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# Human *Lactococcus garvieae* Bloodstream Infection Complicated by Spondylodiscitis, Germany

## Appendix 2

**Appendix 2 Table 1.** Medications at Admission and Past Medical History

| Medication                 | Morning | Noon | Evening | Night | Indication                                    |
|----------------------------|---------|------|---------|-------|-----------------------------------------------|
| Acetylsalicylic Acid, mg   | 100     | 0    | 0       | 0     | Bioprosthetic mitral valve                    |
| Ramipril, mg               | 2.5     | 0    | 2.5     | 0     | Arterial hypertension                         |
| Torsemide, mg              | 2.5     | 0    | 0       | 0     | Peripheral edema (congestive heart failure)   |
| Rosuvastatin, mg           | 0       | 0    | 0       | 5     | Dyslipidemia                                  |
| Pantoprazole, mg           | 0       | 0    | 40      | 0     | Acetylsalicylic Acid                          |
| Hydromorphone, mg          | 2       | 0    | 2       | 0     | Back pain (spinal canal stenosis Th2-3, L3-5) |
| Metamizole, g              | 1       | 1    | 1       | 1     | Back pain (spinal canal stenosis)             |
| Venlafaxine, mg            | 150     | 0    | 75      | 0     | Depression                                    |
| Polyethylene Glycol, g     | 52.5    | 52.5 | 52.5    | 0     | Irritable Bowel Syndrome, credominant         |
| Bioprosthetic mitral valve |         |      |         |       | Mitral regurgitation (severe)                 |

\*Epic E100-29M, Abbott Laboratories, <https://www.abbott.com>.

**Appendix 2 Table 2.** Summary of Clinical, Microbiological, and Therapeutic Characteristics of All 36 Reported *Lactococcus garvieae* Cases with Available Data

| Parameter                        | Value           |
|----------------------------------|-----------------|
| Baseline characteristics         |                 |
| Median age, y (IQR)              | 69 (59.5–78.25) |
| Sex                              |                 |
| M                                | 22 (61.1)       |
| F                                | 14 (38.9)       |
| Comorbidities                    |                 |
| Arterial Hypertension            | 13 (36.1)       |
| Atrial Fibrillation              | 10 (27.8)       |
| Diabetes Mellitus Type 2         | 7 (19.4)        |
| Dyslipidemia                     | 6 (16.7)        |
| Coronary Artery Disease          | 6 (16.7)        |
| Congestive Heart Failure         | 4 (11.1)        |
| Risk Factors                     |                 |
| GI pathology, any                | 24 (66.7)       |
| Gastrointestinal polyps          | 8 (22.2)        |
| Diverticula                      | 5 (13.9)        |
| Gastritis                        | 4 (11.1)        |
| Peptic ulcer disease             | 3 (8.3)         |
| Fish Exposure                    | 16 (44.4)       |
| Ingestion                        | 14 (87.5)       |
| Handling                         | 2 (12.5)        |
| No Fish Exposure                 | 9 (25.0)        |
| Not reported                     | 11 (30.6)       |
| Outcome                          |                 |
| Alive                            | 32 (88.8)       |
| Antimicrobial + Surgical Therapy | 8 (75.0)        |
| Antimicrobial Therapy only       | 24 (25.0)       |
| Monotherapy                      | 7 (29.2)        |
| Combination Therapy              | 17 (70.8)       |

