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Nosocomial outbreak of *Achromobacter* spp. bacteremia due to germicide contamination: a systematic review

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Abstract. – OBJECTIVE: *Achromobacter* spp. are aerobic, non-fermentative Gram-negative bacilli that can be widely found in aquatic environments. Nosocomial outbreaks and pseudo-outbreaks of *Achromobacter* spp. bacteremia have been recognized for decades. Notably, commonly used germicides in hospital settings constitute important sources for these outbreaks. This review aims at summarizing the latest studies and presents the characteristics of nosocomial outbreaks of *Achromobacter* spp. bacteremia caused by germicide contamination.

MATERIALS AND METHODS: A systematic search of the PubMed and EMBASE databases was conducted for articles published in English between January 1, 2000, and June 10, 2022.

RESULTS: Overall, 170 articles were retrieved, and 7 studies were finally included in the systematic review. Whether true or pseudo-bacteremia, positive blood culture results were most commonly reported in immunosuppressed patients or those with indwelling catheters. The most commonly reported contaminated germicide was chlorhexidine solution used as both an antiseptic and disinfectant. Atomizers, dispensers, and various product containers were identified as reservoirs. The prognoses of the affected patients were generally favorable.

CONCLUSIONS: Awareness about the high survival ability of *Achromobacter* spp. in germicides and the possible hospital reservoirs of these microbes will help to improve infection control and prevent nosocomial outbreaks or pseudo-outbreaks caused by *Achromobacter* spp.

Key Words:
Achromobacter, Healthcare-associated infection, Nosocomial outbreak, Bacteremia, Germicide, Antiseptics, Disinfectants, Contamination.

Introduction

Nosocomial infections – namely, healthcare-associated infections – are defined as infections acquired during the course of treatment in healthcare settings (in the strictest sense, acute care hospitals)[1]. Among them, bacteremia is defined as the presence of viable bacteria in the blood[2,3] and can also be associated with increased mortality and morbidity[4,5]. Blood culture is an essential diagnostic tool for detecting live organisms in blood[6]. However, false-positive blood cultures can occur when microorganisms present on the skin or in other environments are introduced in the process of obtaining blood cultures[5]. False-positive results from contaminated blood samples influence the decision of the physician on whether to initiate empirical antimicrobial therapy[7].

Gram-positive bacteria predominate the normal flora of a skin[4,8]. Gram-positive bacteria, such as coagulase-negative staphylococci, non-anthracis *Bacillus* spp., *Corynebacterium* spp., *Propionibacterium* spp., *Micrococcus* spp., *Aerococcus* spp., and alpha-hemolytic streptococci, typically represent > 80% of all cases of blood culture contamination[4,7,8]. In contrast, Gram-negative bacteria constitute only a small proportion of the skin flora and rarely cause blood culture contamination[8]. Thus, clinicians are more inclined to initiate empirical treatment if Gram-negative organisms are identified in blood cultures because of the low chance of a false-positive result in such cases.

The genus *Achromobacter* is an aerobic, non-fermenting, Gram-negative bacilli of the order Burkholderiales[9,10]. The genus *Achromobacter* currently comprises 19 designated species. *Achromobacter* species are commonly referred to as *Achromobacter xylosoxidans* through conventional methods. More accurate species determination can be achieved through multi-locus sequence typing and nrdA gene sequencing[9,11]. *Achromobacter* spp. can cause opportunistic infections in immunocompromised hosts, particularly in patients with cystic fibrosis[9,10]. *Achromobacter* spp.

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are ubiquitous in aquatic environments[10] and can colonize various aqueous solutions, such as dialysis fluid, ultrasound gel, and even disinfectants in hospital settings[10,12,13].

A contaminated healthcare environment (e.g., inanimate surfaces, equipment, hands or gowns of healthcare personnel, and bottled water) can be a reservoir of pathogens and play a significant role in the spread of healthcare-associated infections[14-16]. Therefore, decontamination practices including cleaning, disinfection, sterilization, and appropriate use of germicides are fundamental for the control and prevention of nosocomial infections[17,18]. In particular, procedures that involve contact with sterile tissues or the vessels of patients can increase the risk of transmission of pathogens; therefore, for these procedures, thorough disinfection of equipment and appropriate antiseptic use on the skin are essential[18-20]. However, although germicides may be a source of contamination, it is difficult to identify germicides as the cause of nosocomial infections due to their antimicrobial properties[21]. Furthermore, contaminated germicides tend to be used repeatedly for infection control in hospitals; thus, they can be hidden sources of persistent nosocomial infections[22-24].

