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**Selection of an Appropriate Empiric Antibiotic Regimen in Culture-Negative
Hematogenous Vertebral Osteomyelitis**

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29 **Running head:** Empiric antibiotics for vertebral osteomyelitis

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38 The aim of this study was to determine which antibiotic combinations are appropriate for
39 culture-negative hematogenous vertebral osteomyelitis (HVO), based on the antibiotic-
40 susceptibility pattern of organisms isolated from cases of culture-proven HVO. We conducted
41 a retrospective chart review of adult patients with microbiologically proven HVO in five
42 tertiary-care hospitals over a 7-year period. The appropriateness of empiric antibiotic
43 regimens was assessed based on the antibiotic susceptibility profiles of isolated bacteria. In
44 total, 358 cases of microbiologically proven HVO were identified. The main causative
45 pathogens identified were methicillin-susceptible *Staphylococcus aureus* (33.5%), followed
46 by methicillin-resistant *S. aureus* (MRSA) (24.9%), aerobic gram-negative bacteria (21.8%),
47 and *Streptococcus* species (11.7%). Extended spectrum β -lactamase (ESBL)-producing
48 *Enterobacteriaceae* and anaerobes accounted for only 1.7% and 1.4%, respectively, of the
49 causative pathogens. Based on the susceptibility results of isolated organisms, levofloxacin
50 plus rifampicin was appropriate in 73.5%, levofloxacin plus clindamycin in 71.2%, and
51 amoxicillin-clavulanate plus ciprofloxacin in 64.5% of cases. These oral combinations were
52 more appropriate for treating community-acquired HVO (85.8%, 84.0%, and 80.4%,
53 respectively) than healthcare-associated HVO (52.6%, 49.6%, and 37.6%, respectively).
54 Vancomycin combined with ciprofloxacin, ceftriaxone, ceftazidime, or cefepime was
55 similarly appropriate (susceptibility rates of 93.0%, 94.1%, 95.8%, and 95.8%, respectively).
56 In conclusion, in a setting with a high prevalence of MRSA HVO, oral antibiotic
57 combinations may be suboptimal for treatment of culture-negative HVO and should be used
58 only in patients with community-acquired HVO. Vancomycin combined with fluoroquinolone
59 or a broad-spectrum cephalosporin was appropriate in most cases of HVO in this study.

60

61 **Keywords:** Vertebral osteomyelitis; spondylitis; antibiotic; treatment; resistance

62

63 The incidence of vertebral osteomyelitis has increased over recent years, likely due to longer
64 life expectancies, higher prevalence of chronic disease, and more effective diagnostic
65 techniques (1-4). Furthermore, healthcare-associated infections, such as catheter-related and
66 device-related bloodstream infections, also increase the risk of vertebral osteomyelitis (5, 6).
67 Identification of microorganisms is crucial to guide appropriate antibiotic therapy for
68 vertebral osteomyelitis, but causative microorganisms are frequently not identified. Some
69 authors recommended a second percutaneous needle biopsy in patients with negative blood
70 culture and initial biopsy results, but a microbiological diagnosis was still not achieved in
71 almost one-quarter of cases (7, 8). The incidence of vertebral osteomyelitis without
72 microbiological diagnosis has increased in recent years (1, 3). However, the optimal empiric
73 antibiotic regimens for culture-negative vertebral osteomyelitis have yet to be determined.

74 The selection of an empiric antimicrobial regimen for vertebral osteomyelitis with no
75 microbiological diagnosis should be based on consideration of the most likely causative
76 pathogens and knowledge of local susceptibility patterns. The aim of this study was to
77 evaluate the appropriateness of empiric antibiotic regimens suggested for treatment of
78 culture-negative hematogenous vertebral osteomyelitis (HVO) using the susceptibility data of
79 pathogens isolated from cases of culture-proven HVO. We hypothesized that patients with
80 healthcare-associated HVO would more frequently be infected with antibiotic-resistant
81 organisms than those with community-acquired HVO. Therefore, the appropriateness of
82 empiric antibiotic regimens was also assessed according to the risk of healthcare-associated
83 infection.