| Parameter                                                          | Value                 |
|--------------------------------------------------------------------|-----------------------|
| Embolic Complication during therapy                                | 3 (9.4)               |
| No Embolic Complication during therapy                             | 29 (90.6)             |
| Dead                                                               | 4 (11.1)              |
| Antimicrobial + Surgical Therapy                                   | 2 (50.0)              |
| Antimicrobial Therapy only                                         | 2 (50.0)              |
| Heart Valve                                                        |                       |
| Number of Affected Valves                                          |                       |
| Mono-valvular                                                      | 30 (83.3)             |
| Multi-valvular                                                     | 6 (16.7)              |
| Valve Location                                                     |                       |
| Aortic valve, n = 42                                               | 21 (50.0)             |
| Native, n = 21                                                     | 8 (38.1)              |
| Prosthetic, n = 21                                                 | 13 (61.9)             |
| Mitral valve, n = 42                                               | 20 (41.7)             |
| Native, n = 20                                                     | 15 (75.0)             |
| Prosthetic, n = 20                                                 | 5 (25.0)              |
| Tricuspid valve, n = 42                                            | 1 (2.4)               |
| prosthetic                                                         | 1 (100)               |
| Valve Type                                                         |                       |
| Native, n = 45                                                     | 23 (51.1)             |
| Prosthetic, n = 45                                                 | 22 (48.9)             |
| Biological, n = 22                                                 | 13 (59.1)             |
| Mechanical, n = 22                                                 | 5 (22.7)              |
| not reported, n = 22                                               | 4 (18.2)              |
| Clinical Presentation                                              |                       |
| Duration of Presenting Complaint, median d (IQR)                   | 15.5 (6.75– 30)       |
| Most Common Presenting Complaints                                  |                       |
| Fever                                                              | 22 (61.1)             |
| Pain                                                               | 13 (36.1)             |
| Muscle                                                             | 4 (30.8)              |
| Back                                                               | 3 (23.1)              |
| Head                                                               | 3 (23.1)              |
| Joint                                                              | 2 (15.4)              |
| Chest                                                              | 1 (7.7)               |
| Abdominal                                                          | 1 (7.7)               |
| Anorexia                                                           | 8 (22.2)              |
| Malaise                                                            | 7 (19.4)              |
| Chills                                                             | 6 (16.7)              |
| Dyspnea                                                            | 6 (16.7)              |
| Weakness                                                           | 5 (13.9)              |
| Weight loss                                                        | 5 (13.9)              |
| Laboratory Investigations on Admission, median (IQR)               |                       |
| Hemoglobin, g/dL; n = 14                                           | 9.9 (9.0–10.5)        |
| Leucocytes, cells/ $\mu$ L; n = 25                                 | 12,735 (9,250–15,500) |
| C-reactive Protein, mg/dL; n = 22                                  | 9.1 (5.40–21.33)      |
| Creatinine, mg/dL; n = 10                                          | 1.41 (1.1–1.56)       |
| Microbiology methods used                                          |                       |
| Biochemical                                                        | 15 (41.7)             |
| VITEK 2†                                                           | 9 (25.0)              |
| API Strep (20 or 32)                                               | 6 (16.7)              |
| Rapid ID 32 Strep                                                  | 4 (66.7)              |
| API 20 Strep                                                       | 1 (16.7)              |
| Not reported                                                       | 1 (16.7)              |
| BD Phoenix System‡                                                 | 1 (6.7)               |
| 16s rRNA/DNA-sequencing                                            | 14 (38.9)             |
| MALDI-TOF                                                          | 13 (36.1)             |
| Not reported                                                       | 9 (25.0)              |
| Combination of Microbiological Methods for Pathogen Identification |                       |
| Biochemical                                                        | 3 (8.3)               |
| API Strep                                                          | 1 (33.3)              |
| VITEK†                                                             | 1 (33.3)              |
| Not reported                                                       | 1 (33.3)              |
| + 16s rDNA/rRNA sequencing                                         | 10 (27.8)             |
| + 16s rDNA/rRNA sequencing + MALDI-TOF                             | 2 (5.6)               |
| MALDI-TOF                                                          | 7 (19.4)              |
| + 16s rDNA/rRNA sequencing                                         | 4 (11.1)              |
| Polymerase Chain Reaction                                          | 1 (2.8)               |
| Not reported                                                       | 9 (25.0)              |
| Antimicrobial Therapy                                              |                       |