Several outbreaks and pseudo-outbreaks of bacteremia caused by the Gram-negative bacteria *Achromobacter* spp. have been reported; notably, these outbreaks are often associated with contaminated germicides[24-30]. Unfortunately, the treatment of *Achromobacter* spp. infections is challenging because of their intrinsic or acquired resistance to many antibiotics[9]. Furthermore, germicides cannot always be used eradicate *Achromobacter* spp. and thus can be a source of unexpected nosocomial outbreaks[31]. Both outbreaks and pseudo-outbreaks of bacteremia reflect inadequate infection control processes in healthcare facilities and can increase unnecessary antibiotic use and healthcare costs[7,31,32]. In this study, we aimed at summarizing the latest studies and present the characteristics of nosocomial outbreaks of *Achromobacter* spp. bacteremia caused by germicide contamination.

What Are the Differences Among Germicides, Antiseptics, and Disinfectants?

A precise understanding of terminology is important before starting this systematic review. A germicide is an agent that can inactivate microorganisms, which therefore includes antiseptics and disinfectants. Antiseptics are antimicrobial agents applied to living tissues, such as mucous membranes or the skin, and disinfectants are products used only on inanimate objects. In general, antiseptics are only used on the skin and thus are not for surface or object disinfection, whereas disinfectants are not used on the skin since they would injure the skin and tissues[33,34].

Materials and Methods

This systematic review is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[35].

Search Strategy, Inclusion and Exclusion Criteria, and Data Extraction

Two authors (HK and SHY) searched the PubMed and EMBASE databases for articles published in English between January 1, 2000, and June 10, 2022, using the following terms: ("Achromobacter") AND ("outbreak" OR "bacteremia" OR "nosocomial" OR "healthcare-associated infection" OR "germicide"). A search filter was applied to limit the search to human studies. We included studies that evaluated nosocomial outbreaks of *Achromobacter* spp. bacteremia associated with germicides. Reviews, commentaries, editorials, and laboratory experiments were excluded. The following data were extracted from each report: first author, publication year, country, clinical setting, contaminant(s) (microorganism), contaminated source, patient characteristics, clinical symptoms and/or signs, outbreak management, treatment, and prognosis. We only included studies in which verification of the contaminated sources was feasible.

Results

The literature search yielded 170 articles. Of these, after removing 44 duplicates, 126 articles were screened, and 104 articles were excluded based on the inclusion criteria (Figure 1). From the 22 full-text reviews, 15 studies were excluded as follows: 6 studies reported outbreaks not associated with germicides, and 9 studies reported cases not co-associated with an outbreak and germicides. Therefore, the remaining 7 studies[24-30] were finally included in this systematic review (Figure 1).

Clinical Characteristics of a Nosocomial Outbreak of Achromobacter Spp. Bacteremia

Table I summarizes the characteristics of the included studies. Publications of outbreaks were reported from the following five different countries: France (n = 2), Germany (n = 1), Mexico (n = 1), Spain (n = 2), and South Africa (n = 1). The clinical settings of the outbreaks were a tertiary-care hospital (n = 1), a hemodialysis unit (n = 2), a hematology department (n = 1), internal medicine wards [an intensive care unit and an intermediate care unit] (n = 1), a neonatal care unit (n = 1), and a pediatric onco-hematology department (n = 1).

Most studies[24,25,27,28,30] reported that the affected patients were immunosuppressed or had underlying diseases (e.g., hematological malignancies, human immunodeficiency virus infection, and hemodialysis patients with indwelling intravascular catheters). One study[26] reported that most of the patients with positive *Achromobacter* spp. blood cultures had no clinical symptoms of *Achromobacter* spp. infection; thus, the authors concluded that the outbreak was pseudo-bacteremia. However, other studies[24,25,27-30] reported various incidence rates of clinically significant bacteremia; the most common clinical symptom was fever (Table I).

Contaminated Source

The contaminated germicide materials in the outbreaks were as follows: didecyl dimethyl ammonium chloride (n = 2, Surfanios® solution; used as both an antiseptic and a disinfectant), chlorhexidine solution (n = 3, antiseptic and disinfectant), benzalkonium chloride (n = 1, antiseptic and disinfectant), and a glucoprotamin-based disinfectant (n = 1, Incidin® Plus solution; disinfectant only). The reservoir or transmission devices were as follows: atomizer (n = 2), dispenser (n = 3), and bottles or containers of products (n = 2). Those are commonly used by hospitalized patients and act as aqueous reservoirs of bacteria (Table I).

