Exudative epidermitis or greasy pig syndrome is caused by the coagulase-variable staphylococcal species Staphylococcus hyicus. Treatment of this disease is problematic because of the limited number of antimicrobial agents available for this purpose. Thirteen antimicrobial agents were evaluated for their activities against 100 S. hyicus strains isolated from pigs with exudative epidermitis. Novobiocin was the most active compound tested, with an MIC for 90% of the strains tested (MIC(90)) of less than or equal to 0.06 μg/ml. Enrofloxacin, ampicillin, and ceftiofur were the next most active compounds, with MIC(90)s of 0.25, 0.5, and 1.0 μg/ml, respectively. However, 41.4% of the 99 strains tested were positive for beta-lactamase production. The MIC(90)s of erythromycin, tetracycline, and streptomycin were >32.0 μg/ml. Initial testing with sulfadiazine-trimethoprim yielded an MIC(90) of >64.0 μg/ml, but subsequent testing with thymidine phosphorylase-supplemented medium yielded an MIC(90) of 0.06 μg/ml. Both lincomycin and spectinomycin were relatively inactive against the S. hyicus strains tested, with MIC(90)s of > 64.0 and > 128.0 μg/ml, respectively. However, the combination of the two compounds at ratios of 1:2 (lincomycin to spectinomycin) and 1:8 were more active, with MIC(90)s of 16.0 and 4.0 μg/ml, respectively. These results indicate that novobiocin and sulfadiazine-trimethoprim were the most active compounds tested against the S. hyicus strains isolated from pigs with exudative epidermitis. Furthermore, the combination of lincomycin and spectinomycin was more active than the individual compounds against the strains tested.