84

85 **METHODS**

86 **Study design and setting**

87 This observational cohort study was undertaken at five tertiary-care hospitals in the Republic
88 of Korea, and included all adult patients diagnosed with HVO from January 2005 to
89 December 2012. The study was conducted using the format recommended by the
90 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines
91 (9). This study was approved by the Institutional Review Board of Gyeongsang National
92 University Changwon Hospital (GNUCH 2018-05-010).

93

94 **Inclusion and exclusion criteria**

95 Adult patients (≥ 16 years of age) who presented with microbiologically proven HVO were
96 included in this study. The diagnosis of HVO was established using previously published
97 criteria (10, 11), which included compatible clinical features, radiological evidence of
98 vertebral osteomyelitis, and microbiologic demonstration of bacterial pathogens, either from
99 the site of infection itself (*e.g.*, abscess, intervertebral disc, or vertebral bone) or in the blood.
100 Possible skin contaminants, such as coagulase-negative staphylococci (CoNS) and
101 *Propionibacterium acnes*, were considered as true pathogens if they were isolated from ≥ 2
102 surgical, percutaneous biopsy, or blood cultures. Cases were excluded if there was a
103 nonhematogenous source of vertebral infection, which included (1) penetrating trauma, (2)
104 previously placed hardware, (3) laminectomy within 1 year prior to the vertebral
105 osteomyelitis diagnosis, or (4) the presence of a stage 3–4 decubitus ulcer at the time of
106 diagnosis (10, 11). Cases of tuberculous, brucellar, and fungal vertebral osteomyelitis were
107 excluded.

108

109 **Data collection**

110 Medical records were reviewed retrospectively for demographic information, underlying
111 illness/conditions, presumed source of infection, diagnostic work-up, clinical presentation,
112 and laboratory and radiological data. The present study builds on our previous work on the
113 optimal duration of antibiotic therapy in patients with HVO (10).

114

115 **Microbiological analysis**

116 The species and susceptibility profiles of all isolates were confirmed using either the Vitek2
117 (bioMérieux, Marcy-l'Etoile, France) or Microscan (Dade Behring Inc., Deerfield, IL)
118 automated systems. The susceptibility to 12 antibiotics, alone or in combination, was
119 assessed (amoxicillin-clavulanate, ciprofloxacin, levofloxacin, clindamycin, rifampin,
120 trimethoprim-sulfamethoxazole, fusidic acid, cefazolin, ceftriaxone, ceftazidime, cefepime,
121 and vancomycin). Isolated strains were categorized by the Clinical Laboratory Standard
122 Institute (CLSI) guidelines as susceptible, intermediate, or resistant to antimicrobial agents
123 (12). Given the risk of treatment failure for intermediate strains, strains classified
124 “intermediate” were reclassified as resistant. If the susceptibility results for surgery,
125 percutaneous biopsy, and blood cultures were different, overall susceptibility was classified
126 resistant.

127 The appropriateness of eight antibiotics, alone or in combination, for empiric treatment of
128 HVO were analyzed: three fluoroquinolone-based oral combinations (levofloxacin plus
129 rifampin, levofloxacin plus clindamycin, ciprofloxacin plus amoxicillin-clavulanate), four
130 vancomycin-based intravenous combinations (vancomycin plus ciprofloxacin, ceftriaxone,
131 ceftazidime, and cefepime), and cefazolin monotherapy. For *Staphylococcus* species, overall
132 susceptibility to fluoroquinolone-based combinations was classified as susceptible if the
133 organisms were susceptible to both antimicrobial agents (8, 13), except for clindamycin. For

134 all other species, strains were considered susceptible if they showed susceptibility to at least
135 one of the antimicrobial agent combinations.

136

137 **Definitions**

138 HVO was classified as community-acquired or healthcare-associated HVO according to
139 published criteria (5). Healthcare-associated HVO was defined as (i) onset of symptoms after
140 1 month of hospitalization with no evidence of vertebral osteomyelitis at admission, (ii)
141 hospital admission within 6 months before symptom onset, or (iii) ambulatory diagnostic or
142 therapeutic manipulations within 6 months before symptom onset (long-term central venous
143 catheter use, arteriovenous fistula for hemodialysis, invasive intravascular techniques,
144 urological, gynecological or digestive procedures, and cutaneous manipulations). Cases that
145 did not meet any of the above criteria were classified as community-acquired HVO (5).

