1675. A Novel Murine Pneumonia and Bacteremia Model for Carbapenem-Resistant *Klebsiella pneumoniae* Infection

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Background. The incidence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections has increased significantly in recent years, posing a major public health threat. Invasive CRKP infections may retain *in vitro* susceptibility only to second-line agents such as tigecycline and polymyxins, with mortality as high as 58% in some series. Present clinical data has relied principally on retrospective studies. Developing effective animal models is critical in evaluating future treatment combinations.

Methods. Animal use committee approval was obtained. Following 7 days of acclimation, outbred female Swiss-Webster mice were administered cyclophosphamide 150 mcg/kg four days and 100 mcg/kg one day prior to inoculation to induce neutropenia with hematologic verification. Under isoflurane anesthesia, mice received 50 μL of a 10^8 colony forming units per milliliter (CFU/mL) aerosolized suspension of American Type Culture Collection (ATCC) strain 1705, *K. pneumoniae* via tracheal intubation. Mouse wellness was evaluated using a standardized scoring system to establish a humane marker for euthanasia and was also used as a surrogate of mortality prior to the pre-defined 96-hour end-point. At necropsy, quantitative blood cultures were obtained via terminal cardiac puncture, and lung samples were taken for histologic evaluation and quantitative tissue culture. Specimens were plated on CHROMagar KPC® plates (CHROMagar, Paris, France) to confirm CRKP.

Results. Initially, a lethal dose (LD) study was performed utilizing doses from 10^6-10^9 CFU/mL. A total of 79 mice were inoculated with the 10^8 CFU/mL dose establishing a 75% pre-endpoint mortality (LD 75) with lung bacterial counts averaging 7.46 x 10^{10} CFU/mL and average time to mortality of 69.3 hours. CRKP bacteremia was detected in 79% of infected mice. Lung weights averaged 0.523 grams (normal 0.280 grams/ 21 gram mouse). Gross lung pathology routinely demonstrated moderate to severe consolidative pneumonia often with alveolar hemorrhage.

Conclusion. Findings suggest that sepsis and bacteremia can be reliably produced in neutropenic Swiss-Webster mice via the tracheal inoculation of *K. pneumoniae* (ATCC 1705). This model has promise for future *in vivo* testing of antimicrobial regimens for highly drug-resistant Gram-negative bacilli.

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