Antibiotic resistance has become an immense problem in both hospitals and the community. However, management of orthopedic-related hardware infections is becoming a more difficult issue as traditional treatment is not enough to eradicate these infections. Enterobacteriaceae often produce extended-spectrum beta-lactamase (ESBL) enzymes (ESBL), which is the resistance mechanism used by these bacteria that prevents the successful antimicrobial treatment of these infections. The classification of ESBL is based on the amino acid sequence. Multiple comorbidities, antibiotics, decubitus ulcers, and the presence of orthopedic hardware, such as external fixators, are all risk factors for ESBL infections. The incidence of infections caused by ESBL-producing Enterobacteriaceae has increased significantly in recent years. This increase in the number of community- and hospital-acquired infections has resulted in an increase in the morbidity and level of difficulty in managing these infections.

The most frequently isolated microorganisms in orthopedic prosthetic joint infections (PJI) are gram-positive cocci, including Staphylococcus aureus and coagulase-negative staphylococci. However, gram-negative bacteria constitute 10% to 23% of all cases. The clinical outcomes of gram-negative PJI are less favorable than those caused by gram-positive bacteria. There is little published data on the clinical outcomes of orthopedic-related devices (ORD) placed via open reduction and internal fixation (ORIF) and prosthetic joints in this group of patients.

Prosthetic joint surgeries, including total hip arthroplasty (THA) and total knee
arthroplasty (TKA), account for a significant portion of all prosthetic joints. More than 800,000 TKAs are performed annually in the United States, and the demand for these surgeries is projected to increase significantly in the next 20 years. However, almost 2% of these primary arthroplasties get infected and result in significant morbidity, mortality, and increased costs to the health care system compared with noninfected arthroplasties.

Four local hospitals in the current authors’ region each perform an average of 400 prosthetic joint and 400 to 600 ORD (primarily ORIF) procedures annually. This study examined the clinical characteristics and outcomes of PJI in TKA and THA, and ORD infections (primarily intramedullary rods placed in ORIF procedures) infected with ESBL organisms during a 5-year period in these 4 hospitals.

Materials and Methods
A retrospective chart review was conducted for patients 18 years and older who were admitted to 4 local hospitals for ORD infections related to ORIF or PJI from January 2010 through March 2015. Cases of orthopedic surgeries complicated by ESBL infections were identified for review using data reported by the hospital microbiology laboratory and cross-referencing with International Classification of Diseases, Ninth Revision (ICD-9) codes pertaining to postoperative orthopedic and prostheses infections (eg, 996.6x, 996.66). Data sources included inpatient electronic medical records and paper charts.

Inclusion and Exclusion Criteria
Patients 18 years and older who were admitted to 4 local hospitals between January 1, 2010, and March 1, 2015, with an ESBL organism isolated peroperatively or intraoperatively from an ORD or PJI associated with TKA and THA were included in the study. Both polymicrobial and monomicrobial infections were included if an ESBL organism was identified. Prosthetic joint infections were defined using the International Consensus definition on periprosthetic joint infections provided by the Musculoskeletal Infection Society. Patients with orthopedic infections unrelated to prosthetic joints or orthopedic devices, and orthopedic infections without the isolation of an ESBL organism were excluded from the study.

Data Collected
The following definition of PJI and ORD infections was applied: evidence of local infection to the area, which included redness and drainage from the site, and intraoperative evidence of infection into the joints; isolation of microorganisms from the area during surgery; or having cultured the organism from a sterile aspiration of the site. Information collected included demographic data, comorbidities, clinical features, wound/blood/urine culture results with identification and sensitivities of the isolated organisms, diagnostic imaging, type of hardware or prosthesis placed, surgical procedures involved, antibiotic type and duration, and patient outcome (Table).

Clinical features assessed included fever, leukocytosis, elevated inflammatory markers, and the presence of erythema, drainage, edema, warmth, and pain at the site of infection. Outcomes assessed were the resolution or cure of infection defined by negative clinical evidence of infection at the surgical site after 30 to 60 days of follow-up with normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Outcome failure was defined as persistence of clinical infection at the surgical site with elevated ESR and CRP requiring the extended use of antibiotics, surgery, or both. Descriptive statistics were obtained using median, averages, and proportions.