146

147 **Statistical analyses**

148 Categorical variables are expressed as numbers and percentages and were compared by χ^2 or
149 Fisher's exact test. Continuous variables are expressed as medians and interquartile ranges
150 and were compared using Mann-Whitney U test. All statistical tests were two-tailed, and $P \leq$
151 0.05 was considered to indicate statistical significance. All statistical analyses were
152 performed using SPSS for Windows software (ver. 18.0; SPSS, Inc., Chicago, IL).

153

154 RESULTS

155 In total, 370 patients with microbiologically proven HVO were identified during the study
156 period. Of the 370 cases, 12 were excluded due to incomplete medical records and 358 were
157 included in the final analysis.

158

159 Patients' characteristics

160 The demographic and baseline characteristics of the patients are displayed in Table 1. The
161 median age of the cohort was 65 years, and 186 (52.0%) were males. The most common
162 underlying condition was diabetes (29.3%), followed by liver cirrhosis (9.2%) and
163 malignancy (8.7%). According to the predefined criteria, 225 (62.8%) cases were
164 community-acquired HVO and 133 (37.2%) were healthcare-associated HVO.

165

166 Microbiological findings

167 Of the 358 cases with microbiologically proven HVO, 93 (26.0%) were identified by
168 diagnostic biopsy, 173 (48.3%) by blood cultures, and 92 (25.7%) by both. The most
169 frequently isolated organisms were methicillin-susceptible *Staphylococcus aureus* (MSSA)
170 (33.5%), follow by methicillin-resistant *S. aureus* (MRSA [24.9%]), aerobic gram-negative
171 bacteria (21.8%), and *Streptococcus* species (11.7%; Table 2). Of 78 aerobic gram-negative
172 bacteria, *Enterobacteriaceae* was responsible for 69 (88.5%) cases and other gram-negative
173 bacteria for 9 (11.5%) cases. Of 42 *Streptococcus* species, viridans group streptococci were
174 the most frequently isolated organisms (50.0%), followed by *Streptococcus agalactiae*
175 (35.7%), and *S. pneumoniae* (9.5%). CoNS, *Enterococcus* species, and anaerobes accounted
176 for 2.8%, 2.8%, and 1.4%, respectively.

177 There were some differences in the proportions of pathogens between community-acquired
178 HVO and healthcare-associated HVO. MRSA was more frequent in healthcare-associated

HVO than in community-acquired HVO (43.6% vs. 13.8%; $P < 0.001$), but MSSA was more frequent in community-acquired HVO than in healthcare-associated HVO (44.0% vs. 13.8%; $P < 0.001$). *Streptococcus* species were more frequent in community-acquired cases than in healthcare-associated cases (16.0% vs. 4.5%; $P = 0.001$). The rate of blood culture-proven cases among all culture-proven cases was 81.7% in *S. aureus* HVO, 71.8% in gram-negative bacterial HVO, and 61.9% in streptococcal HVO.

185

186 **Antimicrobial susceptibility profiles of isolated organisms**

The antimicrobial susceptibility testing results of isolated microorganisms are shown in Table 2. About 95% of MSSA isolates were susceptible to fluoroquinolones, compared to only half of the MRSA isolates. Of 69 *Enterobacteriaceae* isolates, 18 (26.1%) were resistant to ciprofloxacin, and 6 (8.7%) were extended-spectrum β -lactamase (ESBL) producers. All of the remaining nine gram-negative bacteria, including five *Pseudomonas aeruginosa* isolates, were susceptible to ciprofloxacin. Of 42 *Streptococcus* species isolates, 40 (95.2%) were susceptible to amoxicillin-clavulanate and 38 (90.5%) were susceptible to levofloxacin. Of the 10 CoNS isolates, 5 (50%) were methicillin-resistant.

