Antibiotic treatment insufficient for established septic arthritis

Staphylococcus aureus experiments in rabbits

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We treated septic arthritis of the knee in 38 rabbits with cloxacillin i.m. once and twice daily combined with probenecid for 7 or 21 days, respectively, or with only cloxacillin i.m. thrice daily for 7 days. The animals were killed weekly in groups up to 5 weeks after inoculation. Aspirated cultures obtained after 4 days of treatment were always negative. Histologic specimens revealed progressive joint destruction, but at a slower rate after frequent treatment independent of the period. We concluded that antibiotic therapy alone could not prevent destruction of articular cartilage once bacterial arthritis was established.

A reproducsible model of septic arthritis in rabbits (Riegels-Nielsen et al. 1987) permits evaluation of cartilage destruction. We have used this model to compare the effects of different dosages and lengths of antibiotic treatment.

Animals and methods

Fifty-two rabbits (New Zealand white type SsC:CPH) weighing 3–4 kg were used. The right knees were inoculated with 10^3 *Staphylococcus aureus* phage type 3C (Riegels-Nielsen et al. 1987). After 72 hours, infection was verified by aspiration and bacterial culture. The left knee served as a control. Four rabbits died of intractable diarrhea, and were omitted from the study.

Group I (N 11) was treated for 7 days with intramuscular cloxacillin 50 mg/kg x 1 and probenecid 250 mg x 1 p.o. *Group II* (N 10) was treated for 7 days with intramuscular cloxacillin 50 mg/kg x 3. *Group III* (N 17) was treated for 21 days with cloxacillin i.m. 50 mg/kg x 2, the second dose combined with probenecid 250 mg p.o.

Microbial evaluation was performed by needle aspirations 48 and 96 hours after starting treatment. The rabbits were killed in groups of two to four — in Groups I and II after 10, 24, 27, and 35 days and in Group III weekly. Bacterial cultures of the joint fluid and synovial tissue were made. The leukocytes in the joint fluid were counted, the cartilage was examined (Riegels-Nielsen et al. 1987), and the loss of glycosaminoglycans was evaluated based on safranin staining (Rosenberg 1971). All the specimens were examined blindly by one author (PR-N). The Kruskall-Wallis test was used.

Results

The infected joints developed classical clinical signs of septic arthritis with positive cultures of *Staphylococcus aureus*. After 48 hours of treatment, only one knee (Group I) had a positive joint-fluid culture; but at 96 hours, all the cultures were negative, as were cultures of fluid and synovial tissue at the time of the rabbits' deaths. Further, bacteria were not visible extracellularly in the synovial membrane or intracellularly in the leukocytes. All the joints were distended with thin purulent exudate containing 10^6–10^{12} leukocytes/μL.

In all the knees the cartilage had lost its normal shiny appearance, and the synovial membrane was edematous with an inflammatory reaction. In half the knees, minor marginal erosions were visible in all the groups after 3 weeks. Microscopically, the specimens in each group exhibited greater variability in cartilage pathology, but without differences between the groups

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Table 1. Septic joint morphology according to the histologic-histochemical scoring system (Salter et al. 1981)

Group	Rabbit No.	Day of killing	Histologic-histochemical scoring[a] Cellularity	Erosion	Pannus	Safranin staining	Score
I	1	10	0	0	0	1	1
	2	10	0	1	0	2	3
	3	10	0	1	1	1	3
	4	24	1	1	0	2	4
	5	24	1	1	1	2	5
	6	27	1	2	2	3	8[b]
	7	27	1	1	2	2	6
	8	27	1	1	1	3	6
	9	35	1	1	0	3	5
	10	35	2	2	2	3	9[b]
	11	35	2	2	2	3	9[b]
II	12	10	0	1	0	1	2
	13	10	0	0	1	2	3
	14	10	0	1	1	1	3
	15	24	1	1	1	2	5
	16	24	1	1	1	2	5
	17	27	2	2	1	2	7
	18	27	0	1	1	2	4
	19	35	2	3	1	3	9[b]
	20	35	2	3	1	3	9
	21	35	1	1	1	1	4
III	22	7	0	0	0	2	2
	23	7	1	0	1	2	4
	24	7	0	0	0	1	1
	25	10	0	0	0	2	2
	26	10	1	0	0	2	3
	27	10	0	0	0	2	2
	28	18	1	1	1	3	6
	29	18	1	1	0	1	3
	30	18	1	1	0	2	4
	31	24	1	1	1	2	5
	32	24	1	1	0	3	5
	33	24	1	1	0	2	4
	34	27	1	1	1	2	5
	35	27	1	1	1	2	5
	36	27	1	1	1	3	6[b]
	37	35	1	1	0	2	4
	38	35	1	1	0	3	5