Results
Six cases of ESBL-producing Enterobacteriaceae were identified at 4 local hospitals between 2010 and 2015. Each hospital performed more than 400 cases of prosthetic joint replacements and 400 to 600 ORD surgeries each year. The total number of prosthetic and ORD cases was 6040. There was a total of 156 cases of documented infections (2.5%). The majority of these infections were due to gram-positive S. aureus and coagulase-negative Staphylococcus, followed by gram-negative pathogens, Escherichia coli, Klebsiella species, and other Enterobacteriaceae. Polymicrobial infections also were noted. Of these infections, 6 infections with ESBL Enterobacteriaceae (3.8%) were isolated that met the inclusion criteria (Table).

All 6 patient records were reviewed. The patients were 5 women and 1 man with a median age of 74 years (range, 68-86 years). The comorbidities reported in these patients were hypertension, diabetes, and cirrhosis. The median duration of follow-up was 45 days (range, 30-60 days) with an average follow-up of 60 days. The ESBL pathogens identified were ESBL E. coli in 5 patients and ESBL Klebsiella pneumoniae in 1 patient. Three of these infections were polymicrobial and 3 were monomicrobial.

Two of the patients had open fractures, and 1 patient had a closed fracture. This posed a problem with identifying the major pathogen in the study. Procedures performed on these patients were 1 THA, 4 TKAs, and 2 ORIFs. In 1 THA, ESBL K. pneumoniae was isolated, and in 4 TKAs, ESBL E. coli was isolated. Hardware initially was retained in all cases with intravenous antibiotic therapy alone. Because this study is retrospective, it was assumed that the orthopedic physicians were allowing time for bone healing to occur before removal of the device. There was 100% failure of therapy for incision and drainage procedures with initial retention of hardware.

Carbapenems were initiated for all patients after the ESBL organism was identified and isolated with appropriate coverage of all organisms in polymicrobial
cultures. After carbapenem was initiated, patients received a median duration of 42 days (range, 42-56 days) of antibiotic therapy. Eventual hardware removal was required due to failure of antibiotic therapy; hardware was removed an average of 30 to 45 days after the start of carbapenem therapy. Resolution of infection occurred a median of 30 days (range, 30-42 days) after hardware removal and carbapenem therapy. Imipenem was used in 2 patients, ertapenem was used in 3 patients, and meropenem was used in 1 patient.

After an initial attempt was made to salvage the ORD or the prosthetic joint, it took approximately 60 to 90 days before failure was noted. Too few cases were identified for statistical significance, but there was no difference in the outcome based on comorbidities, type of carbapenem used, polymicrobial vs monomicrobial etiology of infection, or the type of prosthesis infected. The clinical parameters such as clinical evidence of infection, ESR, and CRP improved 7 to 14 days after removal of the hardware and initiation of antibiotics.

Table

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Comorbidities/Risk Factors</th>
<th>Clinical Presentation</th>
<th>Diagnostic Findings</th>
<th>Treatment and Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/80</td>
<td>Bilateral TKA CAD, HTN, CVD with neurological deficits, chronic venous stasis, arthritis</td>
<td>Left leg wound infection/open</td>
<td>ESBL Escherichia coli, Pseudomonas aeruginosa, Alcaligenes species</td>
<td>Initial: ciprofloxacin and vancomycin Changed to: only imipenem/cilastatin 500 mg every 8 h IV started; D/C for 30 d</td>
</tr>
<tr>
<td>2/F/74</td>
<td>Right knee hardware repair, ORIF, s/p fracture 6 mo prior HTN, cirrhosis</td>
<td>Bilateral sacral and hip wound infections/open</td>
<td>ESBL E coli, Klebsiella pneumoniae</td>
<td>Initial: ceftriaxone 2 g every 24 h IV, levofloxacin 750 mg IVQD, metronidazole 500 mg every 8 h IV, vancomycin 1942.5 g every 12 h IV Changed to: vancomycin 1 g every 12 h IV + piperacillin/tazobactam 4.5 g every 8 h IV D/C on ertapenem 1 g every 24 h for 4 wk</td>
</tr>
<tr>
<td>3/F/77</td>
<td>MVA 1 mo prior with pelvis fracture with reduction, internal fixation, and iliosacral screws × 2 HTN, DM</td>
<td>Left hip wound infection/closed</td>
<td>ESBL K pneumoniae, E coli, Bacteroides fragilis Surgical: multiple I&amp;D</td>
<td>Initial: vancomycin 2 g × 1 IV + piperacillin/tazobactam 4.5 g × 1 IV Changed to: ceftriaxone 1 g every 24 h IV × 10 d + imipenem/cilastatin 500 mg every 8 h IV for 14 d</td>
</tr>
<tr>
<td>4/M/72</td>
<td>DM, OA</td>
<td>Right TKA cellulitis Admission laboratory values: WBC, 10.2; CRP, 10.2; ESR, 76</td>
<td>ESBL E coli Surgical: revision of TKA (2 stage)</td>
<td>IV ertapenem for 6 wk</td>
</tr>
<tr>
<td>5/F/68</td>
<td>HTN, OA</td>
<td>Right ORIF tibia nonhealing wound at operative site, open</td>
<td>ESBL E coli Surgical: I&amp;D with hardware removal</td>
<td>IV ertapenem for 6 wk</td>
</tr>
<tr>
<td>6/F/86</td>
<td>OA, dementia</td>
<td>Right TKA infection Admission laboratory values: WBC, 13.4; CRP, 0.4; ESR, 68</td>
<td>ESBL E coli Surgical: removal of TKA (2 stage)</td>
<td>Meropenem for 6 wk</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; CVD, cardiovascular disease; D/C, discontinue; DM, diabetes mellitus; ESBL, extended-spectrum beta-lactamase; ESR, erythrocyte sedimentation rate; F, female; HTN, hypertension; I&D, irrigation and debridement; IV, intravenous; IVQD, intravenous daily; M, male; MVA, motor vehicle accident; OA, osteoarthritis; ORIF, open reduction and internal fixation; s/p, status post; TKA, total knee arthroplasty; U/A, urinalysis; WBC, white blood cells.
**Discussion**

