Rapid E. Coli Invasion May Cause Sudden Infant Death

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BETHESDA, Md.—Sudden Unexpected Infant Death Syndrome (SUID) in human infants may have the same pathogenesis as infectious diarrhea (scours) and sudden death of newborn calves.

A strong plea has been made for physicians and pediatric researchers to investigate the probability that acute toxemia resulting from rapid and massive invasion of *Escherichia coli* into the highly absorptive portion of the small intestine may be the death mechanism in the human syndrome, just as it is in the disease syndrome in calves and the young of other mammalian species.

Dr. Robert C. Reisinger, research veterinarian with the National Cancer Institute, told an NIH seminar here that there is a definite model in calf research for the Sudden Unexpected Infant Death Syndrome.

"Instead of studying only viruses and slides of fixed tissues physicians and researchers need to do quantitative studies of the bacteria in the anterior intestinal tracts of these children," Dr. Reisinger urges. He points out that slide pathology will not demonstrate the condition—there are no pathognomonic lesions.

By quantitatively culturing the human infants microbial flora at different appropriate levels of the intestinal tract, it would be possible to establish the role of bacteria in the SUID syndrome, he says.

(Dr. Reisinger commented that the recently published proceedings of a Seattle conference on the causes of sudden deaths in infants [Public Health Service Publication No. 1412] contain only three references to bacterial studies—these were not quantitative, and did not include the upper intestinal tract.)

Concerning the relevance of the calf disease syndrome to Sudden Unexpected Infants Death Syndrome, Dr. Reisinger notes that the peak incidence in humans is comparable to that seen in calves when the difference in maturity of the two species is considered. In calves, the peak incidence occurs while the calf is basically a monogastric animal, on a mainly liquid diet. The human infant is also of course on a liquid diet, and it is not difficult to visualize that under this condition it would be relatively more simple for *E. coli* invasion to occur than in the older child or animal when intestinal contents are more firm, the normal intestinal flora more firmly established, and the entire organism more adapted to various stressors.

In his own calf research, he reports that all of more than 60 lethal cases of scours were associated with overgrowth of *E. coli;* several cases of sudden death, with no scours or diarrhea, showed the same overgrowth of these bacteria. Other young animals, including rabbits and pigs, show the same susceptibility and response to multiplication and migration of *E. coli* into the upper digestive tract.

Normally, Dr. Reisinger explains, the gram-negative *E. coli* are found in the lower part of the ileum, and in the cecum, large intestine and rectum. The duodenum, jejunum and upper ileum, where most digestion and absorption of nutrients occur, is normally acid, and inhabited by acid-producing lactobacilli and enterococci; *E. coli* cannot long exist in this acid medium.

When the balance between lower and upper bowel is upset, *E. coli* in great numbers invade the upper more absorptive portion, and diarrhea and/or death occurs. It is well-known that *E. coli* do not normally occur in the upper digestive tract of any mammalian species. When these organisms are present in large numbers in this portion of the intestinal tract, absorption of toxins results in varying degrees of illness and, in the young, often in death. Counts of 10^7 or 10^8 coliform bacteria per cubic centimeter in the more absorptive portions of the small intestine have been found associated with this disease syndrome in newborn calves, and in calves up to 30 days of age.

Other Factors

Adverse contributing factors which aid in precipitating the disease in animals include: 1) cold and wet, rapid climatic temperature changes; 2) overcrowding, which causes buildup of particularly pathogenic organisms; 3) subnormal nutritional status, such as avitaminosis A; 4) virus infections; 5) overfeeding, which dilutes out the acid in the gut and also predisposes to vomiting, ballooning of the intestine, and perhaps reverse peristalsis; 6) prolonged interval between birth and ingestion of the first colostrum.

Dr. Reisinger observes that early feeding of colostrum— within 15 minutes of birth—is the most critical factor in preventing the disease in newborn animals. Colostrum must be present in the anterior gut for its *E. coli* antibody to be effective.

Lack of antibody to *E. coli* does not appear to play a clearly defined role in

the sporadic cases of sudden death in older calves, 14 days to one month of age. *E. coli* invasion into the upper intestinal tract resulting in sudden death without bacteremia may occur in such calves which have nursed their dams from birth as well as in calves separated from their dams and bucket fed on whole milk, or commercial milk replacers.

One would not expect to find appreciable amounts of *E. coli* antibody in either case. However, the mechanism of death is the same in these older calves.

He also reports that oral doses of chloramphenicol have been effective in combatting *E. coli* in the intestinal tract of calves, although it is reported extremely toxic in the premature human infant. The tetracyclines are not recommended in treating calves for diarrhea. Such calves appear to die more quickly than those receiving no treatment.

In response to a comment on the presence, in human infants with the Sudden Death Syndrome, of symptoms relating to the respiratory tree, Dr. Reisinger says that at least four different viruses have been associated with this syndrome in calves, yet the viral agents by themselves do not appear to kill, but to act as triggering agents or stressing factors, which may predispose the calf to *E. coli* invasion, with or without bacteremia.

Viruses are but one of the many "adverse contributing factors" which may trigger the *E. coli* death mechanism. Research should continue on these "adverse contributing factors," he says, but immediate attention should be directed toward confirming, or denying, the decisive role of *E. coli* in the mechanism of death in this syndrome, so that practical preventive measures may be developed.

Throughout his discussion of the research on the Sudden Death syndrome in calves, Dr. Reisinger emphasized that the original work on the pathogenesis of *E. coli* diarrhea of new born calves was largely carried out by Theobald Smith and his co-workers from 1917 through the 1920's. Research since has confirmed this early work and shed some further light on contributing or predisposing factors.

Dr. Reisinger is the first to point out the many direct similarities between the Sudden Death syndrome in the human infant and the young of other mammalian species. He feels that since Theobald Smith, M.D., was the first to definitively demonstrate the role of *E. coli* in the calf disease, it is only fair that a D.V.M. reciprocate by pointing out the similar role of *E. coli* in the disease of the human infant.

Possible Prevention

"I do not presume to know the measure necessary to reduce this infant mortality, but I do know that until the mechanism of death is understood, no preventive measures will be developed—and they are long overdue," Dr. Reisinger says.

In discussing possible practical preventive measures, he suggests that it may be preferable for an infant to sleep on an inclined plane rather than on a horizontal one. In the prone position, Dr. Reisinger points out, the infants's upper intestinal tract is actually his anterior intestinal tract. If the mechanism of death in Sudden Unexpected Infant Death Syndrome is similar to the mechanism existing in other mammals, the change in position may be helpful.

Also, he feels perhaps the pH of the feeding formula should be lowered, or orange juice given as the final night's feeding thereby increasing the acidity of the intestinal tract and possibly holding coliforms in check.

Dr. Reisinger reported one instance of three infants in one family succumbing to the SUID syndrome. A conceivable explanation, he says, is that the infants may have had an inborn lack of acid-production. It would be relatively simple to determine the pH in the duodenum of siblings of children who have succumbed to this syndrome and such information would contribute to our understanding of the mechanism of death.

Another factor requiring additional and continuing investigation is the administration of penicillin, the tetracyclines, and other oral antibiotics more active against gram-positive bacteria than gram negative bacteria.