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Case report

# A case of sepsis due to a rare carbapenem-resistant *Ignatzschineria* species

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ABSTRACT

*Ignatzschineria* species have emerged only recently and few cases have been identified worldwide. It has been determined that maggots likely serve as the vector of transmission and the majority of cases described involved cutaneous myiasis. This article presents the first case of an *Ignatzschineria* species closely related to I. *larvae/I. ureclastica* causing bacteremia in North America. This isolated *Ignatzschineria* species is also unique in its broad antimicrobial resistance pattern to carbapenem antimicrobials, an uncommon finding among global *Ignatzschineria* isolates. Improving the ability to identify *Ignatzschineria* species is an important step to develop the necessary CLSI breakpoints and treatment guidelines. The paucity of information regarding *Ignatzschineria* species and the inability to accurately identify these organisms indicate the need for more research and improved identification techniques of this emerging pathogen.



## Introduction

*Ignatzschineria* species have emerged as human pathogens only recently and few cases have been identified worldwide. It has been determined maggots likely serve as the vector of transmission and the majority of cases described involved cutaneous myiasis. Of the species reported, *I. larvae* and *I. ureiclastica* have been shown to be especially rare. In this case we present a patient who was found to have bacteremia by an *Ignatzschineria* species which was identified to be most similar to *I. larvae* and *I. ureiclastica.* To our knowledge, neither of these species have been reported in North America. Also intriguing was the fact that the bacterium was resistant to both beta-lactams and carbapenems, whereas the majority of cases reported thus far had been fairly susceptible to antimicrobials. Here we explore the genus *Ignatzschineria*, its epidemiology, methods of identification, clinical manifestations, complications as well as treatment and patterns of resistance.

## Case report

A 68-year-old male presented to the emergency department for an infection of the left foot. On presentation, the patient was delirious and unable to provide history. Per the emergency medical services report, the patient had been living in “poor living conditions”. The patient had been known to have a non-healing wound of the dorsum of his left foot but had refused treatment and had a known past medical history of hypertension, heroin use disorder and peripheral arterial disease.

He was found to be tachycardic, otherwise vitals were within normal limits. Physical exam revealed an extensive wound (9 cm × 11 cm × 0.5 cm) with necrotic tissue and maggots on the dorsum of the left foot and visible muscle. Laboratory work up revealed a white blood cell count of 20,900/μL, serum bicarbonate 11 meq/L, BUN 267 mg/dL, creatinine 14.43 mg/dL, lactate 2.0 mmol/L, and CPK 255 IU/L. Plain radiographs of the left foot revealed soft tissue ulceration anterior to the ankle and dorsal to the midfoot and forefoot as well as possible cortical disruption of the dorsal midfoot. The patient subsequently underwent a non-contrast CT of the left lower extremity which was remarkable for acute and/or chronic osteomyelitis.

The patient was started on intravenous fluids as well as the empiric antimicrobials vancomycin and cefepime. While in the emergency department, the podiatry service performed irrigation of the left foot wound with hydrogen peroxide and removed the maggots. The wound was then wrapped with dressings soaked in betadine. He was admitted to the intensive care unit for further management of acute kidney injury, metabolic acidosis and sepsis. The patient’s renal function improved with intravenous fluid hydration and he did not require hemodialysis. The patient underwent

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a left below knee amputation due to the extent of the wound and suspected osteomyelitis.

Blood cultures obtained prior to antimicrobials were positive for a gram negative bacterium which was unable to be identified by MALDI-TOF MS (Alverno Laboratories, Hammond, Indiana). It was then identified by 16 S rRNA gene amplification and sequencing as being most similar in genetic makeup to *I. larvae* and *I. ureiclastica* (ARUP Laboratories, Salt Lake City, Utah). The organism was notable for resistance to aztreonam, cefepime, meropenem, and piperacillin-tazobactam suggestive of beta-lactamase and carbapenamase production; however, it was sensitive to amikacin, gentamicin, levofloxacin and tobramycin.

After 11 days of vancomycin and cefepime the antimicrobials were adjusted to oral levofloxacin monotherapy for 7 additional days. The patient's condition improved and he was discharged to inpatient rehabilitation for intensive physical therapy on hospital day 25.