In 2014, more than 1 million total prosthetic joint surgeries were performed worldwide, and in the United States, approximately 800,000 TKAs and THAs are performed each year. Prosthetic joint infections are the most common and devastating complication of prosthetic arthroplasty surgeries, with an incidence ranging from 1% to 4% after primary TKA and 1% to 2% after primary THA.9-13 Revision surgeries carry an even higher incidence of PJI, occurring in up to 15% of these cases.4

Gram-positive bacteria account for more than 50% of all PJI. *S aureus* and coagulase-negative staphylococci are the 2 most common organisms, with incidence rates of 24% to 43% and 12% to 26%, respectively.9,13 There has been a significant increase in resistant gram-negative bacteria, and this has been a major cause of concern. This is especially true for patients with infected prosthetic joints. Gram-negative bacilli, although not as common, occur in 3% to 10% of PJI cases.9,13 *E coli*, *Enterobacter* species, *Pseudomonas* species, *Proteus* species, and *Klebsiella* species are some of the most common gram-negative bacteria associated with PJI.13

The prevalence of ESBL infections in the world ranges from 26% to 60%, depending on where the study was conducted.3 Currently, there are no data on orthopedic ESBL infections.3 In the United States, the prevalence of ESBL infections is 5.3% to 9%.3

In a study conducted by Martinez-Pastor et al2 describing ESBL-infected prosthetic joints, the most common demographic observed was obese (body mass index > 30 kg/m²) women with a median age of 66 years and multiple comorbidities. Comorbidities included renal failure, diabetes mellitus, and liver cirrhosis. Of 132 PJI, 5.3% were associated with ESBL organisms.3 Four patients failed treatment with irrigation and debridement and antibiotic therapy, which resulted in a high failure rate of 57.2% for ESBL-infected prosthetic joints.2

The current study yielded similar demographics with a female predominance, median age of 74 years (range, 68-86 years), and multiple comorbidities (Table). Hypertension, diabetes mellitus, and liver cirrhosis were the most common comorbidities in the current study. The failure rate without removal of the hardware was almost 100%; however, all of the patients did well with removal of hardware and appropriate antibiotic therapy.

Certain risk factors, which include corticosteroid use, rheumatoid arthritis, and increased body mass index, are associated with PJI. Patients undergoing TKA are at a slightly higher risk than those undergoing THA, and *S aureus* and coagulase-negative staphylococci are the most common causes of PJI.6 An average of 5% to 23% of cases that become infected are the result of gram-negative bacteremia, especially in the elderly population.14-16

Production of device-related biofilms is common in both gram-negative and gram-positive bacteria, which protect the organism against many antimicrobial agents.17 Much of the difficulty in eradicating the infection is related to the slime-forming biofilm that complicates both the ability of the antimicrobials to eradicate the film and the rate of diagnosis due to the bacteria conglomerating and subsequently lowering the culture yield.18,19