195

196 **Relevance of empirical antibiotic regimens for culture-negative HVO**

The relevance of empiric antibiotic regimens for culture-negative HVO is shown in Table 3. Based on the susceptibility results of isolated organisms, levofloxacin plus rifampicin was appropriate in 73.5% of cases, levofloxacin plus clindamycin in 71.2% of cases, and amoxicillin-clavulanate plus ciprofloxacin in 64.5% of cases. These oral combinations were more appropriate for community-acquired HVO (85.8%, 84.0%, and 80.4%, respectively) than healthcare-associated HVO (52.6%, 49.6%, and 37.6%, respectively). After excluding 25 cases of α -hemolytic streptococcal HVO without cefazolin susceptibility test results,

204 cefazolin was appropriate in 61.6% of HVO cases. Cefazolin was appropriate in 78.3% of
 205 community-acquired cases and 35.4% of healthcare-associated cases. Vancomycin combined
 206 with ciprofloxacin, ceftriaxone, ceftazidime, or cefepime was similarly appropriate
 207 (susceptibility rates 93.0%, 94.1%, 95.8%, and 95.8%, respectively). All antibiotic regimens
 208 gave similar results, irrespective blood culture positivity.
 209

210 **DISCUSSION**

211 We evaluated the susceptibility profiles of microorganisms causing HVO and assessed the
 212 appropriateness of several empiric antibiotic regimens for culture-negative HVO. Our data
 213 showed that oral antibiotic combinations may be suboptimal for empiric treatment of culture-
 214 negative HVO, and should be used after definitively ruling out healthcare-associated HVO.
 215 Vancomycin combined with fluoroquinolones or broad-spectrum cephalosporins were
 216 appropriate for most cases of community-acquired and healthcare-associated HVO.

217 In this study, the most frequently isolated organism was *S. aureus*, with 43% being MRSA.
 218 In recent years, the prevalence of MRSA among *S. aureus* vertebral osteomyelitis has been
 219 reported to be 40–57% (11, 14-16). The resistance rate of *Enterobacteriaceae* isolates to
 220 ciprofloxacin was 26% in this study, compared to 31% and 38% in two recent studies
 221 conducted in South Korea and France, respectively (17, 18). Vertebral osteomyelitis caused
 222 by antibiotic-resistant organisms may have a higher risk of treatment failure (16, 19, 20).
 223 Indeed, patients with MRSA vertebral osteomyelitis reportedly have a 4–5-fold higher risk of
 224 recurrence than those with MSSA vertebral osteomyelitis (16, 19). In a study of patients with
 225 gram-negative bacterial HVO, half of those infected with fluoroquinolone-resistant strains
 226 experienced recurrence after 4–8 weeks of antibiotic treatment (20). Thus, the increasing
 227 incidence of antibiotic resistance in causative pathogens of vertebral osteomyelitis should be
 228 considered when selecting an empiric antibiotic regimen for culture-negative HVO.

229 Fluoroquinolone-based regimens have high oral bioavailability and good bone penetration,
 230 allow an early switch to oral therapy, and appear to be the best option for empiric treatment of
 231 culture-negative vertebral osteomyelitis (8, 21). Two previous studies showed that empiric
 232 treatment with levofloxacin plus rifampin had overall response rates of 78% (3) and 84%
 233 (22). In another study, empiric treatment with ciprofloxacin plus amoxicillin-clavulanate had
 234 an overall response rate of 82% (23). All three studies were conducted in an epidemiologic

