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Bacteraemia caused by *Weissella confusa* at a university hospital in Taiwan, 1997–2007

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Abstract

Human infections caused by *Weissella confusa* are rarely reported. Ten patients with bacteraemia caused by *W. confusa* who were treated at a tertiary-care hospital in Taiwan during 1997–2007 were studied. All isolates were initially misidentified as various *Lactobacillus* and *Leuconostoc* species by two commercial automated identification methods, and were confirmed to be *W. confusa* by 16S rRNA sequencing analysis. MICs of these isolates for ten antimicrobial agents were determined by the agar dilution method. The characteristics of these patients included underlying malignancy (n = 4), presence of a central catheter (n = 6), surgery within the previous 3 months (n = 4) and concomitant polymicrobial bacteraemia (n = 5, 50%). Mortality was directly attributed to bacteraemia in two patients. All isolates exhibited high trimethoprim–sulphamethoxazole and ceftazidime MICs (≥128 mg/L) and were inhibited by linezolid, daptomycin, ceftobiprole and tigecycline at 4, 0.12, 2 and 0.12 mg/L, respectively. In conclusion, *W. confusa* should be included in the list of organisms causing bacteraemia in immunocompromised hosts. Novel antibiotics, including daptomycin, moxifloxacin, doripenem and tigecycline, exert good activity against *W. confusa*.

Keywords: Antimicrobial susceptibility, bacteraemia, outcomes, Taiwan, *Weissella confusa*
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Introduction

Isolates of *Weissella* species, first identified in 1993, are Gram-positive, catalase-negative coccobacilli that are intrinsically resistant to vancomycin [1,2]. Bacteraemia caused by *Weissella* species in humans is extremely rare, and its pathogenic role has not been established [3–5]. Isolates of *Weissella* species retrieved from blood culture are easily misidentified as *Lactobacillus* and *Leuconostoc* species by traditional or commercial phenotypic identification methods, and are often considered to be contaminants [3,6]. Among the different *Weissella* species, *Weissella confusa* (basonym *Lactobacillus confusus*) is the most commonly recovered species from clinical samples, and has been linked to infective endocarditis [3,4]. *W. confusa* has been detected in various samples, including fermented foods, sugar cane, milk, otitis samples and human faeces [1,7]. The clinical significance of *Weissella* bacteraemia remains unclear, but the organism has been frequently isolated in patients with complex medical conditions and immunocompromised status [2,3,5].

The aim of this study was to investigate the clinical and microbiological characteristics of patients with *W. confusa* bacteraemia. All isolates were confirmed to the species level by 16S RNA sequencing analysis, and the results were compared with those obtained with two commercial automated identification methods. Susceptibilities of these *W. confusa* isolates to various antibiotics were also determined.

Materials and Methods

Bacterial isolates, patients and setting

This study was conducted at National Taiwan University Hospital, a 2900-bed tertiary-care centre in northern Taiwan. A total of 43 blood isolates of Gram-positive, catalase-negative, vancomycin-resistant coccobacilli, with negative

reactions for pyrrolidonyl arylamidase and leucine aminopeptidase, collected from the Clinical Microbiology Laboratory of the hospital from 1997 to 2007 were studied. These isolates were identified as either *Lactobacillus* or *Leuconostoc* species by traditional or commercial automated identification systems [8].

Clinical characteristics

A standardized case record form was used to collect demographic and clinical data, including patients' age, gender and underlying status, the presence or absence of central vascular access, surgical procedure received, initial clinical presentation, and empirical antibiotic usage and glycopeptide usage within 3 months prior to the acquisition of bacteraemia.

Disease severity was evaluated with the Pittsburgh bacteraemia score and modified APACHE II (Acute Physiology and Chronic Health Evaluation) scores calculated within 8 h after positive blood cultures were obtained [9]. The modified APACHE II score assigned zero points to the items 'P_aO_2' and 'pH' if the data of the two variables were unavailable under the condition that the attending physicians did not perform arterial blood gas analysis [10]. Crude mortality was calculated on day 30 and day 60 as the main patient outcome.