## Discussion

*Ignatzschineria* species are gram-negative rods which are aerobic, non-motile, non-spore forming, and belong to the family Xanthomonadaceae and class gammaproteobacteria [1]. This genus was identified in 2001 by Toth et al. who studied bacterial strains which were isolated from the larvae of the *Wohlfarhtia magnifica* fly [2,3]. It was originally given the name *Schineria* and was later renamed *Ignatzschineria* by the same author in 2007.

To date, there have been four species of Ignatzschinera described *Ignatzschineria indica*, *Ignatzschineria larvae, Ignatzschineria ureiclastica*, and *Ignatzchineria cameli*; the last of which has been identified only recently in 2018 as reported by Tsang et al. [4]. The species isolated in this case was most genetically similar to *Ignatzschineria larvae* and *Ignatzschineria ureiclastica*. *Ignatzschineria* is known to be isolated from the gastrointestinal tract of the first and second larval stages of the fly *Wohlfarhtia magnifica* [1]. These larvae feed on flesh of vertebrates and are known to cause myiasis in animals and less commonly in humans.

This patient presented with the cutaneous form of myiasis as a complication of a neglected wound of his foot. Although more prevalent in tropical and subtropical climates, myiasis can be seen in other geographical regions particularly in patients who are undomiciled, of low socioeconomic status, or have poor hygiene [5,6]. The majority of cases of *Ignatzschineria* infections reported have been bloodstream infections; however it has also been isolated from a breast abscess culture and urine culture [7,8].

*Ignatzschineria* bacteremia is often associated with poor living or working conditions, alcoholism, open wounds/ulcers, and peripheral vascular disease [7–21]. It was reported that this patient had been living in poor conditions in a basement and had also shown behaviors of self-neglect both of which predisposed him to myiasis and therefore *Ignatzschineria* infection.

Although few cases have been described in literature, it is important for clinicians to consider *Ignatzschineria* bacteremia as a potential complication of myiasis especially in patients who present with sepsis.

*Ignatzschineria* species were discovered only recently and less than 20 cases have been reported worldwide. The organism identified in this case was determined to be most genetically similar to *I. larvae* and *I. ureiclastica,* both of which are rarer when compared to *I. indica*. While there have been 11 cases of *I. indica* reported, there have been only three cases of *I. larvae* and two cases of *I. ureiclastica* [1,5–11,13,15,16,18,20,21]. In addition, *I. indica* is the only species to have been reported in North America [7,8,10,11,15,17,20]. Sepsis secondary to *I. ureiclastica* bacteremia has been reported only twice worldwide with one case published by Le Brun et al. in France in 2015 and one case by Tanida et al. Germany in 2019 [19].

The case published in France was that of a 69-year-old male who was found unresponsive in a forest [14]. He was found to be septic and subsequently suffered from cardiac arrest. Physical exam revealed maggots surrounding his genitals as well as a necrotic wound of his right shoulder. Blood cultures were positive for multiple organisms including *Corynebacterium* spp., *Enterobacter cloacae, Enterococcus faecalis, Providencia stuartii*, as well as a gram negative bacilli which was later identified as being most similar to *I. ureiclastica* but also similar to *I. larvae* [14].

The case reported by Tanida et al. [21] in Germany described a 57-year-old homeless male who presented with pain in both extremities due to infected wounds. The patient had the wounds for months without seeking medical care prior to presentation. He was found to be septic with multiple purulent wounds of bilateral lower extremities and maggots were found between the digits. Blood cultures yielded a single organism which was identified as *I. ureiclastica*.

Infected wounds and myiasis were present in both cases as well as history of self-neglect, as was seen in our patient. All patients were also septic upon presentation.

With regards to *I. larvae*, only three cases have been reported -all of which were isolated in patients in France [12,16,19]. In the 2005 case reported by Roudiere et al., the patient was a 39-year-old male with a history of alcohol abuse who presented with trench foot and was found to have maggots in his wounds. The wound culture revealed a polymicrobial infection of *Proteus mirabilis, Providencia stuartii, group G Streptococcus, Streptococcus* sp., and *Enterococcus sp*. Subsequent blood cultures were positive for *I. larvae*.

