

# Septicemic Arthritis with Antibiotic Resistance: A Case Study

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**ABBREVIATIONS:** ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAZ = ceftazidime; CLA = clavulanic acid; CTX = cefotaxime; DIC = disseminated intravascular coagulation; ESBL = extended spectrum  $\beta$ -lactamase; MIC = minimum inhibitory concentration; PT = prothrombin time; PTT = partial prothrombin time.

**INDEX TERMS:** clinical testing for ESBL; extended spectrum beta lactamase; septicemic arthritis.

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## CASE PRESENTATION

A 59-year-old male presented to the hospital with complaint of increasing joint and overall body pain with no other outstanding signs and symptoms. He had a history of rheumatoid arthritis, type II diabetes, viral hepatitis, recent slow healing sternal wound infection from coronary artery bypass surgery, right diabetic foot ulcer with osteomyelitis caused by *Pseudomonas aeruginosa*, and a left foot amputation. He took 20 mg of prednisone daily for his arthritis. At the time of initial examination, he had no clear effusion, swelling of any joints or erythema. The patient described his symptoms to be consistent with his arthritis. He later developed large effusions in his knees that were warm to the touch with slightly warm, swollen ankles. Physicians thought that rheumatoid arthritis was the major physiological disorder in this case and ruled out septic arthritis, leading them to increase the patient's dose of prednisone to 40 mg/day. Despite efforts to control the suspected arthritis, the patient's joint pain worsened with swelling in his elbows. The patient also developed tachycardia, suspected to be from the pain. Physicians ordered blood and synovial fluid cultures while maintaining steroid therapy. The synovial fluid obtained was pus-like in consistency. The patient's health declined as he experienced increasing temperature and blood pressure and deteriorating mental status. The patient's laboratory results are listed in Table 1.

## DISCUSSION

The wound from the patient's amputation was colonized with *Staphylococcus aureus*. The organisms from his local infection seeded into his circulation, causing bacteremia as suggested by the positive blood cultures. Upon admission, the patient's WBC count was normal, indicating that his immune system was still capable of defending against the *Staph. aureus* that was present despite his daily doses of prednisone. The next set of differentials indicated that the increased dose of prednisone physicians administered suppressed the WBCs, which were being depleted in the defense against the already present bacteria.

## CLINICAL PRACTICE

As a result of bacteremia, the patient had an increased PTT and PT caused by DIC due to the consumption of essential clotting factors that are involved in coagulation. While a prolonged PTT may also be caused by cirrhosis due to the liver's inability to produce adequate coagulation factors, the patient's ALT and AST appeared to be normal, ruling out cirrhosis. While an increase in PT may be caused by DIC,  $\beta$ -lactam antibiotics have been observed to interfere with the PT, causing high results.<sup>1</sup>

When treated with the correct therapy (vancomycin and nafcillin), the patient's health improved. Unfortunately, with the continuation of prednisone and antibiotics, the *Staph. aureus* bacteremia was controlled but the steroid therapy decreased his immune system's ability to fight off nosocomial pathogens allowing *E. coli* proliferation. Autopsy findings showed signs supporting septicemia with multi-organ hemorrhages, calcification, and DIC.

### DIAGNOSIS

The patient had septicemic arthritis with an ESBL *E. coli*. The ESBL *E. coli* present was resistant to many  $\beta$ -lactam antibiotics. Table 2 shows the antibiotic susceptibility testing on the *E. coli* isolated from the patient's positive blood culture. The antibiotics given to the patient eliminated the *Staph. aureus* but allowed the *E. coli* to proliferate in the circulation. The antibiotics chosen were proven useless against this resistant organism. All laboratory results supported the septicemia. The patient expired six days after the initial isolation of *E. coli*.

### ANTIBIOTIC RESISTANCE

Many bacteria have mechanisms of resistance to different antibiotics. With every generation of antibiotics synthesized, bacteria are encouraged to develop resistance, causing detrimental outcomes on patient health.

**Table 1.** Patient laboratory data

Date of collection	Sample type	Organisms isolated	WBC results (x10 <sup>9</sup> /L)	Reference range	Test	Result	Reference range
1/15/2007	--	--	9.3	4.5-11	--	--	--
	--	--	--	--	--	--	--
1/16/2007	Blood (2 of 3)	<i>S. aureus</i>	--	--	--	--	--
	Synovial fluid	<i>S. aureus</i>	--	--	--	--	--
1/18/2007	Synovial fluid	<i>S. aureus</i>	--	--	--	--	--
	Blood	<i>E. coli</i>	--	--	--	--	--
1/19/2007	Synovial fluid	<i>S. aureus</i>	0.8	4.5-11	PTT (sec)	79	22-33
	--	--	--	--	PT (sec)	24	11-14
1/20/2007	Blood (2 of 2)	<i>E. coli</i>	0.4	4.5-11	--	--	--
	Tissue (knee)	<i>S. aureus</i>	--	--	--	--	--
	Synovial fluid	<i>S. aureus</i>	--	--	--	--	--
1/21/2007	Synovial fluid	<i>S. aureus</i>	--	--	AST (units/L)	9	5-34
	Wound	<i>S. aureus</i>	--	--	ALT (units/L)	7	7-52