Species identification by commercial automated methods

All 43 isolates from patients with bacteraemia were repeatedly identified with the identification panels (SMIC/ID-100) of the Phoenix Automated Microbiology System (Becton Dickinson Diagnostic, Sparks, MD, USA) and the Vitek 2 system (bioMerieux, Marcy l'Etoile, France) for Gram-positive identification. The last updated versions of the Phoenix (software version 5.02H/4.11B, 20 May 2010) and Vitek 2 (Version 4.02PC, July 2010) databases were obtained from the manufacturers.

16S rRNA gene sequencing analysis

The 16S rRNA sequencing analysis was performed for the 43 blood isolates initially identified as *Lactobacillus* and *Leuconostoc* species. Partial sequencing of the 16S rRNA gene up to 1475 bp was performed for species identification of all isolates, with the following primers: forward, 5′-AGAGTTTG ATCCTGGCTCAG-3′; and reverse, 5′-GGTTACCTTGT TACGACTT-3′ [8]. The results were compared with published sequences in the GenBank database, using the BLASTN algorithm. The closest matches and GenBank accession number were obtained. *Leuconostoc lactis* ATCC 19256 was used as the control strain in each test.

Antimicrobial susceptibility testing

MICs for ampicillin, ampicillin–sulbactam, amoxicillin–clavulanic acid, ceftazidime, trimethoprim–sulphamethoxazole and vancomycin (Sigma, St Louis, MO, USA), moxifloxacin (Bayer, West Haven, CT, USA), azithromycin, linezolid, piperacillin–tazobactam and tigecycline (Pfizer, New York, NY, USA), meropenem (Sumitomo, Osaka, Japan), doripenem (Shionogi, Tokyo, Japan), ceftobiprole (Johnson & Johnson, Raritan, NJ, USA) and daptomycin (Cubist, Lexington, MA, USA) were determined with the broth microdilution method, with horse blood supplementation according to CLSI guidelines [11]. Cation-adjusted broth containing 50 mg/L calcium was used for daptomycin susceptibility testing [12]. *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619 were used as quality control strains.

Results

Species identification

Among the 43 isolates, ten were identified as *W. confusa* by 16S rRNA gene sequencing analysis. Among the other 33 isolates, 15 were identified as *L. lactis*, three as *Leuconostoc citreum*, one as *Leuconostoc mesenteroides*, one as *Leuconostoc pseudomesenteroides*, three as *Lactobacillus fermentum*, eight as *Lactobacillus sallivarius*, one as *Pediococcus acidilactici* and one as *Streptococcus anginosus*. These 33 isolates were also identified with the same 16S rRNA gene sequencing analysis with at least 99% maximal identity (data shown elsewhere).

The results of the identification of the ten isolates with the Phoenix Automated Microbiology System and the Vitek 2 system are presented in Table 1. Half of the ten isolates were misidentified as *L. mesenteroides* by the Phoenix system. Two isolates were identified as *Streptococcus bovis* II, one as *L. lactis* and one as *Staphylococcus hominis*; one pathogen was not identified. The Vitek 2 system categorized four of the ten species as *L. pseudomesenteroides*. Three of these were unidentified organisms, two were *Pediococcus pentosaceus* and one was *Streptococcus agalactiae*/*Streptococcus equinus*. None of the isolates could be correctly identified as *W. confusa* by the Phoenix Automated Microbiology System or by the Vitek 2 system. Significant discrepancy also exists within the two commercial identification systems, as only two isolates were correctly identified to the genus level and none was correctly identified to the species level. The discrepancy possibly resulted from inherent limitations of these identification systems and different times of database development.

Characteristics of patients

The clinical characteristics of the ten patients with *W. confusa* bacteraemia are shown in Table 2 and summarized in Table 3. Of the ten patients, six were female. The mean age

