestinal P-glycoproteins (PGP) and CYP3A5 activities. Due to its potential toxicity, tacrolimus usage requires a close drug monitoring, as well as the early identification of any pharmacological interaction. Here, we report on a novel interaction between tacrolimus and clindamycin in a renal transplant recipient with *Pneumocystis jirovecii* pneumonia (PJP).

A 61-year-old woman underwent kidney transplantation from a deceased donor for end-stage renal disease secondary to chronic glomerulonephritis with IgA deposits. Two months later, she presented with grade IV dyspnoea. Maintenance immunosuppression included modified-release (MR) tacrolimus 15 mg/day, mycophenolate mofetil (MMF) 720 mg/day and prednisolone 4 mg/day. Thorax computed tomography showed bilateral ground-glass opacities compatible with PJP, as confirmed by bronchoalveolar lavage analyses. MMF was interrupted, and sulpha-

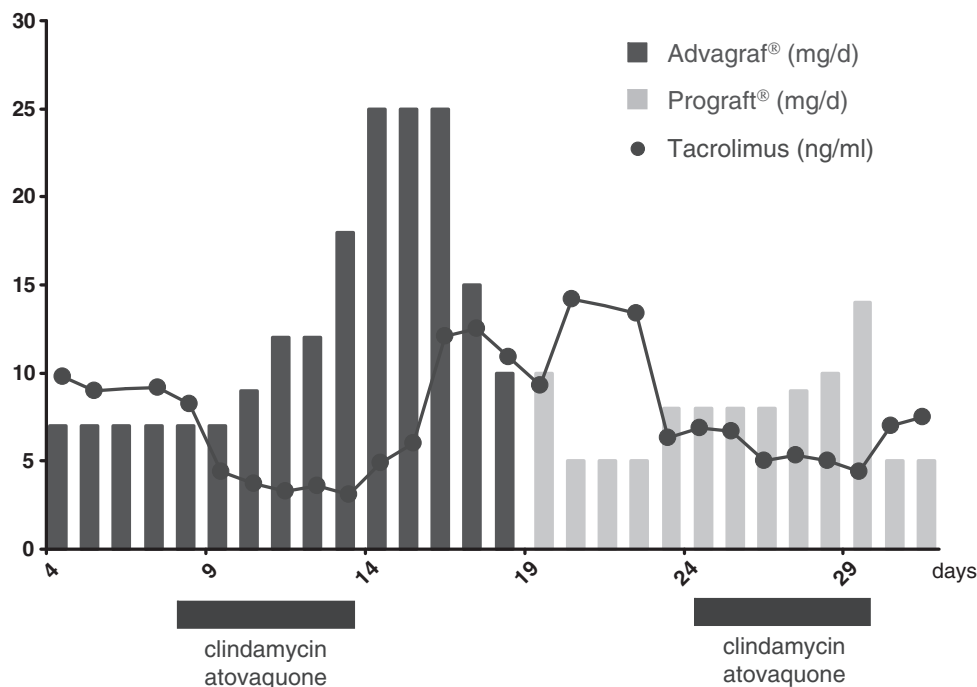


Fig. 1. Changes in tacrolimus blood trough level (nanogram per millilitre) and tacrolimus dose (milligram per day) according to atovaquone/clindamycin therapy from Day 4 at the intensive care unit. Advagraf® and Prograft® represent the modified-release and the twice-a-day form of tacrolimus, respectively.

methoxazole–trimethoprim (4 × 1280 mg/day) was initiated with methylprednisolone (32 mg/day). The patient's condition declined, requiring mechanical ventilation. From that time, medications were given through a nasogastric tube, and tacrolimus trough level remained stable ~10 ng/mL while receiving 7 mg/day (Figure 1). Because sulphamethoxazole–trimethoprim treatment induced type IV renal tubular acidosis, antimicrobial therapy was substituted for atovaquone (1500 mg/day) and clindamycin (2400 mg/day IV) on Day 8. Tacrolimus trough level progressively decreased, while its dosage was accordingly increased (Figure 1). Six days later, both atovaquone and clindamycin were interrupted with a progressive return of tacrolimus trough level to baseline. Since the administration of MR tacrolimus through a nasogastric tube may decrease its disposition, the twice-a-day form was initiated (Figure 1). Fibroscopy was performed 10 days after antibiotic withdrawal and disclosed PJP recurrence. Both atovaquone and clindamycin were resumed for 6 days. Again, tacrolimus trough level significantly decreased (Figure 1) though no other medication was initiated. Renal graft function remained stable.