In the following year 2006, Maurin et al. reported a case of a 72-year-old diabetic male who presented with chronic wounds of bilateral lower extremities as well as fever. Physical exam revealed maggots in the lower extremity ulcerations as well as in ulcers of the scrotum and at the anus. Blood cultures were positive for methicillin-susceptible *Staphylococcus aureus* and an unidentified gram negative bacterium which was later identified as *I. larvae*.

The third case which was reported by Grasland et al. in the year 2020, involved a 72-year-old male who also presented with a wound which was infested with maggots on his foot. *I. larvae* was again identified from blood cultures. To our knowledge, this is the first case reported in North America of sepsis secondary to an Ignatzschineria species most similar to *I. larvae* and *I. ureiclastica*.

*Ignatzschineria* species have proven to be challenging to identify as the organisms are asacharolytic and are unable to be detected by standard techniques [13]. The technique most accurate in identifying the organism is 16S rRNA gene amplification and sequencing which was the technique used in this case [1]. Although 16S rRNA was successful in narrowing down the identification to the *Ignatzschineria* genus, it was unable to determine whether the organism was *I. larvae* or *I. ureiclastica*. It was only able to show that the organism was most genetically similar to these two species. This may be due to the limited database for genomic sequencing on this organism. Another explanation could be that this is a new species of *Ignatzschineria* whose genome is close to that of *I. ureiclastica* and *I. larvae*.

The 16 S rRNA gene sequencing technique has been used to identify *Ignatzschineria* in the majority of the cases published to date; however, MALDI-TOF MS correctly identified *I. indica* in three cases published [10,11,18]. In contrast, MALDI-TOF MS was shown to be unsuccessful in the identification in our organism as well as those in two other cases and therefore may not be a reliable technique [9,13].

The organism is likely underreported due to the difficulty in identification as well as being misidentified as other organisms. *Ignatzschineria indica* was falsely identified in multiple cases as *Alcaligenes faecalis, Acinetobacter lwoffii, Acinetobacter spp., Moraxella* spp. [7,18]. *Ignatzschineria larvae* was also falsely identified as *Oligella urethralis, Oligella ureolytica,* and *Psychrobacter phenylpyruvicus* [16,19].

It is important for *Ignatzschineria* to be considered in patients with myiasis whose blood cultures reveal an unidentified gram negative bacterium. It should also be considered in patients with myiasis and blood cultures which reveal one of the above organisms due to misidentification.

In a review of the literature, *Ignatzschineria* species were only isolated in blood, urine, and abscess cultures; however, interestingly, none were isolated in wound cultures [7–21]. Common complications associated *Ignatzschineria* bacteremia include: sepsis, need for debridement, amputation of limb with the most commonly affected body area being the lower extremities, and acute kidney injury [7,9–13,15,17,18,20,21]. *Ignatzschineria* bacteremia is rarely associated with osteitis/osteomyelitis in the literature though it has been identified and subsequently required debridement or amputation of the affected limb [7,9,12,17].

In Barker et al.'s [7] article *Ignatzschineria indica* was isolated in urine of a patient with recurrent urinary tract infections related to urethrocutaneous fistulas for which nephrostomy tubes were placed. However, the Barker et al. [7] case of *Ignatzschineria* indica isolated in urine culture reported no visible myiasis in contrast to *Ignatzschineria* bacteremia cases in which all presented with visible myiasis.

Abscesses are rarely associated with *Ignatzschineria* bacteremia with only one case in the literature describing abscess in a patient with a cancerous breast mass [8]. Polymicrobial wound and blood cultures are commonly associated with *Ignatzschineria* bacteremia likely related to the complexity, chronicity and/or physical location of wounds including the feet, lower extremities, ear, and back [7,8,11,14–20].