TABLE 1. Species identification of the ten isolates by different methods

Isolate no.	16S rRNA sequencing (maximal identity, %)	Phoenix system (% identity)	Vitek 2 system (% identity)
1	*Weissella confusa*[a] (100)	*Leuconostoc mesenteroides* (90)	*Pediococcus pentosaceus* (86)
2	*W. confusa* (100)	*L. mesenteroides* (99)	*Leuconostoc pseudomesenteroides* (86)
3	*W. confusa* (99)	*Streptococcus bovis* II (99)	Unidentified organism
4	*W. confusa* (100)	*L. mesenteroides* (96)	*Streptococcus agalactiae*/ *Streptococcus equinus* (86)
5	*W. confusa* (100)	*Staphylococcus hominis* (99)	*L. pseudomesenteroides* (92)
6	*W. confusa* (100)	*L. mesenteroides* (90)	*L. pseudomesenteroides*/ *Leuconostoc citreum* (92)
7	*W. confusa* (99)	*L. mesenteroides* (99)	*P. pentosaceus* (86)
8	*W. confusa* (100)	Unidentified organism	Unidentified organism
9	*W. confusa* (99)	*Leuconostoc lactis* (99)	*L. pseudomesenteroides*/*L. lactis* (86)
10	*W. confusa* (99)	*Streptococcus bovis* II (90)	Unidentified organism

[a]GenBank accession number of *W. confusa*, GU138614.1.

of the patients was 56.6 years, and all except one were adults. Four patients had underlying malignancy, including two with haematological malignancy and two with solid organ cancer. Other factors considered to be indicative of immunocompromised status included steroid usage (n = 3), chronic renal insufficiency (defined as creatinine level >2 mg/dL) (n = 3) and diabetes mellitus (n = 1). Six patients had central venous catheters or Port-A-Cath implantations at the time of bacteraemia onset. One paediatric patient had a peripheral venous line implanted and was receiving total parenteral nutrition. Four patients had undergone surgery within the past 3 months.

Fever remained the most common symptom of bacteraemia (80%). Gastrointestinal symptoms, including abdominal pain, vomiting or diarrhoea, were present in four patients. The mean Pitt bacteraemia score was 2.5, and the mean APACHE II score was 19.9. Eight of the ten patients had hospital-acquired bacteraemia. The mean duration of hospitalization was 55.4 days (range 6–257 days). The other two patients were categorized as having healthcare-associated bacteraemia.

All five patients had concomitant polymicrobial infection. The concomitant pathogens isolated included *Acinetobacter baumannii*, *Enterobacter cloacae*, *E. faecalis*, *Candida albicans*, *Bacillus* species, methicillin-resistant *S. aureus*, *Escherichia coli*, *Chryseobacterium indologenes* and *Enterobacter aerogenes*. Among the five monomicrobial bacteraemias, three were detected in more than two blood culture sets, and the remaining two had positive cultures in one blood culture set (two bottles).

Nine patients received initial broad-spectrum β-lactam antibiotics (including ampicillin–sulbactam in two patients, amoxicillin–clavulanate in three, ceftazidime in three and cefepime in one). One patient received no antibiotics at all. One patient received a combination of four antibiotics: trimethoprim–sulphamethoxazole, vancomycin, ciprofloxacin and ceftazidime. Notably, three patients received vancomycin as an empirical antibiotic, which was not effective against *W. confusa*. Four patients had received vancomycin in the previous 3 months. Among the eight patients who survived until initial culture was available, antibiotics were adjusted to ampicillin–sulbactam in two patients, piperacillin–tazobactam in one patient, amoxicillin–clavulanate in one patient, piperacillin–tazobactam in one patient, penicillin in one patient and ciprofloxacin in one patient; no antibiotics were given to one patient.

Six of the eight patients who initially had febrile symptoms achieved defeverence within 72 h. The overall 14-day, 30-day and 60-day mortality rates were 30%, 40% and 50%, respectively. Mortality was directly attributed to bacteraemia in two patients. Only four patients survived until discharge.

Antimicrobial susceptibilities

Table 4 shows the MICs of the ten isolates for 15 antimicrobial agents. The ranges of MICs were as follows: 0.5–1 mg/L for ampicillin, 0.5–2 mg/L for ceftobiprole, 2–4 mg/L for linezolid, 1–16 mg/Lfor meropenem, 0.5–16 mg/L for doripenem, 0.25–0.5 mg/L for moxifloxacin, 0.12–0.12 mg/L for azithromycin, 0.03–0.12 mg/L for linezolid, 0.03–0.12 mg/L for daptomycin, ≥128 mg/L for trimethoprim–sulphamethoxazole, ≥128 mg/L for ceftazidime, 4–8 mg/L for piperacillin–tazobactam, 4–16 mg/L for ampicillin–sulbactam, 0.5–8 mg/L for amoxicillin–clavulanate, and >64 mg/L for vancomycin.