Because of its extensive metabolism, tacrolimus disposition tightly depends on CYP3A4/5 and PGP activities. Here, a significant decrease of tacrolimus trough level was repeatedly observed when co-administered with atovaquone and clindamycin. Atovaquone is 94% excreted unchanged in faeces, with a modest inhibition of CYP2C19 which is not implicated in tacrolimus metabolism [1]. Conversely, clindamycin metabolism primarily requires its oxidation by CYP3A4/5 and exhibits a clear propensity to induce CYP3A4 activity [2,3]. Thus, similarly to former

cases reported under cyclosporine [4], clindamycin may accelerate tacrolimus catabolism. Here, the co-administration of clindamycin and tacrolimus led twice to a significant decrease in tacrolimus trough level. Such temporal relationship is highly suggestive of pharmacological interactions, as supported by a significant Drug Interaction Probability Scale (DIPS) score [5]. In conclusion, the present observation emphasizes the need for a close monitoring of tacrolimus trough level when co-administered with high-dose clindamycin.

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An atypical pneumonia in a renal transplant patient

We report the case of a 27-year-old man who suffered from end-stage renal disease secondary to medullary cystic kidney disease and who received a kidney transplant in November 2007. The post-transplant immunosuppressive regimen consisted of methylprednisolone, tacrolimus and mycophenolate mofetil. One year later, the patient presented with a non-productive cough and pain at the right side of the chest. He did not have fever. Physical examination revealed breath sounds reduction and rales over the right lung. On blood examination, C-reactive protein (CRP) was elevated at 52.3 mg/L (normal range <5 mg/L), and white blood cell (WBC) count was $13 \times 10^3/\text{mm}^3$ (normal range $3.6\text{--}9.6 \times 10^3/\text{mm}^3$) with $9.2 \times 10^3/\text{mm}^3$ neutrophils (normal range $1.4\text{--}6.7 \times 10^3/\text{mm}^3$). Serum creatinine was 177 $\mu\text{mol/L}$ (2.0 mg/dL) (normal range 0.5–1.5 mg/dL), and urea was 8.5 mmol/L (51 mg/dL) (normal range 15–40 mg/dL). Tacrolimus level was in the therapeutic range. Chest radiography showed the presence of an opacity at the right lung. Empirical treatment with intravenous amoxicillin clavulanate and clarithromycin was initiated. After a few days, the patient's symptoms resolved, and CRP and WBC count returned to normal. Antibiotic therapy was continued orally. However, the infiltrate remained radiologically unchanged.

Two months later, our patient was readmitted with general malaise. Laboratory tests at that time showed CRP of 145.5 mg/L, urea of 70 mg/dL, creatinine of 2.5 mg/dL and WBC count of $6.9 \times 10^3/\text{mm}^3$. Chest computed tomography (CT) scan showed no reduction of the pulmonary infiltrate. Therapy with amoxicillin clavulanate was reinitiated. Two sputum cultures and one blood culture yielded growth of Gram-positive coccobacilli, later identified as *Rhodococcus equi*. After susceptibility testing, therapy was switched to oral doxycycline and ciprofloxacin [1], and the patient could be discharged. A week later, he was readmitted for an *Escherichia coli* sepsis of unknown origin. Based on advanced literature study [1,2], it was decided to treat the patient with oral ciprofloxacin (2×500 mg/day) and rifampicin (2×450 mg/day) for at least 6 months. A CT-guided biopsy of the lesion was performed 7 months after initial diagnosis and showed the presence of granulomatous inflammation without necrosis. Additional stains and tissue cultures remained negative, namely for mycobacteria.

Currently, after 1 year of therapy, the patient's symptoms have completely resolved, and chest CT scan shows limited atelectasis but no active pulmonary infiltrate anymore.

Immunosuppressive therapy has not been changed during the whole course of the infection.

R. equi is a bacterium identified in soil and animals [2,3], but since our patient had a negative anamnesis for direct exposure, it still remains unknown how he acquired this type of infection.

This case illustrates the difficulty to establish the diagnosis of causative pathogens in immunocompromised patients, since clinical presentation can be very atypical and the spectrum of possible pathogens is extended. In conclusion, *R. equi* is a rare pathogen that should be considered in the differential diagnosis of atypical pneumonia in transplant patients.

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Should we recommend precautions during a hantavirus endemic?

Sir,

The number of notified hantavirus infections in southwestern Germany increased considerably in the beginning of the year 2007; therefore, the German health institutions put out a press release in the areas with the highest incidence in the southwestern part (Baden-Wuerttemberg) to establish precautions in the case of a possible contact with rodents [1].

During this significant endemic burst of infections, a 43-year-old male patient presented in Baden-Wuerttemberg with fever (>39°C), low back pain and acute renal failure. He told the doctors at the emergency department that he most likely had a hantavirus because he had cleaned his garden cabin 10 days before the presentation in the emergency department, and he had observed several rodents in his garden in the past. Because of the mentioned press release of an increased number of hantavirus infections with a broad discussion in the public, he followed some of the recommended precautions of the gov-