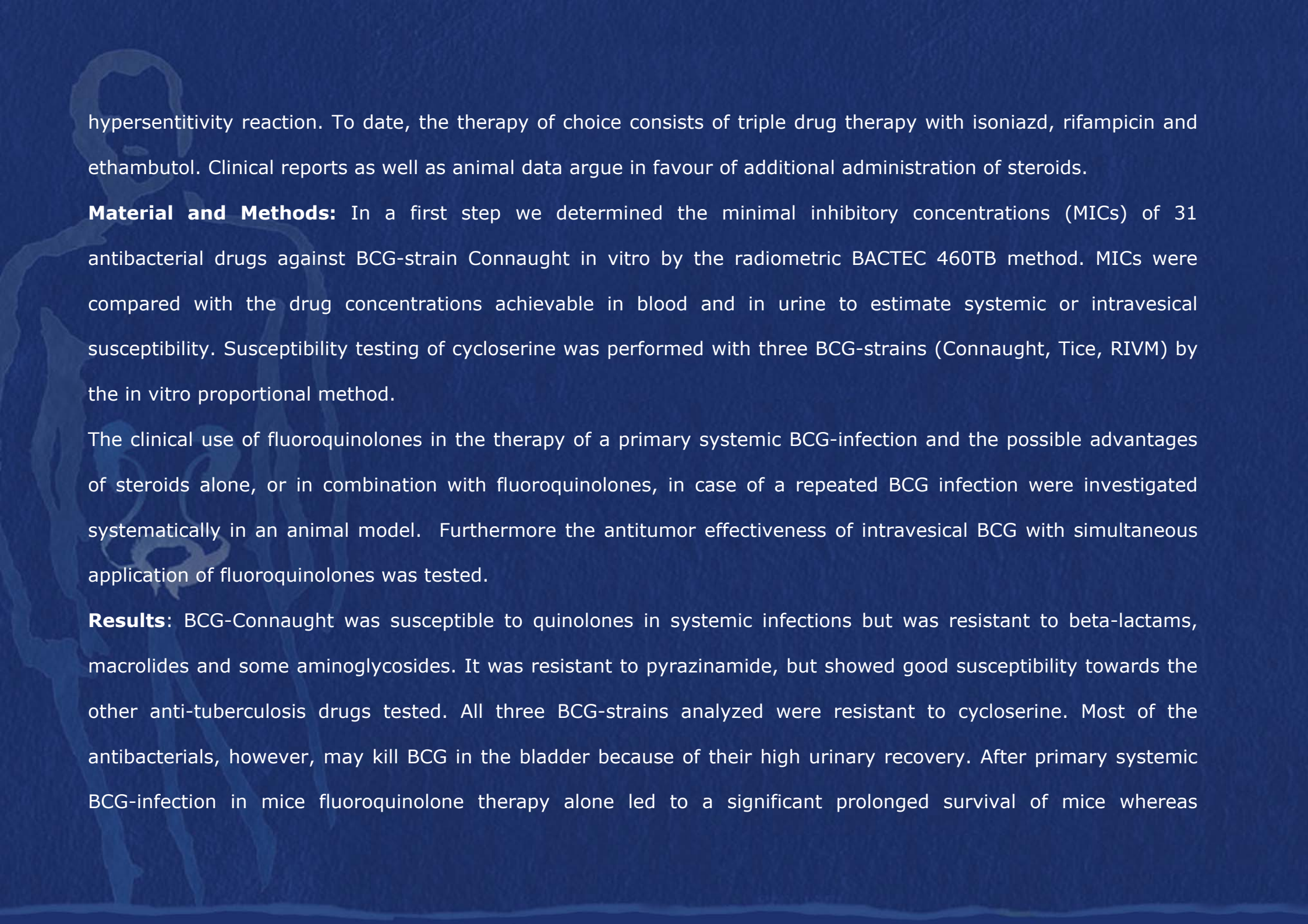


BCG and antibiotics: a solution to side-effects?

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During BCG instillation therapy local side effects such as dysuria, low grade fever and malaise frequently occur. Furthermore, unspecific bacterial cystitis is a common complication of any instillation therapy because of repeated catheterization procedures. In practice modern antibiotics (fluoroquinolones or third-generation cephalosporins) are commonly used for prophylactic purposes and to treat concomitant urinary tract infections. Given their ubiquity, it is important to determine the effects of these drugs on the viability of BCG in order to not induce an unnoticed decrease in its therapeutic efficacy as has been shown with isoniazid (INH) in animal studies where viability of BCG has been proven a crucial factor in obtaining a high therapeutic efficacy.

In rare cases, severe systemic side effects, e.g. sepsis, have been observed. In these cases cycloserine has been proposed as the treatment of choice in the literature. Sudden hypotension, fever and disseminated intravascular coagulation have been reported following repeated BCG-application, which can be regarded as signs of a