[a] Cloning was not observed in any knee.
[b] Vascular crossing of tidemark.

(Table 1). Vascular crossing of the tidemark was observed in five knees.

A time-dependent, slowly progressive score was observed, being especially pronounced for safranin stainability (Table 1). This indicated depletion of glycosaminoglycans, with a minor — but varying — loss during the first week, progressing to a severe loss after 3 weeks. The depletion was never total. Mitotic activity of the chondrocytes (cloning) was not observed in any specimen. The destruction progressed more slowly than in the untreated series (Riegels-Nielsen et al. 1987), being significant after 3 weeks. The difference in destruction between Groups I and III was significant after 3 weeks ($P < 0.003$).

Discussion

It is possible to ensure a concentration of antibiotics in the joint fluid (Dee and Kozin 1977, Hedström et al. 1984, Parker and Schmid 1971, Nelson 1971) and synovial membrane (Frimodt-Møller and Riegels-Nielsen 1987) well above the MIC value for most of the bacteria responsible for septic arthritis. Accordingly, antibiotics given before intraarticular bacterial inoculation may prevent infection (Smith et al. 1987) or necessitate a greater inoculum (Schurman et al. 1975).

In our series the antibiotic treatment was started after 48 hours of established infection, but before the onset of irreversible cartilage changes (Riegels-Nielsen et al. 1987). All the joints exhibited negative cultures after 2–4 days of therapy, which is more rapid than in other series (Bardenheier et al. 1966, Smith et al. 1987). The scoring system (Salter et al. 1981) for septic arthritis proved valuable for recording and comparing the cartilage changes that developed in spite of the early negative cultures. The system is, however, based on a subjective technique, and must be accepted with caution.

The integrity of the tidemark was broken only in a few knees and later than without treatment (Riegels-Nielsen et al. 1987). Although this sign is known from advanced arthrosis (Mankin et al. 1971, Farkas et al. 1987), it was not observed in all the specimens with high scores. Inclusion of tidemark integrity did not alter the result of the statistical analyses.

An early and progressive loss of glycosaminoglycans was also found by Smith et al. (1987) in spite of differences in determination. The depletion of glucosaminoglycans was definitely delayed and diminished compared with untreated joints (Riegels-Nielsen et al. 1987). The proteoglycan loss precedes erosion of the cartilage (Harris et al. 1972, Smith and Schurman 1983).

Antibiotics were thus unable to prevent cartilage destruction, a condition known as sterile progressive postinfectious arthritis (Goldenberg 1985). The causative factor may be lysosomal enzymes (Kobayashi and Ziff 1975) or antigenic bacterial debris (Cromartie et al. 1977, Hadler and Granovetter 1978).

The treatment in Group I with antibiotics given once a day was insufficient. We believe that bacteria may survive in small clusters in the synovium or pannus tissue, or even adhere to the cartilage collagen meshwork (Nade and Speers 1987), and thus are not accessible for the culture method we used. However, bacteria were not visible in any parts of the specimens. The result after 1 week of antibiotics administered thrice daily was comparable to 3 weeks of treatment, for practical reasons given only twice daily. The effect of the last dose

was prolonged with probenecid, which may explain this result.

The clinical consequence of our experiment is that antibiotic treatment of septic arthritis is insufficient; the therapy must also include some sort of joint lavage or even synovectomy.

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