Treatment and Prognosis

Most of the included studies[24,27-30] initiated empirical systemic antibiotics (n = 5,71%) and revised the regimens according to the results of antimicrobial susceptibility testing[24,27,28] (Table II). The following antibiotics were mainly used: carbapenems (e.g., imipenem and meropenem), piperacillin-tazobactam, ceftazidime, fluoroquinolones (e.g., ciprofloxacin and levofloxacin), and a combination with or without aminoglycosides[24,27-30]. In addition, intravascular catheters were typically removed since these could be a sustained contaminated source of infection[25,27,30]. However, some patients were cured without catheter removal[25,27,30] (Table II).

The prognosis was generally good. Most affected patients were cured after treatment with the proper antibiotics and/or removal of the indwelling catheters in all the included studies. No further cases were reported during the follow-up periods after the removal of the contamination sources, if reported. One patient developed endocarditis, probably as a septic complication of the bacteremia, but was successfully treated with imipenem[27] (Table II).

Discussion

Nosocomial infections are associated with increased morbidity, mortality, and medical costs in patients and contribute to antimicrobial resistance[36,37]. Due to the high potential risk of bacterial transmission from environmental sources, appropriate hand hygiene and environmental

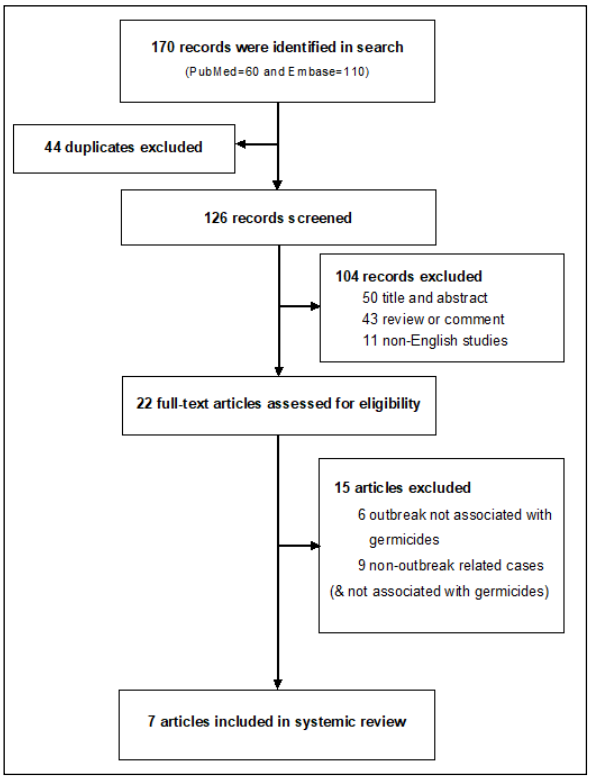

Figure 1. Flow chart of the study selection process.

Table I. Characteristics of the included studies.

First Author/Year	Country	Setting	Contaminant	Sample	Clinical symptom/sign	Contaminated source [device]	Patient characteristics
Said 2022*[24]	South Africa	Tertiary care Academic hospital	*Achromobacter denitrificans*	Blood (63%)	Clinical signs of sepsis (25%) †	Chlorhexidine solution [dispenser]	Immunocompromised (e.g., HIV infection, malignancy, and chronic steroid use; 42%), intravascular catheters (42%)
Vázquez Castellanos 2022§[25]	Mexico	Hemodialysis unit	*Achromobacter xylosoxidans* (59%) and *Achromobacter denitrificans* (41%)	Blood	Chills (100%), fever (35%), tachycardia (71%), hypotension (24%), and tachypnea (6%)	Benzalkonium chloride solution [bottles used in the hemodialysis area and unopened containers from the warehouse]	Intravascular catheter (100%)
Günther 2016[26]	Germany	Internal medicine wards: intensive care unit and intermediate care unit	*Achromobacter xylosoxidans*	Blood	Pseudo-bacteremia¶	Incidin ® Plus solution; (glucoprotamin-based disinfectant) [dispensers]	Patients treated in internal medicine wards
Hugon 2015**[27]	France	Pediatric onco-hematology department	*Achromobacter* spp.	Blood	Fever (100%)	Surfanios® solution (didecyl dimethyl ammonium chloride 0.25%) [plastic atomizers]	Immunocompromised (e.g., acute leukemia, auto-immune hemolytic anemia being treated with steroids; 100%), intravascular catheters (100%)
Siebor 2007[28]	France	Hematology department	*Achromobacter xylosoxidans subsp. xylosoxidans* ††	Blood	Fever (56%) ¶¶	Surfanios® solution (didecyl dimethyl ammonium chloride 0.25%) [dispenser]	Hematological malignancies being treated with intensive chemotherapy
Molina-Cabrillana 2007[29]	Spain	Neonatal care unit	*Achromobacter xylosoxidans*	Blood (52%) ***	17% of the newborns with signs and symptoms of infection without another source †††	Chlorhexidine solution [reusable containers]	Newborns (100%); Preterm (52%) ¶¶¶
Tena 2005****[30]	Spain	Hemodialysis unit	*Achromobacter xylosoxidans subsp. xylosoxidans*	Blood	Fever without external signs of a catheter-related infection (100%)	Chlorhexidine solution [atomizer]	Hemodialysis patients with long-term intravascular catheters (100%)

