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PERSPECTIVE

Use of serum antistreptolysin O titers in the microbial diagnosis of orthopedic infections

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Summary The utility of serologic tests in the microbial diagnosis of orthopedic infections is unknown. Antistreptolysin O titer determination is inexpensive and accurate in the diagnosis of β-hemolytic group A, C, and G streptococci. In patients with negative culture results and positive titers, antibiotics might be reduced to the narrowest spectrum, penicillin.

Introduction

Orthopedic infections present a heavy burden for patients and hospitals in terms of morbidity and associated costs. An accurate microbiological diagnosis is the key factor for successful antibiotic therapy, along with appropriate surgical intervention and a multidisciplinary approach.

Stain or culture for identification of bacterial pathogens must always be the first priority. Unfortunately the pathogens cannot always be identified,[1—3] frequently due to empirically initiated antibiotics prior to hospital admission. When the initial oral antibiotic regimen fails, clinicians feel obliged to change to another empirical agent that usually has an even broader spectrum than the first agent. Thus the advantages of a targeted antibiotic treatment such as lower costs, fewer adverse effects, and less antibiotic resistance are lost. Polymerase chain reaction (PCR) techniques for microbiological diagnosis are useful in partially treated infections, but are relatively expensive, not always available, and require specimens from sterile body sites to avoid contamination. PCR is rarely available in many clinical settings. Serologic tests in the timely diagnosis of acute musculoskeletal infections are useless.[4]

Although staphylococcal infections comprise up to two-thirds of orthopedic infections,[5,6] streptococci represent 7%[5] or 9%[6] of all causative pathogens in large series of orthopedic infections. We investigated the value of obtaining serum antistreptolysin O (ASO) titers in the diagnosis of orthopedic infections due to streptococci.

Materials and methods

The University Hospital of Geneva is a 2200-bed tertiary hospital with 41 000 annual admissions. The Orthopedic Sur-

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Table 1 Key characteristics of the patients with specimens for serum antistreptolysin O.

Patient	Sex	Age, years	Immunosuppression	Infection	Pathogens	Bacteremia	Delay, infection—ASO[a]	ASO titer[b]
1	M	44	-	Hip prosthesis	*Staphylococcus epidermidis*	-	57 days	<100
2	F	92	Diabetes	Hip prosthesis	*Staphylococcus epidermidis*	-	Unknown	<100
3	M	82	Diabetes, hepatic carcinoma	Diabetic foot infection, abscess	*Staphylococcus aureus*	-	40 days	<100
4	F	73	-	Knee arthritis	*Staphylococcus aureus*	-	12 days	<100
							15 days	<100
5	F	40	-	Knee arthritis	*Staphylococcus aureus*	-	105 days	<100
6	F	42	-	Tibial hardware	*Staphylococcus aureus*	-	32 days	200
							78 days	200
7	M	64	Diabetes	Hallux infection	*Staphylococcus aureus*	-	14 days	<100
8	M	66	Diabetes	Shoulder arthritis	*Staphylococcus aureus*	Yes	84 days	200
9	F	83	Diabetes, steroids for pulmonary fibrosis	Foot erysipela	*Staphylococcus aureus*	-	11 days	<100
10	M	47	Diabetes	Osteomyelitis femur, leg abscess	*Staphylococcus aureus*	-	5 days	<100
							12 days	<100
11	M	77	Diabetes	Diabetic foot infection, abscess	*Staphylococcus aureus*	-	12 days	<100
					Pseudomonas aeruginosa *Enterobacter cloacae*		19 days	<100
12	M	41	-	Calcaneal hardware	*Enterobacter cloacae* *Pseudomonas aeruginosa* *Enterococcus faecalis*	-	21 days	<100
13	F	73	Diabetes, Horton's disease	Foot erysipela	*Escherichia coli* *Klebsiella oxytoca*	-	16 days	<100
14	M	37	-	Arm phlegmon	*Peptostreptococcus spp*	-	9 days	<100
15	M	67	Diabetes	Leg erysipelas, cutaneous abscess	Group C β-hemolytic streptococci	-	3 days	100
16	F	80	-	Knee prosthesis	Group B β-hemolytic streptococci	Yes	9 days	110
							15 days	<100
17	M	21	-	Myositis leg	*Streptococcus pyogenes*	-	16 days	400
							18 days	500
18	M	63	-	Abscess leg	*Streptococcus pyogenes*	-	18 days	600
							24 days	600
							25 days	600
19	M	67	-	Thumb phlegmon	*Streptococcus pyogenes*	-	6 days	300
							8 days	600
							9 days	600
20	M	17	-	Foot abscess	Group C β-hemolytic streptococci	-	12 days	400
21	M	50	-	Knee arthritis	Group G β-hemolytic streptococci	Yes	7 days	600
							10 days	800

ASO, antistreptolysin O; M, male; F, female.
[a] Time delay between the clinical onset of infection and the day of the dosage of ASO.
[b] The cut-off for positive ASO titers is >200 U/ml.

gery Service has 119 acute care beds including a septic ward with 22 beds, and performed 5374 surgical interventions in 2007. We searched the septic orthopedic database for patients in whom the ASO titer was obtained along with species identification in the bacteriological laboratory. Inclusion criteria were adult patients with orthopedic-related infections and ASO titer samples during hospitalization for that infection. To be included, patients had to have had a

diagnosis of infection based on the presence of pus and the growth of pathogens in microbiological cultures obtained from intra-operative musculoskeletal biopsies or joint aspiration. Exclusion criteria were culture-negative infections, patients with infections other than orthopedic infections, patients with post-streptococcal reactive arthritis,[7,8] and patients with rheumatic fever[7,8] or sacroiliac joint disorders.[9,10]

The culture of pathogens was performed according to standard procedures.[11] The ASO kit was a semi-quantitative test with a cut-off value of 200 U/ml, and was based on neutralization of rabbit blood hemolysis by the patient's serum antibodies. The streptolysin O for hemolysis was purified from *Streptococcus pyogenes* cultures. The cost of one blood specimen for ASO titer (ASL-kit, bioMérieux Genève) was US$21.90.