Discussion

Since the reclassification of *L. pseudomesenteroides* as a member of the *Weissella* genus because of its distinct 16S rRNA phylogenetic profile [1], more than ten species (including *W. confusa*, previously *Lactobacillus confusus*) have been included in this novel genus. Invasive *Weissella* species infection is extremely rare. Most reports include *W. confusa* bloodstream infection, with endocarditis being the focus of

TABLE 2. Clinical characteristics of ten patients with *Weissella confusa* bacteraemia

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Gender/age (years)	F/58	M/68	F/62	F/92	F/27	F/62	M/73	M/52	F/8	M/64
Chief diagnosis	NHL	COPD, pneumonia	B-cell lymphoma	CRF, vascular dementia	Thyroid goitre, AS	Ischaemic bowel, NSTEMI, ESRD	Cancerous peritonitis, asphyxia	Oesophageal cancer	Ileus	SAH
Polymicrobial	*Acinetobacter baubaumannii, Enterobacter cloacae, Candida albicans, Bacillus* species	No	MRSA	No	*Escherichia coli*	No	*Chryseobacterium indologenes*	No	No	*Enterobacter aerogenes*
Catheter/TPN	Port-A/No	CVC/Yes	CVC, Port-A/No	No/No	No/No	CVC/Yes	CVC/Yes	Port-A/No	PVL/Yes	No/No
Hospital stay (days)	11	257	51	13	0	73	14	1	18	6
PBS/APACHE II score	3/21	1/20	1/22	2/27	1/6	0/22	12/48	2/13	2/11	1/9
Treatment regimen	VAN, CAZ	Amp–Sulba	VAN + CAZ + GM	Amp–Sulba	Amox–Cla	No	CFP for 1 day	Amox/Cla	VAN + CIP + CAZ + TMP–SMX	Amox/Cla
Outcome	Died on the 19th hospitalization day	Died on the 90th hospitalization day	Died on the 5th hospitalization day	Died on the 6th hospitalization day	Survived at discharge	Died on the 41st hospitalization day	Died on the 1st hospitalization day	Survived at discharge	Survived at discharge	Survived at discharge

Amox–Cla, amoxicillin–clavulanate; Amp–Sulba, ampicillin–sulbactam; AS, ankylosing spondylitis; CAZ, ceftazidime; CFP, cefepime; CIP, ciprofloxacin; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVC, central venous catheter; ESRD; F, female; GM, gentamicin; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; NHL, non-Hodgkin's lymphoma; NSTEMI, non-ST elevation myocardial infarction; PBS, Pitt bacteraemia score; PVL, peripheral venous line; SAH, subarachnoid haemorrhage; TMP–SMX, trimethoprim–sulphamethoxazole; TPN; VAN, vancomycin.

TABLE 3. Comparison of clinical characteristics of 60-day survivors and non-survivors of *Weissella confusa* bacteraemia

	All (*n* = 10)	Survivors at 60 days (*n* = 5)	Non-survivors at 60 days (*n* = 5)
Male/female	4/6	3/2	1/4
Mean age (years)	56.6	43.8	69.4
Overall malignancy, no. (%)	4 (40)	1 (20)	3 (60)
Prior chemotherapy within 3 months, no. (%)	3 (30)	1 (20)	2 (40)
Presence of central vascular catheter, no. (%)	6 (60)	2 (40)	4 (80)
Surgery within 3 months, no. (%)	4 (40)	3 (60)	1 (20)
Hospitalization days prior to acquisition of bacteraemia	44.4	56.4	32.4
Mean Pitt bacteraemia score	2.5	1.4	3.6
Concomitant polymicrobial bacteraemia (%)	5 (50)	2 (40)	3 (60)

infection [3–5]. Correct identification of *Weissella* species cannot be achieved by commercial phenotypic identification methods [3]. Modern molecular techniques, including multiplex PCR, restriction of internal spacer region-amplified fragments, genus-specific PCR analysis and 16S rRNA gene sequencing, have been described for the identification of *Leuconostoc* and *Weissella* species [6,13–15].