| Parameter                                                    | Value      |
|--------------------------------------------------------------|------------|
| Antibiotic regimen                                           |            |
| Combination therapy                                          | 26 (72.2)  |
| Monotherapy                                                  | 10 (27.8)  |
| Median therapy duration among 32 surviving patients, d (IQR) | 42 (42–42) |
| <42 days                                                     | 5 (15.6)   |
| 42 days                                                      | 18 (56.3)  |
| >42 days                                                     | 6 (18.8)   |
| Not reported                                                 | 3 (9.4)    |
| Most Common Antimicrobials Used                              |            |
| Gentamicin                                                   | 28 (77.8)  |
| Ceftriaxone                                                  | 22 (61.1)  |
| Aminopenicillin (Amoxicillin or Ampicillin)                  | 18 (50.0)  |
| + beta-Lactamase-Inhibitor                                   | 4 (11.1)   |
| Vancomycin                                                   | 12 (33.3)  |
| Penicillin                                                   | 9 (25.0)   |
| Levofloxacin                                                 | 4 (11.1)   |
| Antimicrobial Resistance, n = 24                             |            |
| Penicillin§                                                  | 6 (25.0)   |
| Gentamicin                                                   | 4 (16.7)   |
| Penicillin                                                   | 1 (4.2)    |
| Ampicillin                                                   | 2 (8.3)    |
| Ampicillin/Sulbactam                                         | 1 (4.2)    |
| Piperacillin/Tazobactam                                      | 1 (4.2)    |
| Rifampin                                                     | 1 (4.2)    |
| Norfloxacin                                                  | 1 (4.2)    |
| Bacitracin                                                   | 1 (4.2)    |

\*Values are no. (%) except as indicated. MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight.

†bioMérieux, <https://www.biomerieux.com>.

‡Becton, Dickinson and Company, <https://www.bd.com>.

§When used as monotherapy in infective endocarditis according to clinical breakpoints issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for viridans group streptococci.

**Appendix 2 Table 3.** Results of Antimicrobial Susceptibility Testing

| Medication              | Disk diffusion | E-test (MIC, mg/L)   |
|-------------------------|----------------|----------------------|
| Penicillin              | Resistant      | Resistant (1)        |
| Ampicillin              | Resistant      | ND                   |
| Ampicillin/Sulbactam    | Resistant      | ND                   |
| Piperacillin/Tazobactam | Resistant      | ND                   |
| Cefuroxim               | Resistant      | ND                   |
| Cefotaxim               | Susceptible    | ND                   |
| Ceftriaxone             | Susceptible    | Susceptible (0.38)   |
| Vancomycin              | Susceptible    | ND                   |
| Clindamycin             | Resistant      | ND                   |
| Tetracycline            | ND             | Susceptible (0.38)   |
| Levofloxacin            | ND             | Intermediate (0.75)† |
| Gentamicin              | ND             | Resistant (1.5)      |

\*The isolate from blood cultures on day 2 underwent disk-diffusion susceptibility testing; by this method, minimal inhibitory concentrations (MICs) are not generated. Following the initial disk-diffusion testing, the stored isolate was retested later using an E-test, enabling determination of MICs.

Susceptibility results are based on breakpoints from alpha-hemolyzing *Streptococcus* spp. for penicillin (using the endocarditis-specific breakpoint), ceftriaxone and gentamicin (Screen), as well as *Staphylococcus* spp. for tetracycline and levofloxacin. ND, not done.

†Susceptible at increased exposure.

