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Fatal Septicemia Due to *Staphylococcus aureus* 502A

Report of a Case and Review of the Infectious Complications of Bacterial Interference Programs

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During a bacterial interference program in a newborn nursery 38 (5.9%) of 644 deliberately colonized babies developed disease related to the *Staphylococcus aureus* 502A blocking strain. Thirty infants had pustules, six had conjunctivitis, and one infant developed an abscess. An infant of a diabetic mother developed septicemia and meningitis, probably secondary to passing an umbilical vein catheter through the colonized umbilical stump. *Staphylococcus aureus* 502A and *Escherichia coli* were isolated from blood culture before death and from autopsy cultures of blood and peritoneum. A meningeal culture grew *S aureus* 502A. Gram-positive cocci were identified in liver, lung, heart, and meninges. Only two (0.5%) minor 502A infections were seen in 444 spontaneously colonized infants. The benefits of *S aureus* 502A programs far outweigh their hazards. Disease due to the 502A strain is more frequent when the inoculum applied to the infant is large than when it is kept below 4,000 bacteria. The fatal case emphasizes that bacteria of extremely low virulence may produce serious disease in compromised hosts and that catheterization through a contaminated umbilical stump may induce bacteremia.

In the past decade bacterial interference between *Staphylococcus aureus* 502A and more virulent staphylococci has been used several times to halt epidemics of staphylococcal disease in newborn nurseries. Shinefield et al[1] recently reviewed the experience with this procedure, and stressed both the efficacy and the safety of deliberate colonization of newborns with the interfering strain of low virulence. They stated that more than 4,000 infants had been colonized without a single case of serious disease in an infant or in a household contact due to *S aureus* 502A. Minor disease due to the colonizing strain has been reported. Conjunctivitis was seen rarely and from 5% to 15% of babies developed tiny periumbilical vesicles.

During a six-week period in November and December 1967 a bacterial interference program was carried out in the nurseries of Parkland Memorial Hospital in Dallas in a successful attempt to eliminate an entrenched epidemic of *S aureus* 80/81 disease. Details of the outbreak and methods will be presented elsewhere (J. A. Horne, unpublished data). Colonization of the nose and umbilical cord with *S aureus* 502A was done in 644 infants and spontaneous acquisition of the strain occurred in 444 additional babies. The colonizing strain

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was obtained from Heinz F. Eichenwald, MD, and was from the batch of *S aureus* 502A used in the original investigations.[2]

Thirty-eight (5.9%) of the 644 deliberately colonized infants developed disease thought to be due to *S aureus* 502A. Thirty infants had pustules and six had mild conjunctivitis with the 502A strain isolated from the lesions. Before aspirating pustules for culture the area was treated with povidone-iodine to avoid contamination with skin bacteria. The pustules were superficial, few in number, and responded rapidly to locally applied medication. One infant developed an abscess of the toe and one infant had fatal septicemia and meningitis. One case of conjunctivitis and one of pustules related to *S aureus* 502A were seen among the 444 who were colonized spontaneously. Disease due to the colonizing strains was detected only once among household contacts of these infants. An older sibling of a colonized baby developed pustules from which *S aureus* 502A was recovered. The two cases of serious infection are presented in detail.

Report of Cases

CASE 1.—A female infant who weighed 3,147 gm (7 lb 15 oz) was of American Indian ancestry. The mother had a subtotal thyroidectomy for a benign thyroid nodule 18 months before delivery. Diabetes mellitus was diagnosed at that time. During the pregnancy the mother received 0.2 mg thyroxine and 40 units of insulin zinc suspension daily. Labor began spontaneously at eight months' gestation; the labor and delivery were otherwise normal. Apgar score was seven at one minute. The infant was flushed and appeared to be an immature infant of a diabetic mother with thin skin, full cheeks, and large abdomen. *Staphylococcus aureus* 502A was administered to the nares and umbilical cord at 3 hours of age with a cotton swab moistened with broth solution containing 2.5×10^6 viable bacteria per milliliter.

The course during the next 24 hours was characterized by intermittent tachypnea and sluggishness. The blood glucose determination at eight hours of age was 25 mg/100 ml. Attempts to maintain a peripheral vein infusion of glucose were unsuccessful. A polyethylene catheter was inserted into the umbilical vein and 15% glucose infusion begun. X-ray examination of the chest showed only slight prominence of lung markings.

After a relatively stable period, apnea with cyanosis developed at 68 hours of age. This was relieved by stimulation and oxygen. Another x-ray film of the chest revealed opacification of the lower lobe of the left lung and prominent infiltrates through the right lung. Femoral blood cultures were obtained and treatment with methicillin sodium and kanamycin sulfate was started. There was progressive dyspnea and abdominal distention and the baby died at 84 hours of age. A blood specimen for culture obtained five hours before death grew *S aureus* 502A and *Escherichia coli*.