In a comparison with two commercial automated systems, *W. confusa* species were often misidentified as *Leuconostoc* species, followed by *P. pentosaceus* and *Streptococcus bovis* II. Given the fact that ten of 43 blood isolates of Gram-positive, catalase-negative and vancomycin-resistant coccobacilli turned out to be *W. confusa* by the 16S rRNA gene sequencing method, the actual incidence of *W. confusa* bacteraemia was undoubtedly underestimated. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry is increasingly being shown to be a fast, cost-effective and accurate method for the routine identification of bacterial isolates and Gram-negative isolates causing bacteraemia, including *W. confusa* [16–18]. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry should be considered as a potential alternative method for the correct identification of this pathogen [18].

W. confusa has been reported to be a pathogenic microorganism in primates (*Cercopithecus mona*) [19]. For human beings, there are only three formal case reports on *W. confusa* bacteraemia in the English-language literature. One case was a 46-year-old male with a history of abdominal aortic dissection status after repair, complicated by ischaemic bowel, who developed concomitant *Klebsiella pneumoniae* and *W. confusa* bacteraemia. No focus of infection could be identified, and the patient recovered after piperacillin–tazobactam therapy [5]. Infective endocarditis was identified as a focus of infection in the other two patients. One patient was a 49-year-old male with a diagnosis of *W. confusa* infective

TABLE 4. Antimicrobial susceptibilities of ten blood isolates of *Weissella confusa* according to the agar dilution method

	MIC (mg/L)														
Isolate no.	AM	SAM	AMC	CAZ	CBP	TZP	MEM	DOR	Moxi	VA	DAP	LIN	AZI	SXT	TGC
1	0.5	8/4	0.5/0.25	128	1	4/4	1	0.5	0.5	>64	0.03	2	0.12	128	0.06
2	0.5	8/4	0.5/0.25	>128	1	4/4	1	0.5	0.5	>64	0.03	4	0.12	>128	0.12
3	0.5	8/4	0.5/0.25	>128	0.5	8/4	2	0.5	0.25	>64	0.12	2	0.12	>128	0.06
4	0.5	8/4	0.5/0.25	>128	2	8/4	2	2	0.25	>64	0.03	2	0.12	128	0.03
5	0.5	8/4	0.5/0.25	>128	2	4/4	8	8	0.5	>64	0.03	2	0.12	>128	0.06
6	0.5	8/4	0.5/0.25	>128	2	4/4	16	8	0.25	>64	0.12	4	0.12	16	0.06
7	0.5	4/2	0.5/0.25	>128	1	4/4	1	0.5	0.25	>64	0.03	2	0.12	128	0.06
8	0.5	8/4	0.5/0.25	>128	1	4/4	1	0.5	0.25	>64	0.03	2	0.12	128	0.03
9	1	16/8	8/4	>128	2	4/4	16	16	0.5	>64	0.12	4	0.12	>128	0.12
10	0.5	8/4	0.5/0.25	>128	0.5	4/4	1	0.5	0.25	>64	0.03	2	0.12	>128	0.06

AM, ampicillin; AMC, amoxicillin–clavulanate; AZI, azithromycin; CAZ, ceftazidime; CBP, ceftobiprole; DAP, daptomycin; DOR, doripenem; LIN, linezolid; MEM, meropenem; Moxi, moxifloxacin; SAM, ampicillin–sulbactam; SXT, trimethoprim–sulphamethoxazole; TGC, tigecycline; TZP, piperacillin–tazobactam; VA, vancomycin.

endocarditis. This patient died 4 days after discharge, without any antibiotic treatment, and autopsy examination showed septic emboli with bacterial colonies in multiple organs [4]. The third patient underwent valve replacement followed by prolonged antibiotic usage, and eventually recovered [3].