Of the isolated *Ignatzschineria* species, the majority are susceptible to beta-lactam antimicrobials with few exceptions including intermediate susceptibility to piperacillin-tazobactam, carbapenem resistance and positive beta-lactamase testing [7,8,10,11,13–21]. Any degree of resistance to non-beta-lactam antimicrobials is even more rare with only the finding of intermediate susceptibility to ciprofloxacin in one case, intermediate sensitivity to tetracycline in one case, and resistance to fosfomycin in two cases both of which occurred in France [7,12,14,20]. Fosfomycin resistance is also notable in that it occurred in a case of definitively identified *I. larvae* while the second case was in an incompletely identified *Ignatzschineria* species which had characteristics closely related to both *I. ureclastica* and *I. larvae* [12,14]. These two cases raise the possibility of the relationship between *I. larvae* species and fosfomycin resistance.

Given the presence of any antimicrobial resistance in the isolated *Ignatzschineria* species, there are concerns for the ability of *Ignatzschineria* species to develop or acquire antimicrobial resistance [7,10,13,14]. The *Ignatzschineria* species case presented here has a notable pattern of resistance to aztreonam, cefepime, meropenem and piperacillin/tazobactam with sensitivity to amikacin, gentamicin, levofloxacin and tobramycin. This sensitivity profile supports Heddema et al.'s [13] suggestion of the potential for inducible beta-lactamase production given their unidentified *Ignatzschineria* isolate's "*in vitro* sensitivity to amoxicillin.in conjunction with a positive beta-lactamase test" and Deslandes et al. [10] findings of a historical strain of *I. indica* with carbapenem resistance.

It is unclear if the potential for antimicrobial resistance is unique to one particular species of *Ignatzschineria* or able to be generalized across all *Ignatzschineria* species. LeBrun et al. [14] reports their *Ignatzschineria* isolate as being identified as *I. ureclastica* with the reported percentage of genetic similarity with *I. larvae* was 99% identical for 16s rRNA sequences with 92% *gyrB* sequence also noted to be genetically similar to *I. ureclastica* 99% identical for 16s rRNA sequences with 96% *gyrB* genetic testing. Given the small percentage differences between genetic sequences of the *I. ureclastica* and the *I. larvae* in LeBrun et al.'s [14] case, for discussion and analysis purposes this isolate will be referred to by both species. A comparison point for the finding in the relatively resistant *Ignatzschineria* species isolated in the case presented in this article is the difference in this sensitivity profile to the previously isolated *I. larvae*/*I. ureclastica* organism by LeBrun et al. [14] with noted sensitivity to beta-lactams, aminoglycosides, fluoroquinolones, colistin, and trimethoprim/sulfamethoxazole however noted resistance to fosfomycin. It is difficult to ascertain if the *I. larvae*/*I. ureclastica* isolates have any commonality despite their both being *Ignatzschineria* species that have been not definitively identified though both possess genetic markers most closely related to *I. larvae*/*I. ureclastica*.

The *I. larvae* isolates were noted to be sensitive to beta-lactams, fluoroquinolones, aminoglycosides and cotrimoxazole [12,16]. Chloramphenicol was only noted on Maurin et al.'s [16] *I. larvae* sensitivity profile and this was sensitive as well. A unique note for Gasland et al.'s [12] *I. larvae* was the resistance to fosfomycin which was also present in LeBrun et al.'s [14] *I. ureclastica*/*I. larvae* isolate. The *I. larvae* or species closely related to *I. larvae* isolates could potentially demonstrate a characteristic resistance to fosfomycin. In contrast, *I. ureclastica* organism isolated in Germany was pan-susceptible though with a more limited panel of antimicrobials was provided [21].

*Ignatzschineria* species bacteremia treatment presents a clinical challenge due to the paucity of cases and difficulty identifying organisms leading to a lack of CLSI guidelines for MIC breakpoints and a lack of treatment guidelines [8,10,18,20]. Minimum inhibitory concentrations (MICs) for antimicrobials were interpreted using the CLSI non-Enterobacteriaceae breakpoints by Fear et al. though utilization of those breakpoints was not stated as standard in articles reporting *Ignatzschineria* species infections. (Table 1).

