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Commentary

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# Review of Pilot Study and Experimental Evidence for Decreased Risk of Complications of Infection associated with Use of Calcium Channel Blockers and Calcineurin Inhibitors

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## Commentary

Despite many negative studies beyond the scope of this brief review, there are areas that involve employment of calcium channel blockers to decrease risk of bacterial infection or parasitic infestation [1]. If calcium channel blockers can avert antibiotic resistance, this would benefit individual patient care and the healthcare budget as newer medications are developed. While many potential mechanisms leading to antibiotic resistance have been researched, the mechanism that has drawn most attention is rapid extrusion of antibiotic from zones of the invading pathogen. The routes of extrusion appear to be channels that can be blocked by calcium channel blockers even if not identified as traditional calcium channels. When these channels are successfully blocked, higher concentrations of antibiotic remain in a position to attack the invading pathogen.

Three retrospective studies of infection in hypertensive populations drew attention to the finding of benefit for study groups treated with calcium channel blockers versus equivalent study groups treated with a different class of anti-hypertensive agent. The groups ranged from general [2,3] to immune suppressed populations [4] in which pneumonia was the leading, but by no means the only, infectious outcome of concern. At this point we are aware of studies evaluating pneumococcal pneumonia resistant to quinolones [5] and pulmonary tuberculosis resistant to rifampicin [6] in which the investigators found benefit with use of calcium channel blockers. Other Gram positive organisms that have been shown to employ the antibiotic extrusion mechanism include Bacillus, Clostridium Listeria, and Staphylococcus while Gram negative organisms that have been shown to use the antibiotic extrusion mechanism include Bacteroides, Brucella, Enterobacter Hemophilus, Neisseria, Pseudomonas, and Vibrio. As newer primary treatments for these serious infections are developed, there may be reduced cost with the assistance of calcium channel blockers, which would require prospective investigation looking at benefit to patient health with the goal of reducing development of antibiotic resistant strains that can be expected when higher antibiotic doses are ordered more frequently.

Beyond *in vitro* studies of bacteria, several parasite species have been demonstrated to extrude antibiotics, including Plasmodium falciparum [7], Schistosoma mansoni [8], Leishmania amazonensis [9], and Trypanosoma cruzi [9], and Toxoplasma gondii [10] in fashions that are common world-wide sources of resistance.

The calcium/calmodulin/calcineurin pathway may be inhibited by both calcineurin inhibitors (cyclosporin, tacrolimus) useful for immunosuppression in solid organ transplantation and by calcium channel blockers. Both calcineurin inhibitors and calcium channel blockers have been demonstrated to inhibit the parasite of malaria Plasmodium falciparum as well as various members of the yeast family of potential pathogens, including Aspergillus fumigatus [11], Candida albicans [12], and Cryptococcus neoformans [13]. These studies of yeast are *in vitro* with no clinical reports to our knowledge.

The most extensive antibiotic resistance problems listed here are tuberculosis for which there is currently a new medication [14] and malaria for which there is currently a new monoclonal antibody [15] that may not yet be in wide spread distribution. Some geographical locations where tuberculosis and malaria may be overlapping may also be centers of COVID infection where there is not yet wide spread distribution of vaccine or immune globulin. In that connection a physician might be faced with long term treatment of a bacterium, a parasite, and a virus. Study of the role of calcium channel calcium blockers and calcineurin inhibitors may become a greater necessity if patients require long term treatment.

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