At autopsy examination the umbilical catheter tip was located at the junction of the ductus venosus and hepatic veins. There was purulent material at this site and microscopic examination revealed an inflammatory infiltrate with clusters of gram-positive cocci. The liver was grossly normal but within the parenchyma were clusters of gram-positive cocci. The posterior portions of both lungs were firm and atelectatic with foci of hemorrhage and a pink, fluffy material exuding from the cut surface. Microscopic sections showed multifocal areas of septic emboli in the pulmonary vasculature containing innumerable gram-positive cocci and inflammatory cells. In the parenchymal areas there were inflammatory infiltrates, hemorrhage, and focal areas of atelectasis. In the heart many smaller arterioles were occluded by bacterial septic emboli, and gram-positive cocci were seen in the adjacent perivascular infiltrate. There were several small petechiae on the external surface of the brain. The meninges were cloudy but not grossly purulent. The small meningeal vessels microscopically demonstrated gram-positive coccal embolic foci. Hypertrophy and hyperplasia of the islets of Langerhans were seen in the pancreas.

Postmortem cultures of the meninges grew *S aureus* 502A. Cultures from the blood and peritoneum had both *S aureus* 502A and light growth of *E coli*. Identification of *S aureus* 502A was based upon a consistent antibiogram and phage type pattern 7/47/53/81.

CASE 2.—A female infant weighing 3,070 gm (6 lb 12 oz) was delivered of a 19-year-old multigravida girl who had preclampsia and megaloblastic anemia during the pregnancy. Labor and delivery were uncomplicated and the infant had an Apgar score of nine at one minute. Results of the physical examination of the newborn were normal. At 1½ hours of age the infant's nasopharynx and umbilical cord were inoculated with *S aureus* 502A by the method previously described.

The infant was retained in the nursery while the mother convalesced following elective surgery. The first nine days of hospitalization were uneventful. Screening cultures of the anterior nares and umbilicus on the seventh day of life showed successful colonization with *S aureus* 502A. On the tenth hospital day a superficial abrasion was noted medial to the nail bed of the left great toe. The area became erythematous and swollen and one the following day it was fluctuant. The abscess was incised and drained and methicillin therapy was started because of the clinical suspicion of *S aureus* 80/81 disease. Cultures of purulent material from the first and subsequent drainage grew pure cultures of *S aureus* 502A, phage type 7, 42E, 53, 55, 75/76, 81, 83A. The infant had no systemic signs of infection and continued to take formula and gain weight satisfactorily. The infection cleared and methicillin therapy was discontinued after eight days. There was no recurrence of disease in this patient.

Comment

In 1963 Shinefield et al[2] correctly predicted that on occasion illness due to the 502A strain of *Staphylococcus* might prove to be severe in an unusual baby. For this reason they cautioned against the "routine" use of bacterial interference programs in nonepidemic situations. Theoretically infants with deficiency of immune mechanisms or of leukocyte function would be at especial risk.

In the fatal infection reported here autopsy examination did not suggest a defect of humoral or cellular immunity but nothing is known about possible deficiency in leukocyte function or other aspects of host responsiveness. Other factors were contrib-

utory. The infant was premature by dates and had the characteristic features of an infant of a diabetic mother. Prematurity is, of course, associated with an increased risk of sepsis.[3] Hypoglycemia may coexist with sepsis of the newborn[4] but it is not clear whether it predisposes to sepsis. Presumably the infection was introduced by passage of the umbilical vein catheter through the contaminated umbilical stump. Transient bacteremias are known to occur by this means.[5] In retrospect, it might have been advisable to initiate antibiotic therapy when the umbilical catheter was introduced in anticipation of induced bacteremia since the umbilicus was known to be heavily contaminated. Whether this would have altered the outcome is speculative. *Escherichia coli* was present in addition to *S aureus* 502A in the antemortem and postmortem blood cultures and in culture of the peritoneum. Only the 502A strain was cultured from the meninges. *Escherichia coli* participated in the septic process; however, the septic emboli and clusters of gram-positive cocci seen in several tissues and the absence of gram-negative rods on microscopic sections at autopsy indicate that *S aureus* 502A played the dominant role in this patient's infection.

The involved bacteria were susceptible in vitro to the antibiotics used, but therapy was delayed until shortly before death because initial symptoms were attributed to hypoglycemia rather than to sepsis.

The abscess of the great toe was clearly due to *S aureus* 502A. The predisposing event was thought to be a self-inflicted skin abrasion which provided a portal of entry through the skin for the *Staphylococcus*.