Beta-lactams are a mainstay of treatment though varying degrees of susceptibility have been noted in the literature including beta-lactamase production, resistance to carbapenems, and intermediate susceptibility to piperacillin-tazobactam [7,8,10–14,16,18–20]. Most common non-beta-lactam treatments included: ciprofloxacin, ofloxacin, and clindamycin [9,19,21]. Variable susceptibility to non-beta-lactam antimicrobials also been described including intermediate susceptibility to ciprofloxacin and resistance to fosfomycin [7,12,14]. Treatment regimens often involved more than one intravenous antimicrobial during the treatment course then de-escalation to oral antimicrobial monotherapy with amoxicillin, amoxicillin/clavulanic acid and/or ciprofloxacin [7–12,15–17,19–21]. Monotherapy throughout the treatment course was rare [13,14,18].

Often antimicrobial therapy was given in conjunction with removal of the larvae by wound cleaning, debridement, or amputation [7,9–13,15,17,19–21]. All treatments were considered effective with the patient surviving to discharge from the hospital with the exception of one *I. larvae*/*I. ureclastica* bacteremia patient who died of unknown causes during hospitalization [7–13,15–21]. Duration of therapy for *Ignatzschineria* bacteremia varied based on patient hospitalization course, concurrent infections and extent of illness. The most common duration of antimicrobial therapy was 14 days particularly in patients status post-surgical intervention, including amputation or debridement, or abscess drainage [7–10,13]. The range of antimicrobial therapy varied from 3 days, after which the

**Table 1**
Sensitivity profile of *Ignatzschineria larvae/Ignatzschineria ureiclastica* isolate.

| Antimicrobial | MIC | Interpretation |
|---|---|---|
| Amikacin | 4 | S |
| Aztreonam | ≥ 64 | R |
| Cefepime | ≥ 64 | R |
| Gentamicin | 1 | S |
| Levofloxacin | ≤ 0.25 | S |
| Meropenem | ≥ 16 | R |
| Piperacillin/Tazobactam | ≥ 128/4 | R |
| Tobramycin | 1 | S |

**Table 2**
Literature review of *Ignatzschineria indica* infections.

| Author/country/year | *Ignatzschineria indica* culture type | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| Barker et al., U.S.A., 2014 Case #1 | *I. indica* Blood culture | Myiasis, L foot osteomyelitis with *I. indica* bacteremia | IV ampicillin-sulbactam and IV vancomycin × 3 days Discharged on PO cephalexin | Lost to follow-up |
| Barker et al., U.S.A., 2014 Case #2 | *I. indica* Blood culture | Myiasis, L foot osteomyelitis with *I. indica* bacteremia | IV piperacillin- tazobactam and clindamycin × 1 day IV vancomycin and PO ciprofloxacin × 14 days | N/A |
| Barker et al., U.S.A., 2014 Case #3 | *I. indica* Urine culture | Urinary tract infection | N/A | N/A |
| Cipolla et al., Argentina, 2018 | *I. indica* Blood culture | Sepsis with L lower extremity wound myiasis | IV ciprofloxacin and IV clindamycin × 14 days | N/A |
| Deslandes et al., Canada, 2020 | *I. indica* Blood culture | Sepsis with L lower extremity wound myiasis | IV piperacillin-tazo-bactam × 7 days then PO amoxicillin-clavulanic acid × 7 days | Discharge to home with home wound care services resulting in full wound healing |
| Fear et al., Canada, 2019 | *I. indica* Blood culture | Sepsis with L lower extremity wound myiasis | IV vancomycin (unclear duration of therapy) and IV piperacillin-tazobactam × 10 days then PO amoxicillin-clavulanate × 14 days | N/A |
| Lysaught et al., U.S.A., 2018 | *I. indica* Blood culture | Sepsis with LLE myiasis and wound | IV vancomycin and IV clindamycin and IV piperacillin-tazobactam × 3 days then IV cefepime × 6 days | Follow-up with outpatient wound care allowed for wound healing at 6 months |
| Mejias et al., U.S.A., 2016 | *I.indica* Abscess culture | Left breast abscess Left axillary abscess Invasive mammary carcinoma (mucinous type) | IV piperacillin-tazobactam for 14 days | Discharged with follow up with Oncology, started on chemotherapy, referred for mastectomy but declined |
| Muse et al., U.S.A., 2017 | *I.indica* Blood culture | Septic shock with myiasis of decubitus ulcers and osteomyelitis | IV vancomycin and IV piperacillin-tazobactam for 7 days piperacillin-tazobactam discontinued day 7, started on IV cefepime and IV metronidazole vancomycin discontinued day 8 metronidazole discontinued day 10 After 17 days of cefepime was de-escalated to PO levaquin to complete 6 weeks | N/A |
| Rodriguez-Zuniga et al., Spain, 2019 | *I.indica* Blood culture | Sepsis with myiasis of RLE wound | IV amoxicillin/clavulanic acid for 10 days | N/A |
| Snyder et al., U.S.A., 2020 | *I.indica* Blood culture | Sepsis with bilateral lower extremity wounds with myiasis | IV vancomycin and cefepime Then IV ceftriaxone for 2 weeks | Clinically improved, discharged |