The common features of patients in this study included the presence of underlying immunocompromised status, central catheter use and concomitant polymicrobial bacteraemia. Malignancy was the most common factor associated with immunocompromised status and also signified complicated medical status. Three patients had chemotherapy in the 3 months prior to bacteraemia onset, and this might also have predisposed these patients to having impaired immune status. Breakdown of the gastrointestinal mucosal barrier under conditions of abdominal surgery might serve as a portal of entry for *W. confusa*. Six patients in this series either had gastrointestinal symptoms at time of bacteraemia or had undergone abdominal surgery in the previous 3 months. Among the remaining four patients, two had received chemotherapy within the previous 3 months, causing varying degrees of mucositis.

The portal of entry of *W. confusa* among our patients remained unclear. *W. confusa* was also found in fermented foods, sugar cane, milk and carrot juice [1,7,20,21]. *W. confusa* has also been detected in clinical samples of dog faeces, human faeces, peritoneal fluids and the abdominal walls of patients [2,7,22]. Furthermore, *Weissella cibria*, the species that is most closely taxonomically related to *W. confusa*, was detected in traditional Taiwanese fermented foods (suan-tsai, fu-tsai and yang-dong-gua) [23,24]. Skin defect resulting from central vascular catheter implementation was considered to be the portal of entry for *Leuconostoc* species [25,26]. Up to 60% of our patients had a central vascular catheter at the time of bacteraemia onset; however, none of the catheter tips gave a positive cultures for *W. confusa*. Furthermore, half of our patients had polymicrobial bacteraemia, indicating that gastrointestinal mucosal breakdown might be another probable route of entry for *W. confusa* resulting in bacteraemia.

The pathogenic role of *Weissella* species remained unclear in this study. Five of our patients had *W. confusa* monomicrobial bacteraemia. Four of these patients were febrile, and for three, the organism was grown in at least two sets of blood cultures. The mean Pitt bacteraemia score was 1.4 (range 0–2). The severity of polymicrobial bacteraemia did not differ significantly from that of monomicrobial bacteraemia.

The antimicrobial susceptibilities of *W. confusa* are not well understood. Low MICs of penicillin (0.38 mg/L), ampicillin (0.5 mg/L), imipenem (0.06 mg/L), erythromycin (0.13 mg/L), clindamycin (0.06 mg/L) and ciprofloxacin (0.5 mg/L) were found in a previous study [27]. High-level resistance to co-trimoxazole (>32 mg/L), metronidazole (>256 mg/L), vancomycin (>256 mg/L) and teicoplanin (>256 mg/L) was also reported [27]. In this study, we further demonstrated the presence of high-level resistance to ceftazidime (MIC ≥128 mg/L). Amoxicillin–clavulanate, ampicillin–sulbactam, piperacillin–tazobactam, daptomycin, moxifloxacin, doripenem and tigecycline exerted good *in vitro* activity against the *W. confusa* isolates tested. However, the *in vitro* activities of linezolid, meropenem and cefobiprole against the isolates tested varied. It is also noteworthy that three patients who received cephalosporins (ceftazidime in two and cefepime in one) as initial antibiotics had poor prognoses. In addition to penicillin, ampicillin, imipenem, clindamycin, erythromycin, moxifloxacin, doripenem, daptomycin and tigecycline may be considered as alternative antimicrobial agents for the treatment of *W. confusa* bacteraemia.

Vancomycin usage may alter the intestinal flora, and is considered to be a possible mechanism of *Lactobacillus* translocation [28,29]. Four of our patients had previously used vancomycin. Two patients had previously used metronidazole. The use of vancomycin and metronidazole, to which

the *Weissella* species are resistant, may be considered as a risk factor for *Weissella* bacteraemia.

In conclusion, *W. confusa* should be included in the list of organisms causing bacteraemia in immunocompromised hosts. The most probable portal of entry is surgery-related or chemotherapy-related compromise of the gastrointestinal mucosal barrier. An inherent problem with commercial phenotypic identification is outdated databases, preventing accurate identification, and 16S rRNA gene sequencing is able to identify *W. confusa*. Novel antibiotics, including daptomycin, moxifloxacin, doripenem and tigecycline, exert good *in vitro* activity against *W. confusa*. Clinicians should keep in mind that when growth of Gram-positive cocci is found in the blood cultures of hospitalized susceptible hosts, vancomycin-resistant species, including *W. confusa*, should be considered.

Transparency Declaration

All authors declare no conflicts of interest.

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