In the eight previously reported experiences with bacterial interference programs in newborn nurseries the only lesions related to the 502A strain have been mild conjunctivitis and pustulovesicular lesions said to resemble erythema toxicum. Summarizing their preliminary experience and four nursery programs, Shinefield et al[2] stated that among 524 infants deliberately or spontaneously colonized with *S aureus* 502A only five lesions were related to the 502A strain. Three infants had mild conjunctivitis. Two infants had impetiginous lesions from which not only the 502A strain but *S aureus* 80/81 was isolated. The infecting inoculum to each site in those studies was 4,000 or fewer viable bacteria delivered by microburet.

Light et al[8] used between 2,000 and 50,000 *S aureus* 502A as inoculum to 470 full-term infants and to 114 premature babies. Fewer than 5% had pustules related to the 502A strain. Conjunctivitis was not mentioned. In a later outbreak Light et al[7] varied the inoculum size and found a statistically significant difference in the frequency of 502A disease. One group of 85 babies received an estimated 10 million viable bacteria at each site from a cotton swab dipped into broth solution containing 10^8 bacteria per milliliter. Twelve (14%) of the babies developed pustules from which 502A organisms were cultured. Among 687 infants receiving an estimated 25,000 bacteria at each site from broth contain 2.5×10^5 bacteria per milliliter only 24 (3.5%) developed pustules. Occasional infants were said to have conjunctivitis but exact data were not given.

Blair and Tull[9] used a large 502A inoculum with a swab moistened in broth containing 10^8 bacteria per milliliter and observed pustules due to the colonizing strain in 17 (34%) of 50 babies. They attributed this high incidence to increased number of mutants that occurred during culture transfers coupled with the large inoculum delivered. Albert et al[9] using an estimated 25,000 bacteria for inoculation mentioned that occasional infants had pustular lesions but gave no details.

Our experience of 4.7% incidence of pustular lesions among the inoculated babies (30/644) is similar to the 3.5% incidence observed by Light et al[7] when the same method of implanting the 502A strain was used.

There appears to be a direct relation between the frequency of pustular lesions due to *S aureus* 502A and the size of inoculum employed for attempted colonization. The incidence was 0.4% with inocula below 4,000 bacteria, up to 5% with approximately 25,000 inoculum size and 14% and 24% in the two situations in which approximately 10 million 502A organisms were employed. The frequency of positive "takes" is not significantly increased with increasing inoculum size,[7,10,11] as shown in the Table. Therefore, it would seem advisable to limit the inoculum in order to decrease the frequency of infectious complications. Our experience with only two instances of 502A lesions among 444 cross-infected infants, or 0.5%, suggests that the risk is lower in those who acquire the 502A strain spontaneously. Inoculum size may be

Frequency of "Takes"* in Relation to Inoculum of *S aureus* 502A

Authors	Method and No. of Organisms per Inoculum	Site of Inoculation	No. of Patients	Takes No.	Takes %
Shinefield et al[10]	Microburet 2,000-4,000	Nose	42	39	93
		Umbilicus	42	30	72
Boris et al[11]	Microburet 2,000-4,000	Nose	25	21	84
		Umbilicus	25	23	92
Light et al[7]	Cotton swab moistened with broth containing 2.5×10^4/ml (estimated 2,000-50,000)	Nose	584	530	91
		Umbilicus	584	520	89

* "Take" indicates presence of marker 502A strain detected at 24 hours after inoculation.

a factor in these cross-infections because one would suspect relatively small numbers of bacteria are involved in spontaneous acquisition.

Bacterial interference has been used in older individuals with chronic furunculosis. Lesions related to *S aureus* 502A have been noted in 11 of 587 patients (1.9%).[1] One diabetic patient had pyarthrosis due to the 502A strain. The other lesions were external otitis (one patient), impetigo (two patients), pustules (four patients), and styes (three patients). Drutz et al[12] reported that a patient with a chronic skin disorder developed multiple abscesses due to 502A. They speculated that topical steroid therapy may have been an important determinant in that unusual patient.

It is concluded that the risk of serious infection due to *S aureus* 502A is extremely low and its benefits as an effective means of aborting epidemics of serious staphylococcal disease due to more virulent strains far outweigh the small risk. The experience with a single fatal case of septicemia and meningitis emphasizes that ordinarily benign procedures may under unusual circumstances have unfortunate consequences. Perhaps more importantly, it should give one pause to perform umbilical vessel catheterization when the umbilicus is heavily colonized, even when those bacteria have low virulence potential.

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POLIOMYELITIS PRIOR TO AD 1850

An occasional physician surely must have pondered the question why a healthy child should suddenly become paralyzed in one or both limbs, with the added tragedy that this paralysis was apt to last throughout life. But, physicians and laymen alike were beset by so many imponderables about illness in the mid-19th century and before that they accepted these tragedies as inexplicable episodes which occurred in the natural course of man's journey through life. Paul JR: *A History of Poliomyelitis*. New Haven, Yale University Press, 1971.