235 setting featuring a low prevalence of MRSA (3, 22, 23), and the appropriateness of these
 236 regimens in high-MRSA-prevalence settings was not evaluated. In the current study, based on
 237 the susceptibility profiles of isolated bacteria, these combination regimens were appropriate
 238 in 74% and 67% of cases, respectively. We also found that levofloxacin plus clindamycin
 239 exhibited activity against 71% of causative organisms of HVO. Fluoroquinolone plus
 240 clindamycin is suggested for the treatment of culture-negative vertebral osteomyelitis by
 241 British guidelines (4), but clinical data on this regimen in this setting are limited. The marked
 242 inappropriateness of fluoroquinolone-based regimens in the current study may be due to the
 243 high prevalence of MRSA (25%). Almost half of our MRSA isolates were resistant to
 244 fluoroquinolones, and the resistance rates to their companion drugs, such as rifampin and
 245 clindamycin, were high (22% and 58%, respectively). Recently, Desoutter *et al.* reported the
 246 susceptibility patterns of microorganisms isolated from 101 cases of non-bacteremic vertebral
 247 osteomyelitis by percutaneous needle biopsy (17). According to the antibiotic susceptibility
 248 profiles, fluoroquinolone-based regimens were appropriate in 58–77% of cases (17). In
 249 contrast to our study, MRSA was responsible for only one case of vertebral osteomyelitis, but
 250 CoNS was the most frequent isolate, with 20% of isolates being resistant to fluoroquinolones
 251 (17). Also, the almost 40% rate of fluoroquinolone resistance in *Enterobacteriaceae* isolates
 252 contributed to the relatively low suitability of fluoroquinolone-based regimens (17). To
 253 minimize the risk of microbiological failure, we reassessed the suitability of empiric
 254 regimens in community-acquired and healthcare-associated cases. These analyses indicated
 255 that fluoroquinolone-based regimens were appropriate in up to 86% of community-acquired
 256 HVO cases, but in only 38–53% of healthcare-associated HVO cases. Thus, based on current
 257 data, as well as previous clinical experience (3, 22, 23), fluoroquinolone-based regimens may
 258 be useful for empiric treatment of community-acquired HVO, but they should not be used for
 259 healthcare-associated HVO.

260 In this study, vancomycin plus ciprofloxacin or broad-spectrum cephalosporins were
 261 appropriate in most cases of community-acquired and healthcare-associated HVO. Although
 262 ESBL-producing *Enterobacteriaceae* accounted for 9% of the *Enterobacteriaceae* isolates, it
 263 accounted for only 2% of all causative organisms. The prevalence of anaerobes was 1% in
 264 this work, and up to 4% in two recent studies (3, 21). Thus, antibiotic coverage of such rare
 265 organisms (with carbapenems or metronidazole) may be not required initially, and should be
 266 limited to patients who show no clinical improvement after empiric treatment and negative
 267 results of repeated biopsies. As a companion drug to vancomycin, fluoroquinolones and
 268 broad-spectrum cephalosporins were similarly effective in healthcare-associated HVO.
 269 Taking into consideration the bone penetration of antibiotics (24), we prefer fluoroquinolones
 270 over broad-spectrum cephalosporins as companion drugs to vancomycin.

271 For culture-negative vertebral osteomyelitis, some authors suggest a first-generation
 272 cephalosporin for community-acquired cases and vancomycin-containing regimens for
 273 post-surgical cases, and have reported favorable outcomes with this approach (25, 26). A
 274 first-generation cephalosporin is an acceptable alternative in patients unable to tolerate
 275 anti-staphylococcal penicillin (27), but clinical experience with this agent for streptococcal
 276 and gram-negative bacterial osteomyelitis is limited. In addition, first-generation
 277 cephalosporins show varying activity against α -hemolytic streptococci, unlike β -hemolytic
 278 streptococci (28), and susceptibility testing of this agent against α -hemolytic streptococci is
 279 not recommended (12). Even after excluding 25 cases of α -hemolytic streptococci without
 280 susceptibility data (viridans group streptococci [n = 21] and *S. pneumoniae* [n = 4]), cefazolin
 281 was appropriate in only 62% of cases. Given its poor penetration of bone tissue, oral
 282 cephalosporin is not recommended for the treatment of vertebral osteomyelitis by the
 283 Infectious Disease Society of America (IDSA) (21) and French (13) guidelines. More data on

284 the efficacy of first-generation cephalosporins are required before they can be widely used for
285 culture-negative vertebral osteomyelitis.

286 Our study had several limitations. First, some cases lacked antibiotic susceptibility test
287 results and so exclusion of these cases may have introduced bias. Second, we assessed the
288 appropriateness of empiric antibiotic regimens for culture-negative HVO based on the data of
289 organisms isolated from microbiologically proven cases. However, culture-negative vertebral
290 osteomyelitis may be more closely related to cases caused by low-virulence pathogens, such
291 streptococci and CoNS (3, 29), and the prevalence of these organisms may have been
292 underestimated in our analysis. In this study, *Streptococcus* species were less likely to be
293 detected in blood cultures than *S. aureus* (62% vs. 82%). Finally, this study included only
294 patients with HVO, and so our findings should not be extrapolated to cases of post-surgical
295 vertebral osteomyelitis, in which CoNS and antibiotic-resistant organisms may be more
296 common.

