

In-vitro efficacy of carbapenem-loaded calcium sulfate beads against a series of carbapenem-resistant enterobacteriaceae

Davis LS, Delury CP, Laycock PA

Biocomposites Ltd, Keele Science Park, Keele, Staffordshire, ST5 5NL, UK

Aims:

In Jan of 2017, the CDC published a report which detailed the case history of a patient who was admitted to hospital with osteomyelitis of the right femur and hip¹. A carbapenem resistant *Klebsiella pneumoniae* was isolated as the infective organism. The isolate was resistant to more than 26 antibiotics. As a result, the patient developed septic shock and died.

Infections with carbapenem-resistant enterobacteriaceae (CRE) are associated with high complication rates and poor outcomes, with optimal treatments largely unknown. In cases of multidrug resistance (MDR), carbapenems are the drug of choice, however this is not suitable if the organism is carbapenem resistant. It is suggested that high levels of antibiotics released locally from calcium sulfate beads may overcome resistance in some strains. Here, the efficacy of antibiotic-loaded recrystallised calcium sulfate beads (RCSB) to inhibit bacterial growth against three CRE strains was investigated.

Method:

Three strains of carbapenem resistant *K.pneumoniae* (KPC-3- NCTC 13438, NDM1- NCTC 13443, OXA-48- NCTC 13442) were assessed in a modified Kirby-Bauer assay. RCSB* were loaded with meropenem ('Meropenem' Milpharm,1000mg/10cc), ertapenem ('Invanz' MSD 1000mg/10cc), imipenem/cilastatin ('Primaxin' MSD, 500mg/500mg/10cc) or colistimethate sodium ('Promixin' Alloga, 6MIU/10cc). Beads were placed onto agar plates seeded with *K.pneumoniae* strains, and incubated (Figure 2). Zones of inhibition (ZOI) were photographed, measured and average ZOI sizes recorded.

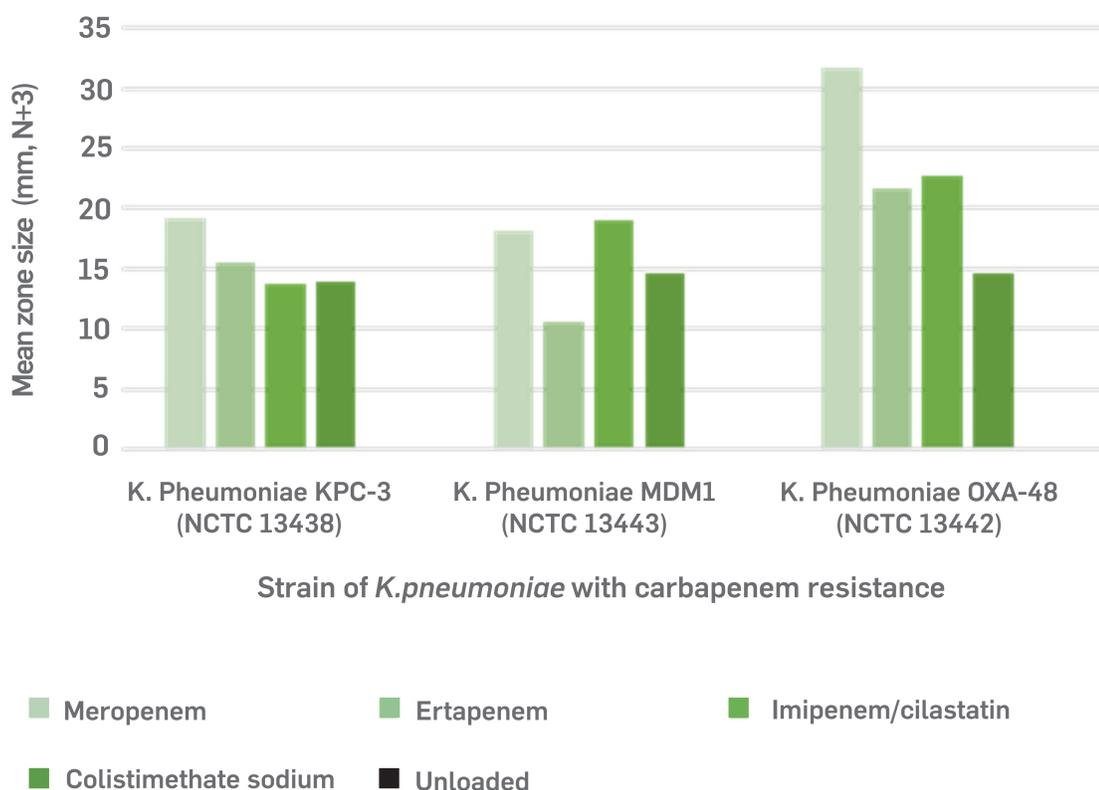


Figure 1- Mean zone sizes of 5 bead types against each of 3 carbapenem-resistant strains of *K.pneumoniae*

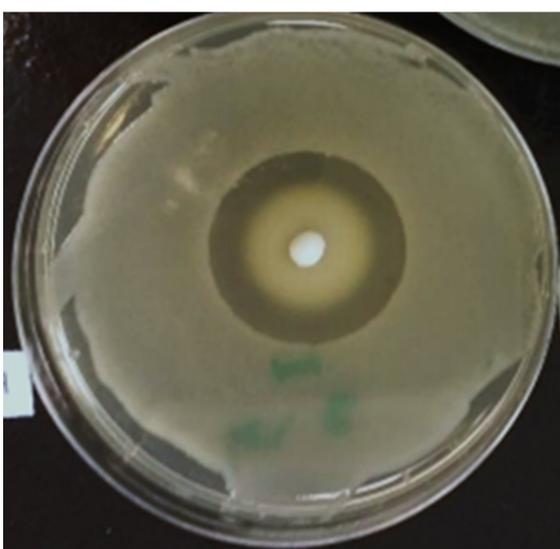


Figure 2- Meropenem-loaded calcium sulfate bead against *K.pneumoniae* (OXA-48) showing a zone of inhibition

Results:

All of the antibiotic-loaded beads produced clear ZOIs against each of the resistant organisms (Figure 1/2). Meropenem produced the greatest zones against the KPC-3 and OXA-48 strains. Imipenem/Cilastatin loaded beads were most effective against the NDM-1 *K.pneumoniae*. Colistimethane sodium beads produced zones of similar size against all strains.

Conclusions:

The results indicate that local release of antibiotics from RCSB may be useful in the treatment of resistant *K.pneumoniae* strains. High concentrations of antibiotics released locally were sufficient to prevent bacterial growth *in-vitro* despite the selected strains having various genes responsible for resistance to the carbapenem drugs tested. Differences observed between RCSB loaded antibiotics, may be a result of variations in specific antibiotic mechanisms of action.

References:

¹https://www.cdc.gov/mmwr/volumes/66/wr/mm6601a7.htm?s_cid=mm6601a7_w

*Stimulan Rapid Cure, Biocomposites