Key: LLE = left lower extremity
RLE = right lower extremity
N/A = not applicable or not reported in the literature

**Table 3**
Literature review of *Ignatzschineria/Schineria larvae* infections.

| Author/country/year | *Ignatzschineria*/*Schineria* larvae culture type | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| Grasland et al., France, 2020 | *I. larvae* Blood culture | Right foot wound and myiasis, right hallux osteitis | IV ceftriaxone × 16 days and IV gentamicin × 4 days then PO amoxicillin × 5 days | RLE surgical site healed |
| Maurin et al., France, 2007 | *Schineria larvae* Blood culture | Bilateral lower extremity, scrotum and anal margin myiasis | Amoxicillin/clavula-nate and ofloxacin, switched to oxacillin/oflaxacin for 34 days total treatment | Wounds healed during hospitalization, discharged after 27 day hospital course |
| Roudiere et al., France, 2007 | *Schineria larvae* Blood culture | "Trench foot" with myiasis | Ofloxacin plus cefotaxime for 2 weeks (first admission)<br>Ofloxacin puls cefotaxime for 2 weeks then ciprofloxacin plus amoxicillin/clavulanic acid for 20 days (second admission) | Clinical improvement and sterilization of blood cultures<br>Readmission 3 months later, clinical improvement then transfer to addition center |

**Table 4**
Literature review of *Ignatzschineria ureclastica* infections.

| Author/country/ year | *Ignatzschineria* ureclastica culture type | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| Tanida et al., Germany, 2019 | *I.ureiclastica* Blood culture | Sepsis due to bilateral lower extremity wounds with myiasis | IV ampicillin/sulbactam for 6 days Then oral ciprofloxacin for 2 weeks | Clinical improvement, no need for debridement, discharged |

**Table 5**
Literature review of *Ignatzschineria species* infections unable to be identified.

| Author/country/ year | *Ignatzschineria* species unable to be identified culture type | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| Heddema et al., Netherlands, 2016 | *Ignatzschineria* species unable to be identified Blood culture | R foot myiasis with sepsis | Amoxicillin-clavulanic acid × 14 days | Discharged home |
| LeBrun et al., France, 2015 | *Ignatzschineria* species closely related to *I. larvae/I. ureclastica* Blood culture | Sepsis with R shoulder necrotic lesion and genital myiasis | Ceftriaxone × 10 days | Death "from no evident cause" on day 10 of hospitalization |

patient was lost to follow-up, to 50 days in a patient with concurrent sacral osteomyelitis [7,17]. Table 2 provides further literature review regarding course of treatment. (Table 3–5).

Management of the case of *Ignatzschineria* bacteremia presented in this article includes multiple antimicrobials utilized in the initial stages of hospitalization, wound cleaning of the affected area and imaging of affected limb consistent with osteomyelitis eventually requiring amputation of the affected limb due to infection and peripheral arterial disease. The patient was able to transition to oral fluoroquinolone to complete the course of treatment with successful outcome of patient survival. Though lack of treatment guidelines precludes any standardized treatment for *Ignatzschineria* bacteremia, frequently used beta-lactam or beta-lactam/beta-lactamase inhibitor antimicrobials have shown to be effective though clinicians should be aware of the potential for antimicrobial resistant organisms and use antimicrobial susceptibility profiles to guide treatment when available.

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