HIV, human immunodeficiency virus. *The percentage was calculated based on the total number of included patients (n = 43). †Clinical signs of sepsis include fever, tachycardia, hypotension, increased procalcitonin and C-reactive protein levels and white blood cell counts. §The percentage was calculated based on the total number of included patients (n = 17). ¶Most of the patients did not show any symptoms of an *Achromobacter xylosoxidans* infection. **The percentage was calculated based on the total number of included patients (n = 7). ††Detected in 12 blood cultures from 9 patients. ¶¶ The percentage was calculated based on the patients with axillary temperature > 37.2°C (n = 5) divided by the total number of included patients (n = 9). ***The percentage was calculated based on the total number of included samples (n = 56). †††The authors did not describe the specific signs or symptoms, and the percentage was calculated based on the total number of patients with a positive blood culture (n = 29). ¶¶¶The percentage was calculated based on the total number of included patients (n = 52). ****The percentage was calculated based on the total number of included patients (n = 4).

Table II. Management and prognosis of *Achromobacter* spp. bacteremia in the included studies.

First Author/Year	Management* [Antibiotics]	Prognosis†
Said 2022[24]	Systemic antimicrobial therapy for the patients with serious underlying conditions [carbapenem→ piperacillin-tazobactam or continued carbapenem or discontinued for colonization]	N/A
Vázquez Castellanos 2022§[25]	Hospitalization (53%) [N/A]; catheter removal (18%)	All cured
Günther 2016[26]	N/A¶	N/A
Hugon 2015[27]	Systemic antimicrobial therapy** and/or catheter removal	All cured (one of the 7 patients developed endocarditis 2 months post-bacteremia)
Siebor 2007[28]	Systemic antimicrobial therapy¶¶ [imipenem; imipenem + tobramycin; imipenem + ciprofloxacin + amikacin; ciprofloxacin + tobramycin; piperacillin-tazobactam + netilmicin; ceftazidime + netilmicin; ceftazidime + amikacin; ticarcillin-clavulanate + amikacin; ticarcillin-clavulanate + ciprofloxacin]	N/A***
Molina-Cabrillana 2007[29]	Systemic antimicrobial therapy for all the symptomatic patients [ceftazidime or meropenem]	All cured; all the colonized patients had a good clinical course without antibiotics; 8% of the total number of included patients died due to other clinical conditions¶¶¶
Tena 2005****[30]	Systemic antimicrobial therapy (100%) [levofloxacin ± trimethoprim-sulfamethoxazole]; catheter removal (25%); if the catheters were not removed, the patients were also treated with antibiotic lock therapy with levofloxacin (75%)	All cured

N/A, not available. *All the studies suspended their use of contaminated sources. †No further cases were reported during the follow-up periods. § The percentage was calculated based on the total number of included patients (n = 17). ¶Most of the patients were clinically asymptomatic, and the authors concluded that the outbreak was pseudo-bacteremia. **The authors used the following antibiotics as the primary and revised regimens: ceftazidime; ceftriaxone/piperacillin-tazobactam; piperacillin-tazobactam/ciprofloxacin; ceftazidime/vancomycin; ceftriaxone → imipenem/vancomycin; ceftazidime/amikacin → imipenem; ceftazidime/vancomycin/imipenem → imipenem; piperacillin-tazobactam. ¶¶ In some cases, the authors used the following antibiotics as the primary and revised regimens after identification of the causative pathogen and antimicrobial susceptibility testing: ceftriaxone + netilmicin → piperacillin-tazobactam + netilmicin or ceftazidime + netilmicin; imipenem + ciprofloxacin + amikacin → ticarcillin-clavulanate + amikacin; ceftriaxone + netilmicin → ticarcillin-clavulanate + ciprofloxacin; ciprofloxacin + tobramycin → ceftazidime + amikacin. *** None of the patients developed septic complications during this outbreak episode. ¶¶¶ The percentage was calculated based on the total number of included patients (n = 52). **** The percentage was calculated based on the total number of included patients (n = 4).

