

## Commentary

### Why sulfonamides are contraindicated in Rocky Mountain spotted fever

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Dermatology Online Journal 20 (2): 3

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## Abstract

Sulfonamide antibiotics are not effective for the treatment of Rocky Mountain spotted fever (RMSF). Patients suspected of having RMSF based on history and physical exam should be treated with doxycycline and not a sulfonamide to avoid increased morbidity and mortality.

**Keywords:** Rocky Mountain, spotted fever, *Rickettsia rickettsii*, sulfa, sulfonamide, cotrimoxazole

## Commentary

The ineffectiveness of sulfonamides in the treatment of Rocky Mountain spotted fever (RMSF) was first described in 1939 and 1943 in experimentally infected guinea pigs and rabbits [1, 2]. All sulfa drugs are contraindicated throughout the course of a rickettsial infection [3]. The prompt administration of doxycycline is the treatment of choice for suspected RMSF [4]. We sought to answer the question: Why are sulfa drugs contraindicated in the treatment of RMSF?

Prior to the availability of doxycycline, para-aminobenzoic acid (PABA), an analogue of sulfonamide, was shown to be successful in the treatment of guinea pigs infected with RMSF. However, PABA required frequent dosing and administration of bicarbonate in order to maintain a therapeutic blood concentration and prevent urinary precipitation [5]. Although the rickettsiostatic mechanism of PABA remains unclear and is only of historic interest now, PABA may be associated with the interference of bacterial utilization of para-hydroxybenzoic acid [6].

Sulfonamides (e.g., sulfamethoxazole) are structural analogs and competitive inhibitors of PABA. Sulfonamides bind to dihydropteroate synthetase (DHPS) and inhibit the first step of dihydrofolic acid synthesis. Trimethoprim (TMP), which is administered with sulfamethoxazole (SMX) in the TMP-SMX sulfonamide antibiotic, binds to dihydrofolate reductase (DHFR) and inhibits conversion of dihydrofolic acid to tetrahydrofolic acid. *Rickettsia rickettsii*, the bacterium that is responsible for Rocky Mountain spotted fever, lacks the *folP* gene that encodes DHPS, making it resistant to sulfamethoxazole. Other rickettsial species also lack *folA*, which encodes DHFR. Consequently, rickettsial organisms as a group demonstrate significant resistance to sulfa drugs [7].

Administration of sulfonamides to patients who have not been definitely diagnosed with RMSF leads to further delay in diagnosis and treatment, which results in increased morbidity and mortality. Thus, all patients suspected of having RMSF based on history and physical exam should be treated with doxycycline, preferably within the first five days of symptom development [8].

## References

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