Results

General

Data were retrospectively retrieved for 21 patients (seven females, 14 males; median age 64 years) with 21 musculoskeletal infections in whom ASO titer was performed in the calendar year 2008 (Table 1). All patients had signs of infection according to the inclusion criteria. The mean maximum C-reactive protein value was 117.4 mg/l (range 5—499 mg/l). More than one specimen was obtained for ASO titer determination in nine patients. The first specimen was obtained at a median of 13 days (range 3—105 days) after the clinical onset of infection, and the last specimen at a median of 16 days. Test results were available within 1 and 5 days.

In those patients without ASO elevation, median titers were 100 U/ml (range $<$ 100—200 U/ml).

Elevated ASO titers

Five patients had elevated ASO titers (11 specimens; median titer 600 U/ml, range 300—800 U/ml). These specimens were taken between day 6 and day 25, with a median value of 14 days for the first specimen. One patient with elevated titers had only one specimen sampled. Among the four other patients with elevated ASO titers and multiple specimens, the titers reached a plateau at day 8 and day 18 in two patients, respectively, while they continued to rise at day 10 and day 18 in two other patients, respectively. All five patients with elevated ASO titers were treated with intravenous penicillin or amoxicillin. All were cured with no recurrence during a follow-up period of at least three months.

The pathogens documented in the patients with elevated ASO titers were *S. pyogenes* (β-hemolytic streptococci of Lancefield group A; $n = 3$), β-hemolytic streptococci of group G ($n = 1$), and β-hemolytic streptococci of group C ($n = 1$). The pathogens of the patients without elevated ASO titers are shown in Table 1.

Discussion

In the diagnosis of musculoskeletal infections by ASO, we found that the titers were consistently elevated only in infections due to *S. pyogenes* (β-hemolytic streptococci of group A) and group G streptococci, and always negative for all other pathogens including Enterococcus, Peptostreptococcus, and β-hemolytic streptococci of group B. A negative ASO titer was also documented in one patient with group B arthritis.[12] For group C streptococci, ASO titers were positive in one patient and negative in another patient. The negative result may have been due to the fact that the specimen was obtained only 3 days after the onset of the infection and hence the time interval was too short for the antibodies to have risen. We found only one report describing high ASO titers in five patients with septic arthritis, however in the group with β-hemolytic streptococci, the ASO level, and other details were not reported.[9] We did not have any false-positive results, i.e., elevated titers in non-streptococcal infections.

Streptolysin O is an exotoxin that repels leukocytes and disrupts their membrane by pore forming or enzymatic attack on phospholipids. It is produced by group A, C, and G streptococci and *Streptococcus canis*.[13,14] The streptolysin O of *S. pyogenes* is within 90% genetic homology to the streptolysins of *S. canis* and of group C streptococci.[15] This explains why the ASO titers in our series were only elevated among A, C, and G streptococci and not in other streptococci or Enterococcus.

In the infectious disease literature, ASO titers have been used almost exclusively for epidemiological studies and the clinical diagnosis of *S. pyogenes* infection[16,17] and its sequelae, such as rheumatic fever, glomerulonephritis, and reactive arthritis after throat infections.[7—9] Gray et al. showed that a single ASO titer greater than 400 U/ml correlated with a sensitivity of 66% and specificity of 82% with upper respiratory tract infections due to *S. pyogenes* in adults.[17] According to the rheumatology literature, ASO titers may be elevated in non-infectious arthritis[9] and sacroiliac joint disorders in genetically susceptible patients.[10] β-Hemolytic streptococci may trigger reactive arthritis as well as rheumatic fever.[9] Consequently the distinction between reactive disease and pyogenic infection has to be made clinically, which generally is not difficult since orthopedic infections rarely affect sacroiliac joints symmetrically in adults.[12,18,19]

Limitations of our study include its retrospective design and small numbers of patients. Nevertheless, we think that ASO titers are of value in cases of severe orthopedic infections whenever microbiological cultures remain negative. ASO titer determination is relatively inexpensive and accurate in the diagnosis of β-hemolytic groups A, C, and G streptococci. These are the known pathogens in severe infections such as necrotizing fasciitis[20,21] and streptococcal shock syndromes.[20,22] Moreover, all three streptococci are sensitive to penicillin G or amoxicillin.[5,23] Therefore in patients with a compatible clinical presentation, negative culture results, and a positive result from titer evaluation, antibiotics might be reduced to the narrowest but highly active spectrum, i.e., penicillin. This attitude would support the standard policy to narrow the antibiotic spectrum as much as possible while preserving maximum activity, but it has yet to be confirmed in large prospective trials.

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