Examples of antimicrobial resistant organisms include extended spectrum  $\beta$ -lactamase *Enterobacteriaceae*, methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococci* spp. (VRE), and penicillin resistant *Streptococcus pneumoniae*.  $\beta$ -lactamases excrete an enzyme that breaks the  $\beta$ -lactam ring (the functional portion shown in Figure 1) of the antibiotic, rendering it useless. Enzymatic inactivation by organisms is a common route for antibiotic resistance.

The most common method used to classify  $\beta$ -lactamases is the Bush and others classification, which includes twelve different classes of  $\beta$ -lactamases (Table 3). Clavulanic acid (derived from *Streptomyces clavuligerus*), a  $\beta$ -lactamase inhibitor is sometimes used synergistically with antibiotics (penicillins and cephalosporins) to overcome *in vitro* bacterial resistance to antibiotics. It competitively inhibits  $\beta$ -lactamases.<sup>2</sup>

Many different gene mutations contribute to bacterial resistance to  $\beta$ -lactams which includes plasmid mediated gene mutations for TEM and/ or the SHV (different series of enzymes found in *Enterobacteriaceae*),<sup>2</sup> The  $\beta$ -lactamases mentioned contain serine or zinc in the active site which contributes to breaking the  $\beta$ -lactam ring. The four important groups of  $\beta$ -lactamases include the ESBLs,  $\beta$ -lactamases that are unaffected by  $\beta$ -lactamase inhibitors, AmpC, and  $\beta$ -lactamases that break down carbapenem.<sup>3</sup>

In the 1970s and 1980s, second and third generation cephalosporins were synthesized and in 1983, ESBLs were discovered. The first reported outbreak of *Klebsiella* spp. ESBL was in Germany in 1983. Thereafter, other cases of nosocomial pathogens have been reported in Europe and the United States.<sup>4</sup> The first reported case of an ESBL organism in the United States happened in 1988.<sup>5</sup> To be considered an ESBL, the organisms must be able to break down third and fourth generation cephalosporins (cefotaxime, ceftriaxone, cefepime, and ceftazidime) as well as aztreonam. The enzymes the ESBL organisms synthesize are TEM - 1 and 2 (named after Temoneira in whom the organism was first found) and SHV - 1 (sulfhydryl variable). The mutations affect the amino acid sequence on the organism's active site.<sup>6</sup>

**CLINICAL TESTING FOR ESBL**

ESBL organisms may produce false results during *in vitro* testing. Many times with modern instrumentation and disk diffusion techniques, organisms may appear to be susceptible to third and fourth generation cephalosporins as well as aztreonam. A dilution of the organism is made and is then swabbed onto a Mueller Hinton plate. Usually, in antimicrobial susceptibility testing, the zone of inhibitions around the third and fourth generation cephalosporins and aztreonam is between 2-8 mm (susceptible = < 8 mm). If the zone is 8 mm, then an ESBL organism is suspected. A screening test is then performed with clavulanic acid. If the organism is an ESBL, the zone of inhibition will increase by at least 5 mm with clavulanic acid. A confirmatory test performed with a broth dilution will result in a decrease in MIC by  $\geq 3$  doubling dilutions.<sup>7</sup> Figure 2 shows a comparison of positive and negative ESBL plates.

Another test with a higher specificity assesses the breakdown of indicator drugs. Jacoby and Han developed a test based on a "double disk test in which a  $\beta$ -lactamase inhibitor potentiates activity of an indicator drug against an ESBL - producing strain" using oxyimino- $\beta$ -lactam antibiotics with 20 mg sulfate added.<sup>3</sup> An increase in the zone of inhibition by  $\geq 5$  mm with sulbactam compared to the antibiotic alone is a positive confirmation for an ESBL organism. An Etest may also be performed using strips impregnated with ceftazidime on one end and ceftazidime with clavulanic acid on the other. The results of the Etest are similar to broth dilutions in that ESBL organisms will yield a decrease of  $\geq 3$  doubling dilutions. The Vitek 2 can now perform ESBL testing on suspicious organisms as well.<sup>3</sup> With every new technological advance in antibiotic therapy, there will always be an organism that will be a match for the new antibiotic, resulting in the mutation of a fiercer strain of bacteria.