decontamination are recommended to prevent nosocomial infections[38,39]. In this study, we reviewed nosocomial infections resulting from negligible environmental sources and germicide contamination. The evidence from our systematic review shows that nosocomial outbreaks of *Achromobacter* spp. bacteremia caused by germicide contamination were mostly reported in immunosuppressed patients or those with indwelling catheters, regardless of whether the infection was true bacteremia or pseudo-bacteremia. According to the patient's characteristics, empirical antibiotics had to be administered in most cases. If an outbreak of pseudo-bacteremia occurred, an increase in healthcare costs and unnecessary antibiotic use could also inevitably occur.

Before the 2000s, the case-fatality rate from *Achromobacter xylosoxidans* bacteremia was reportedly 30% (but only 3% among cases of primary or catheter-associated bacteremia) and up to 80% in neonates[40]. Mortality was also noted among the newborns (8%) included in this systematic review, but the authors explained that other clinical conditions caused the deaths, and all the symptomatic newborns recovered[29]. Although the reported mortality rate was low, *Achromo-*

Table III. Preventive measures for outbreaks caused by contaminated germicides.

Germicides should be used at the recommended dilution concentrations (avoiding use of over-diluted germicides)
Sterile water should be used when diluting germicides.
Germicides should be used with the recommended contact duration.
Germicides should be prepared using the recommended procedures.
Small-volume dispensers should be used until they are empty and then only re-used after adequate disinfection. Preferably single use only.
Germicides should be selected appropriately according to their purpose.
Germicides should be stored according to the manufacturer's recommendations.

bacter spp. bacteremia can cause various clinical symptoms and even serious complications, such as endocarditis. Thus, appropriate antimicrobial therapy with or without removal of indwelling catheters according to the clinical characteristics of the patient and antimicrobial susceptibility testing is needed. Regarding antimicrobial therapy, *Achromobacter* spp. have several intrinsic antibiotic resistance mechanisms, such as multidrug efflux pumps and chromosomal OXA-114-like β-lactamases[9]. Due to these mechanisms, *Achromobacter* spp. are generally resistant to most β-lactams and aminoglycosides (e.g., gentamicin and amikacin) but susceptible to ceftazidime, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, and carbapenems and show variable susceptibility to fluoroquinolones[9,24,27]. However, acquired resistance to carbapenems has been increasing[9,24].

Regarding the aspect of microbial resistance to germicides, the outer membrane of Gram-negative bacteria provides a barrier against the uptake of germicides[33,34,41]. In addition, biofilm-producing *Achromobacter* spp. can survive germicide use, resulting in healthcare-related outbreaks[26,27]. Biofilms offer increased protection for microbes against the biocidal actions of germicides[42,43]. Chromosomal mutations or plasmid-mediated gene acquisition may also cause resistance to germicides[34,41,44]. Along with their bacterial properties, use of over-diluted solutions, use of unfiltered water for dilution, re-use of small containers (dispensers) refilled from large-volume containers, contact with the outside surfaces of intravascular catheters or medication syringes, and contact of patient skin with contaminated aerosols from atomizers are the presumed sources that may have caused the outbreaks in the included studies[24,27,28,34].

Thus, the measures and recommendations for preventing outbreaks associated with contaminated germicides are as follows[26,33,34,45-47]: germicides should be used at the recommended dilution concentrations (avoiding use of over-diluted germicides); sterile water should be used when diluting germicides; germicides should be used with the recommended contact duration; germicides should be prepared using recommended procedures; small-volume dispensers should be used until they are empty and then only re-used after adequate disinfection (e.g., thoroughly cleaned, disinfected, rinsed with sterile, filtered, or high-quality tap water, and then completely dried before re-filling; preferably single-use only), germicides should be appropriately selected according to their purpose (e.g., avoiding use of antiseptics to disinfect medical devices); finally, germicides should be stored according to the manufacturer's recommendations (Table III).

Conclusions

Proper infection control strategies and continuous attention and alertness to potential outbreaks resulting from the contamination of commonly used germicides in hospital settings would decrease the risk of infection by *Achromobacter* spp. among high-risk patients. In addition, further investigations may be warranted to identify the exact incidence of nosocomial outbreaks resulting from contaminated germicides.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Data Availability
All data generated or analyzed during this systematic review are included in this manuscript.

Informed Consent
Not applicable.

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