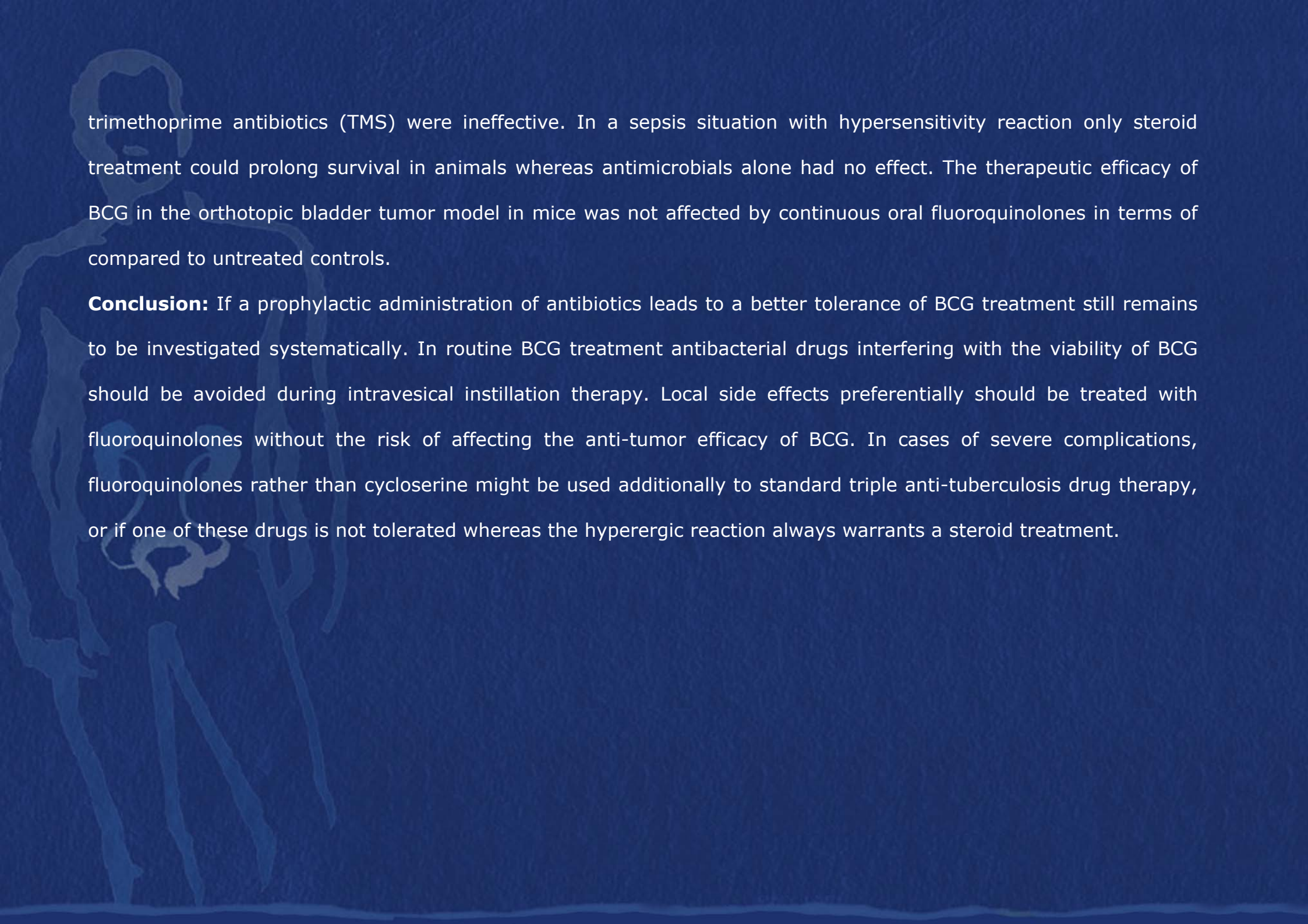


hypersensitivity reaction. To date, the therapy of choice consists of triple drug therapy with isoniazid, rifampicin and ethambutol. Clinical reports as well as animal data argue in favour of additional administration of steroids.

Material and Methods: In a first step we determined the minimal inhibitory concentrations (MICs) of 31 antibacterial drugs against BCG-strain Connaught in vitro by the radiometric BACTEC 460TB method. MICs were compared with the drug concentrations achievable in blood and in urine to estimate systemic or intravesical susceptibility. Susceptibility testing of cycloserine was performed with three BCG-strains (Connaught, Tice, RIVM) by the in vitro proportional method.

The clinical use of fluoroquinolones in the therapy of a primary systemic BCG-infection and the possible advantages of steroids alone, or in combination with fluoroquinolones, in case of a repeated BCG infection were investigated systematically in an animal model. Furthermore the antitumor effectiveness of intravesical BCG with simultaneous application of fluoroquinolones was tested.

Results: BCG-Connaught was susceptible to quinolones in systemic infections but was resistant to beta-lactams, macrolides and some aminoglycosides. It was resistant to pyrazinamide, but showed good susceptibility towards the other anti-tuberculosis drugs tested. All three BCG-strains analyzed were resistant to cycloserine. Most of the antibacterials, however, may kill BCG in the bladder because of their high urinary recovery. After primary systemic BCG-infection in mice fluoroquinolone therapy alone led to a significant prolonged survival of mice whereas



trimethoprim antibiotics (TMS) were ineffective. In a sepsis situation with hypersensitivity reaction only steroid treatment could prolong survival in animals whereas antimicrobials alone had no effect. The therapeutic efficacy of BCG in the orthotopic bladder tumor model in mice was not affected by continuous oral fluoroquinolones in terms of compared to untreated controls.

Conclusion: If a prophylactic administration of antibiotics leads to a better tolerance of BCG treatment still remains to be investigated systematically. In routine BCG treatment antibacterial drugs interfering with the viability of BCG should be avoided during intravesical instillation therapy. Local side effects preferentially should be treated with fluoroquinolones without the risk of affecting the anti-tumor efficacy of BCG. In cases of severe complications, fluoroquinolones rather than cycloserine might be used additionally to standard triple anti-tuberculosis drug therapy, or if one of these drugs is not tolerated whereas the hyperergic reaction always warrants a steroid treatment.