**Appendix 2 Table 4.** Antimicrobial Resistance Profile of *Lactococcus garvieae* Isolates Reported in the Literature

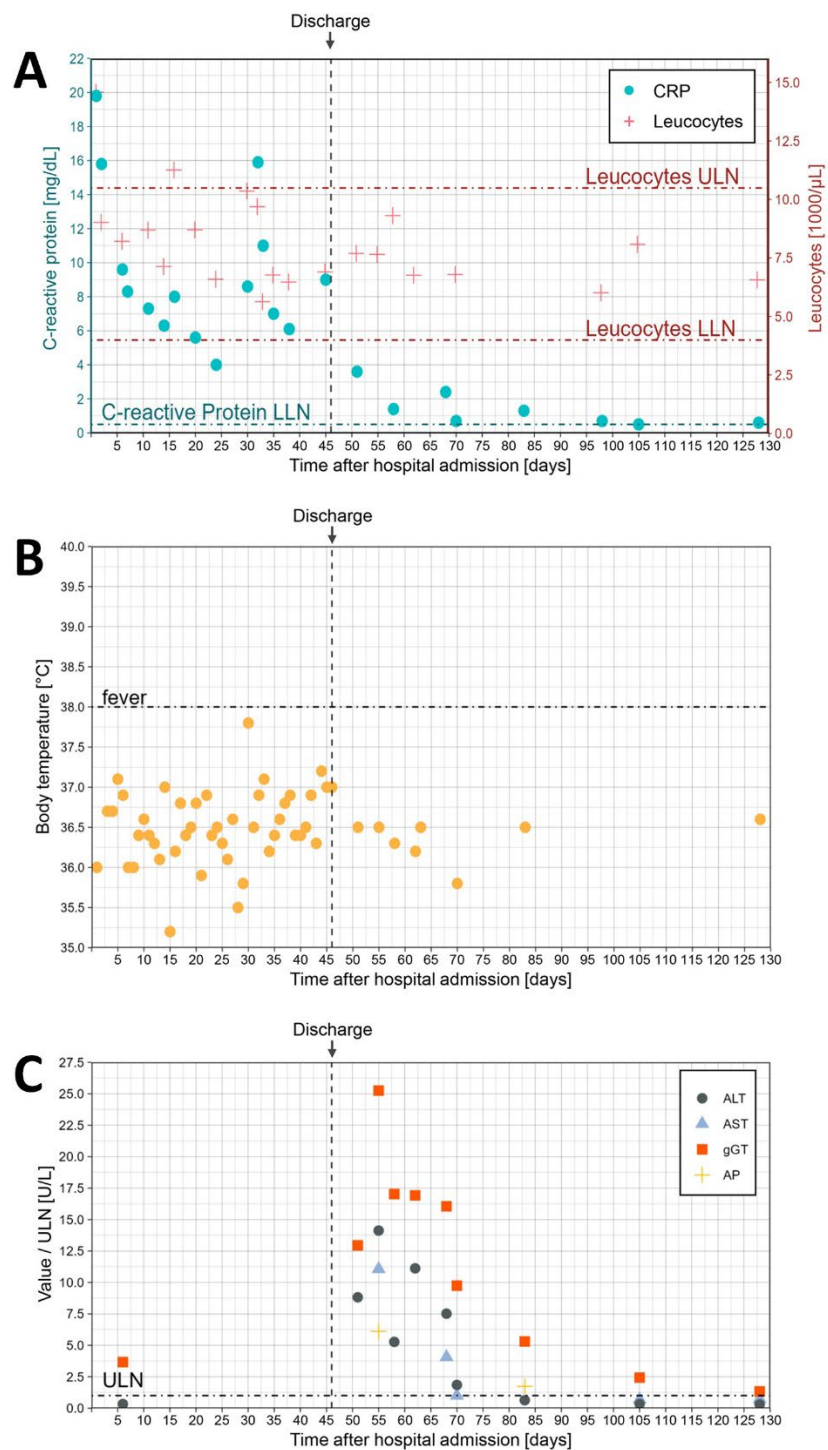
| Author<br>(reference no.) | Year | Country                          | Breakpoint from                                                                                                                      | Susceptibility (MIC, mg/L)                                                        |                                                |                                                                                                                                                                                                                                                     |
|---------------------------|------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |      |                                  |                                                                                                                                      | Resistant                                                                         | Intermediate                                   | Susceptible                                                                                                                                                                                                                                         |
| Fleming (1)               | 2012 | USA<br>(acquired in South Korea) | CLSI recommendations for viridian streptococci                                                                                       | Clindamycin, Ampicillin, Gentamicin                                               | /                                              | Vancomycin, Ampicillin/Sulbactam, Ceftriaxone, Piperacillin/Tazobactam                                                                                                                                                                              |
| Russo (2)                 | 2012 | Italy                            | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Clindamycin (>64), Rifampin (>64), Bacitracin (>64), Norfloxacin, Penicillin* (2) |                                                | Erythromycin (0.125), Cefotaxime (0.5), Levofloxacin (0.5), Tetracycline (0.5), Imipenem (0.023), Ampicillin (0.25), Amoxicillin/Clavulanic Acid (0.5), Ciprofloxacin (0.75), Daptomycin (0.125), Vancomycin (2), Gentamicin (2), Teicoplanin (0.5) |
| Vinh (3)                  | 2006 | Canada                           | CLSI criteria for <i>Streptococcus spp.</i> other than <i>Streptococcus pneumoniae</i><br>CLSI criteria for <i>Enterococcus spp.</i> | Clindamycin<br><br>Clindamycin, Norfloxacin                                       | Penicillin<br><br>Erythromycin, Nitrofurantoin | Ampicillin, Vancomycin<br><br>Penicillin G, Chloramphenicol, Ciprofloxacin, Ofloxacin, Levofloxacin, Tetracycline, and Vancomycin, Gentamicin, Streptomycin                                                                                         |
| Kitagawa (4)              | 2024 | Japan                            | Not specified                                                                                                                        | Gentamicin                                                                        | /                                              | Penicillin, Ampicillin, Cefazolin, Cefmetazole, Imipenem, Minocycline, Vancomycin                                                                                                                                                                   |
| Cabrales (5)              | 2020 | Colombia                         | Not specified                                                                                                                        | Gentamicin                                                                        | /                                              | Ampicillin, Ceftriaxone, Ciprofloxacin                                                                                                                                                                                                              |