Of note, sonication of the explanted prosthesis aids in higher culture results and should be used if this is suspected.18 Martinez-Pastor et al2 reviewed 5076 cases of arthroplasties between 2000 and 2007 and found a total of 132 infections (2.6%). Seven of the 132 infections (5.3%) were due to ESBL-producing *Enterobacteriaceae*. *E coli* was found in 6 cases, and *K pneumoniae* in 1. All of the patients received intravenous antibiotics with open debridement and retention of the implant as the first surgical approach. Interestingly, relapse was documented in 4 of the 7 cases with remission in 3, resulting in a global failure rate of 57.2%.2 In contrast to the Martinez-Pastor et al2 study, the success rate for staphylococcal acute PJI treated with open debridement without the removal of the implant and a prolonged course of antibiotics is reported to be approximately 75%.16,20-24

The success rate in the Martinez-Pastor et al2 study was 28.5% using intravenous carbapenems. It would be useful to combine a fluoroquinolone along with a beta-lactam antibiotic to treat these infections; however, in many cases, this is not possible as the organisms are resistant to the quinolones. Extended-spectrum beta-lactamase and carbapenem-resistant organisms have been reported in a small percentage of cases involving prosthetic joints.2-4 The successful management of ESBL infections depends on a combination of antimicrobial and surgical therapy. Because this infection is rare, there are no recommendations regarding the duration of antimicrobial therapy; however, the average duration seems to be between 6 and 8 weeks.

There does not appear to be a current standard of care in the management of these patients in terms of a 1-stage revision, 2-stage revision, or a modification of a 1-stage revision with the polyethylene components being retained in place. However, incision and drainage with retention of the prosthesis does not appear to work in these patients as previously described. In a case series of 53 patients with PJI secondary to a gram-negative pathogen, the prosthesis survival rate was 20% in 2 years with debridement and retention of the prosthesis.25 It is evident that for treatment to be successful in these cases, removal of the hardware with appropriate initiation of intravenous antibiotics for a prolonged period of time is necessary. Reimplantation should occur only after lack of residual infection has been documented. Sonication of the explanted hardware could prove to be useful in these cases to detect the specific type of infection. The use of intra-articular antibiotics has shown a success rate of approximately 87%, but little data exist using this method with ESBL PJI.26
However, even if the affected hardware is removed, antibiotic selection can be challenging. Without any randomized controlled trials targeting the treatment of infections with ESBL-producing organisms, most recommendations are based on in vitro and observational studies. In vitro studies have shown that the carbapenems as a class have the most consistent activity against ESBL-producing organisms and are widely considered the drugs of choice for these infections.\textsuperscript{27-30}

Antibiotics such as fosfomycin and nitrofurantoin also have been shown to be effective against ESBL-producing organisms; however, they are only effective for uropathogens because of their systemic distribution. Other antibiotic classes, such as cephalosporins and fluoroquinolones, usually are not an option for treatment as resistance to these antibiotic classes is associated with ESBL production.\textsuperscript{27-30}

Tigecycline, a glycylcycline with in vitro bacteriostatic activity, may be an alternative to carbapenems for ESBL-associated infections. Tigecycline susceptibility rates up to 97.5\% have been reported in a hospital and community area of influence in Madrid, Spain.\textsuperscript{27} Tigecycline would be especially helpful in PJI due to its high volume of distribution and tissue penetration. Despite these approaches, the risk of failure is still high and considerable.

**Conclusion**

Despite ESBL being an uncommon pathogen in ORD and PJI, the salvage rates of these infections remain poor. With the small number of patients documented in the literature, including the 7 patients from the study by Martínez-Pastor et al,\textsuperscript{2} it appears that ESBL *E coli* is the most common pathogen of these infections. However, with the small number of cases described in the literature, it is difficult to define the clinical characteristics, risk factors, and outcomes in these patients. In addition, simple irrigation and debridement does not appear to be sufficient to cure these infections. For this reason, a combination of hardware removal and carbapenems should be used in all cases. The prolonged period that occurs may be avoided by removal and treatment with an appropriate antibiotic, thereby reducing morbidity, time, and cost.

This study is limited by its retrospective nature, small size, and short follow-up. However, in this study, all ESBL-infected prosthetic joints and ORD failed management with antibiotic therapy alone and subsequently required removal of the hardware to cure the infection. Hence, appropriate early surgical management at identification of infection by an ESBL or resistant gram-negative organism appears to be an important factor in treatment. In patients with carbapenem resistance or intolerance, fosfomycin or tigecycline may need to be considered as an alternative approach.

**References**

23. Legout L, Senneville E, Stern R, et al. Treat-