297 In summary, in a setting in which MRSA is a frequent causative organism of HVO,
298 cautious selection of empiric antibiotics is required. Oral empiric antibiotic combinations
299 may be suboptimal for culture-negative HVO, and should be used only in
300 community-acquired cases. Vancomycin combined with fluoroquinolone or a broad-spectrum
301 cephalosporin is appropriate in most cases of HVO. The clinical efficacy of empiric antibiotic
302 regimens for culture-negative HVO reported here should be verified in further studies.

303

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310

311 **Conflicts of interest**

312 The authors declare no potential conflicts of interest.

313

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 413

414 **Table 1.** Demographic and baseline characteristics of 358 patients with hematogenous
415 vertebral osteomyelitis

Variable	All patients (<i>n</i> = 358)
Age, median years (IQR)	65 (58–72)
Male sex	186 (52.0)
Underlying illness/conditions	
Diabetes mellitus	105 (29.3)
Liver cirrhosis	33 (9.2)
Malignancy	31 (8.7)
Immunosuppression	20 (5.6)
End-stage renal disease	15 (4.2)
Rheumatic disease	12 (3.4)
Healthcare-associated HVO	133 (37.2)
Presumed source of infection	
Urinary tract	35 (9.7)
Skin and subcutaneous tissues	30 (8.4)
Intra-abdomen	26 (7.3)
Infected vascular access	25 (7.0)
Endocarditis	19 (5.3)
Unknown	223 (62.3)
Clinical data	
Time to diagnosis, median days (IQR)	22 (8–40)
Back pain	319 (89.1)

Body temperature > 38°C	190 (53.1)
Neurologic deficit at diagnosis	61 (17.0)
Concurrent metastatic infection	46 (12.8)
Laboratory data	
White blood cell count, $\times 10^9/L$, median (IQR)	114 (79–162)
C-reactive protein, mg/dL, median (IQR)	13 (6–22)
Erythrocyte sedimentation rate, mm/h, median (IQR) ^a	76 (55–100)
Positive blood cultures	265/339 (78.2)
Radiologic data	
Involvement of > 2 vertebral bodies	125 (34.9)
Involvement of cervical spine	31 (8.7)
Involvement of thoracic spine	85 (23.7)
Involvement of lumbosacral spine	283 (79.1)
Epidural involvement ^b	194 (54.2)
Paravertebral involvement ^b	192 (53.6)
Psoas involvement ^b	126 (35.2)

416

417 Data are no. (%) of patients, unless otherwise indicated.

418 Abbreviations: HVO, hematogenous vertebral osteomyelitis; IQR, interquartile range

419 ^a Measured in 287 patients.

420 ^b Either abscess or phlegmon.

421

422 **Table 2.** Antibiotic susceptibility testing results for 358 isolated microorganisms

	Percentage of isolates susceptible to											
	AMX-CL	CIP	LEVO	CLM	RIF	TMP-SMX	FA ^a	CFZ	CTR	CAZ	FEP	VAN
Methicillin-susceptible <i>S. aureus</i> (<i>n</i> = 120)	100	94.2	95.8	88.3	97.5	100	74.1	100	NA	NA	NA	100
Methicillin-resistant <i>S. aureus</i> (<i>n</i> = 89)	0	53.9	56.2	41.6	77.5	92.1	81.2	0	NA	NA	NA	100
Gram-negative bacteria (<i>n</i> = 78)	69.2	76.9	76.9	NA	NA	76.9	NA	80.8	82.1	89.7	89.7	NA
<i>Streptococcus</i> species (<i>n</i> = 42)	95.2	NA	90.5	76.2	NA	NA	NA	100 ^b	95.2	NA	NA	100
Coagulase-negative staphylococci (<i>n</i> = 10)	50.0	70.0	70.0	70.0	80.0	80.0	NA	50.0	NA	NA	NA	100
<i>Enterococcus</i> species (<i>n</i> = 10)	90.0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	100
Other (<i>n</i> = 9) ^c	55.6	11.1	11.1	NA	NA	NA	NA	0	11.1	11.1	11.1	NA