**Table 2.** Patient's *E. coli* antibiotic susceptibility test results

Antibiotic	Susceptibility	Interpretation
Amikacin	< 16	S
Ampicillin	> 16	R
Cefazolin	> 16	R
Tobramycin	8	I
Trimeth/Sulf	> 2/38	R
Gentamicin	> 8	R
Imipenem	< 4	S
Ceftazidime	> 16	R
Cefepime	< 2	S
Levofloxacin	> 4	R
Cefotetan	> 32	R
Ciprofloxacin	> 2	R
Ceftriaxone	32	I
Sulbactam/Ampi	> 16/8	R
Cefuroxime	> 16	R
Pipercillin/Ta	32	I

**PREVENTION**

Several factors may increase a person's risk of acquiring an infection with an ESBL organism. Prolonged hospital stays have been observed to increase risks of developing an infection. Data obtained from those who acquired an infection while in a hospital stayed for a range of 11-67 days. Heavy use of antibiotics may also increase a person's risk as does surgery and urinary catheters.<sup>6</sup>

In the case of the 59-year-old patient, many of these factors were present. Although his most recent stay at the hospital was only for nine days, it did not include his stay at the hospital two months prior for his amputation. Physicians made an empirical diagnosis of his arthritis and gave him a corticosteroid to control inflammation. After finding out about the *Staph. aureus* infection, physicians put him on a vancomycin and nafcillin without taking him off of prednisone. The steroids inhibited antibody production that made the patient more susceptible to nosocomial pathogens such as an ESBL organism.

**Table 3.** Bush and others' classification of  $\beta$ -lactamases

Groups	Antibiotic resistance	Characteristics
1	Cephalosporinases	Not inhibited by clavulanic acid
2	Penicillinases/ cephalosporinases	Inhibited by clavulanic acid
2a	Penicillinases	Contains just penicillinases
2b	Broad spectrum $\beta$ -lactamases	Can inactivate penicillins and cephalosporins at the same rate
2be	Extended spectrum $\beta$ -lactamases	Can inactivate third generation cephalosporins (ceftazidime, cefotaxime, and cefpodoxime) as well as monobactams (aztreonam)
2br	Inhibitor resistant $\beta$ -lactamases	Reduced binding to clavulanic acid and sulfate; inhibitor resistant TEM derivative enzymes; susceptible to tazobactam
2c	Carbenicillinases	Inactivate carbenicillin > benzylpenicillin; some effect on cloxacillin
2d	Cloxacillinases	Inactivates oxazolympenicillins (oxacillin, cloxacillin, dicloxacillin), cloxacillin > benzylpenicillin; some activity against carbenicillin; not inhibited by clavulanic acid; some ESBLs
2e	Cephalosporinases	Breaks down monobactams; inhibited by clavulanic acid
2f	Carbapenamase	Serine based carbapenamases
3	Metalloenzymes	Zinc-based $\beta$ -lactamases; breaks down penicillins, cephalosporins, and carbapenamams
4	Penicillinases	Not inhibited by clavulanic acid

**SUMMARY**

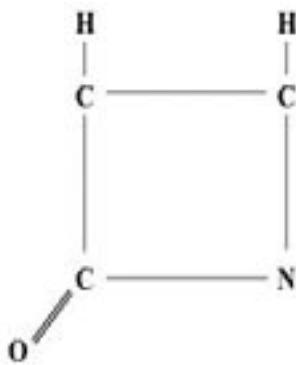
This article demonstrates how rheumatoid arthritis can be confused with septicemic arthritis. Effective diagnosis and treatment depends on timely and effective confirmation of the cause for arthritis. In the future, if such a case were presented, actions must be taken as soon as the bacteremia has been confirmed since the organism is the primary cause of the inflammation and not rheumatoid arthritis. If this is done immediately, the patient's body will be more effective at fighting off nosocomial infections resulting in a better prognosis.

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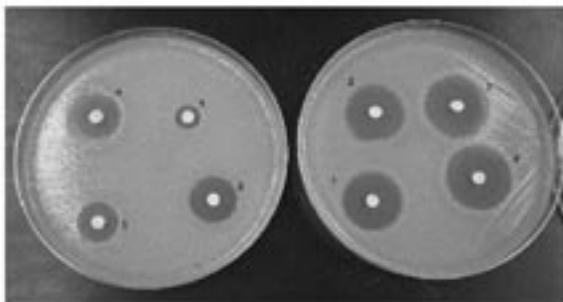
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**Figure 1.** β-lactam ring



**Figure 2.** Susceptibility testing for ESBL positive and negative organisms



1) CAZ 30 mg; 2) CAZ 30 mg/ CLA 10 mg; 3) CTZ 30 mg; 4) CTX 30 mg/ CLA 10 mg. Left = positive organism, right = negative organism