Bacille-Calmette Guérin Vaccine Improves Survival from Murine Neonatal Sepsis

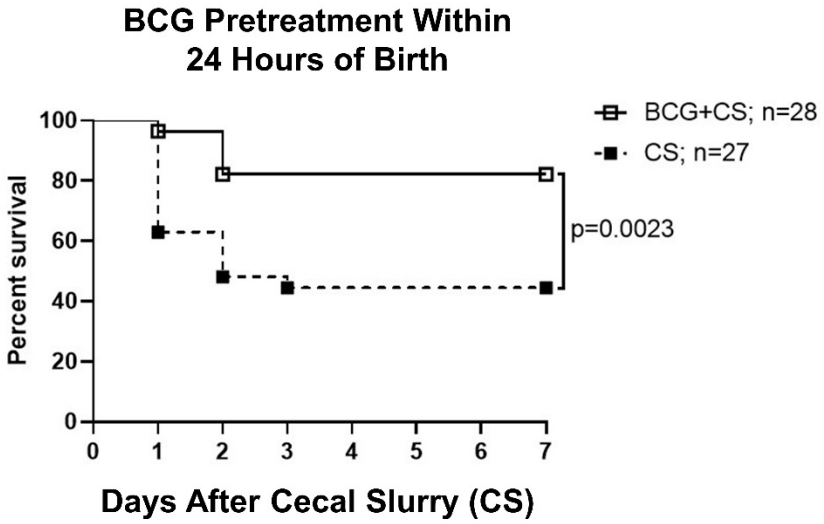
Author: Russell B Hawkins, MD
Secondary Authors: Jaimar C Rincon, PhD; Philip A Efron, MD; Lyle L Moldawer, PhD; Shawn D Larson, MD

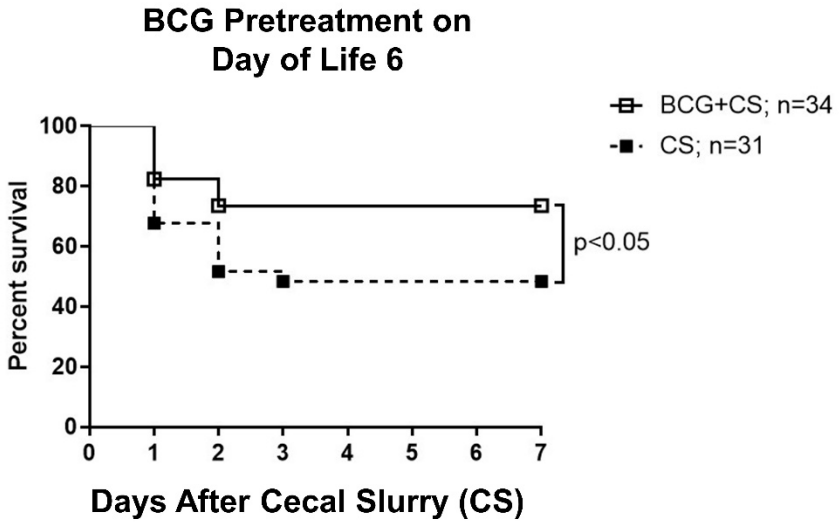
Introduction: Sepsis is a leading cause of neonatal mortality, resulting in over 1 million deaths each year worldwide. Traditionally, neonates are thought to have diminished immune responses when vaccinated at birth due to immaturity of their immune system. Emerging evidence suggests, however, that Bacille-Calmette Guérin (BCG) vaccination at birth is associated with decreased sepsis mortality in large population studies, but the mechanism of this effect is unclear and reverse translation to an animal model is necessary. We hypothesized that perinatal administration of BCG vaccine results in a reduction of mortality from neonatal sepsis, and that timing of vaccine administration impacts survival benefit.

Methods: Neonatal wild-type (C57BL/6) mice were utilized for experiments. Pups were pretreated with BCG vaccine (10^6 colony forming units [CFUs]) or control injection (saline) subcutaneously at one of three different time-points: < 24 hours of birth, day of life 4, and day of life 6. Following pretreatment, all pups received an intraperitoneal injection of cecal slurry (CS) (1.1-1.3 mg/g body weight) on day of life 7 to induce sepsis (LD_{40-70}) as we previously described. Survival was tracked for 7 days. A subgroup of control and BCG-pretreated mice underwent peritoneal lavage and culture of peritoneal wash 24 hours after cecal slurry. Peritoneal CFUs were counted after 24 hours of incubation.

Results: BCG pretreatment was associated with a significant survival benefit following CS (Figure 1). The greatest survival benefit was observed when BCG was administered <24 hours of birth, with BCG-treated mice having 18% mortality vs. 56% mortality in control mice ($p=0.0023$). The survival benefit in neonatal sepsis was attenuated with BCG pretreatment on day of life 6 (29% vs. 47% mortality compared to control; $p<0.05$). BCG-pretreated pups had 2.7 ±2.3 log CFUs/100 µL from peritoneal wash vs. 4.3 ±0.4 log CFUs/100 µL in controls.

Conclusion: BCG vaccine, administered at birth or shortly thereafter, results in a significant reduction in mortality from sepsis in our neonatal murine model. The greatest reduction was observed with perinatal BCG administration 1 week before induction of sepsis, suggesting that early vaccination alters the innate immune response and improves survival likely by alterations in innate immune effector cells with development of “trained” immunity. This novel finding is contradictory to dogma that neonates are unable to mount effective vaccine responses. Furthermore, these results highlight the applicability of this animal model to human population data seen with BCG vaccination and raise the possibility of utilizing immune adjuvants clinically to reduce neonatal sepsis mortality.


BCG Pretreatment Within
24 Hours of Birth
BCG+CS; n=28
CS; n=27
p=0.0023
Percent survival
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Days After Cecal Slurry (CS)


BCG Pretreatment on
Day of Life 6
BCG+CS; n=34
CS; n=31
p<0.05
Percent survival
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Days After Cecal Slurry (CS)