423

424 Abbreviations: AMX-CL, amoxicillin-clavulanate; CFP, cefepime; CAZ, ceftazidime; CFZ, cefazolin; CIP, ciprofloxacin; CLM, clindamycin;

425 CTR, ceftriaxone; FA, fusidic acid; LEVO, levofloxacin; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*;

426 RIF, rifampin; TMP-SMX; trimethoprim-sulfamethoxazole; VANC, vancomycin.

427 ^a Susceptibility data for fusidic acid against methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* isolates were available in 112

428 and 85 cases, respectively.

429 ^b Excluding 25 streptococcal isolates without susceptibility data (21 viridans group streptococci and 4 *S. pneumoniae*); the remaining 17

430 *Streptococcus* isolates were susceptible to cefazolin.

431 ^c Included *Bacteroides fragilis* ($n = 2$), *Bacteroides ureolyticus* ($n = 1$), *Prevotella melaninogenica* ($n = 1$), *Prevotella oralis* ($n = 1$),

432 *Micrococcus* species ($n = 1$), *Enterococcus faecium*/viridans group streptococci ($n = 1$), *Klebsiella pneumoniae*/*Enterobacter aerogenes* ($n =$

433 1), and methicillin-susceptible *S. aureus*/methicillin-resistant *Staphylococcus schleiferi* ($n = 1$).

434

Table 3. Relevance of empiric antibiotic therapy based on the susceptibility results of organisms isolated from cases of culture-proven hematogenous vertebral osteomyelitis

Organism	LEVO + RIF	LEVO + CLM	AMX-CL + CIP	CFZ ^a	VAN + CIP	VAN + CTR	VAN + CAZ	VAN + FEP
All cases (<i>n</i> = 358)	73.5	71.2	66.5	61.6	93.0	94.1	95.8	95.8
Microorganisms								
Methicillin-susceptible <i>S. aureus</i> (<i>n</i> = 120)	93.3	88.3	100	100	100	100	100	100
Methicillin-resistant <i>S. aureus</i> (<i>n</i> = 89)	50.6	41.6	0	0	100	100	100	100
Gram-negative bacteria (<i>n</i> = 78)	76.9	76.9	71.8	80.8	76.9	82.1	89.7	89.7
<i>Streptococcus</i> species (<i>n</i> = 42)	90.5	97.6	100	100 ^a	100	100	100	100
Coagulase-negative staphylococci (<i>n</i> = 10)	70.0	70.0	50.0	50	100	100	100	100
<i>Enterococcus</i> species (<i>n</i> = 10)	0	0	90.0	0	100	100	100	100
Other (<i>n</i> = 9)	11.1	44.4	66.7	0	22.2	22.2	22.2	22.2
Onset of infection								
Community-acquired (<i>n</i> = 225)	85.8	84.0	80.4	78.3	94.2	96.9	97.3	97.3
Healthcare-associated (<i>n</i> = 133)	52.6	49.6	37.6	35.4	91.0	89.5	93.2	93.2
Blood culture								
Non-bacteremic HVO (<i>n</i> = 93) ^b	77.4	79.6	66.7	61.4	91.7	86.0	92.5	92.5
Bacteremic HVO (<i>n</i> = 265)	72.1	68.3	63.8	61.6	92.8	97.0	97.0	97.0

437

438 Data are no. (%) of isolates, unless otherwise indicated.

439 Abbreviations: AMX-CL, amoxicillin-clavulanate; FEP, cefepime; CAZ, ceftazidime; CIP,

440 ciprofloxacin; CFZ, cefazolin; CLM, clindamycin; CTR, ceftriaxone; HVO, hematogenous

441 vertebral osteomyelitis; LEVO, levofloxacin; RIF, rifampin; VAN, vancomycin.

442 ^a Excluding 25 streptococcal isolates without susceptibility data (21 viridans group

443 streptococci and 4 *S. pneumoniae*); the remaining 17 *Streptococcus* isolates were susceptible

444 to cefazolin.

445 ^b Included patients with negative blood culture results ($n = 74$) and those from whom blood
446 cultures were not obtained ($n = 19$).