| Clavero (6)               | 2017 | Chile                            | CLSI (2015) for $\beta$ -hemolytic streptococci                                                                                      | Clindamycin, Penicillin*                                                          | /                                              | Vancomycin, Cefotaxime                                                                                                                                                                                                                              |
| Fihman (7)                | 2006 | France                           | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Penicillin* (0.75)                                                                | /                                              | Amoxicillin (0.5), Cefotaxime (0.38), Vancomycin (1.5), Teicoplanin (0.38)                                                                                                                                                                          |
| Lim (8)                   | 2017 | England                          | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Penicillin* (1)                                                                   |                                                | Gentamicin                                                                                                                                                                                                                                          |
| Lim (9)                   | 2018 | Singapore                        | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Penicillin* (0.75)                                                                |                                                | Ceftriaxone (0.25), Gentamicin (3.0)                                                                                                                                                                                                                |
| Rasmussen (10)            | 2014 | Sweden                           | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Penicillin* (0.5)                                                                 |                                                | Tobramycin (2)                                                                                                                                                                                                                                      |
| Watanabe (11)             | 2011 | Japan                            | EUCAST (2026; v 16.0) breakpoints for Viridans group streptococci                                                                    | Clindamycin (>256), Penicillin* (0.5)                                             |                                                | Ceftriaxone (0.38), Erythromycin (0.25), Vancomycin (0.38), Linezolid (2)                                                                                                                                                                           |

\*When used as monotherapy in infective endocarditis according to clinical breakpoints issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Viridans group streptococci.

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**Appendix 2 Figure.** Temporal Trends in Laboratory Biomarkers and Body Temperature. A) C-reactive Protein and Leucocyte Count. B) Body temperature, measured using a digital ear thermometer. C) Liver enzymes, displayed relative to their respective upper limit of normal. ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; CRP, C-reactive protein; gGT, gamma-glutamyl transferase; LLN, lower limit of normal; ULN, upper limit of normal.