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REVIEW

Increasing multidrug resistance in leech borne infections. Should we adjust antibiotic treatment regime in plastic surgery? A systematic review

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Abstract

Background A growing number of reports of serious wound infections during medical leech therapy over the last decades caused by the leech gut symbiont *Aeromonas* spp. led to the standard use of single antibiotics. With more published data about raising multidrug resistance of *Aeromonas* species in leech guts, there is probably a need for adjustment of existing treatment regimens.

Methods We screened PubMed, Scopus, and Web of Science databases using relevant keywords including the last five decades addressing this issue. The review process was based on the PRISMA guidelines. Two independent reviewers screened the abstracts; extracted data were pooled and analyzed for antimicrobial resistance. Meta-analysis was not conducted, based on the poor quality of the included studies.

Result A total of 43 studies were included in this review. All of the studies were reports or case series—except one—and the quality was combined overall good. Evidence was not found for using special antimicrobial agents as first line therapy.

Conclusions Concluding this work, the survey revealed a growing number of more resistant or partially multi-resistant bacterial strains against different commonly used antibiotics, most probably based on increasing resistance in the environment. Taking these data into account, we advise combining leech therapy with minimal dual antibiotic drug administration with ciprofloxacin and co-trimoxazol in the first place and leech gut sampling before inset for antibiotic drug resistance monitoring, and increased awareness during and after leech therapy.

Level of Evidence: Not ratable

Keywords Leech therapy · Antibiotic drug resistance · Soft tissue reconstruction · Aeromonas · Hirudo

Introduction

The use of leeches to treat soft tissue with congestion in plastic surgery gained over the last decades a sort of renaissance even with the parallel further development of micro- and supermicro surgery. Main indications for this since 2004 FDA-approved medical device are often ring avulsion injuries, amputation of smaller parts, other mangled tissue with venous vessels too small to suture, or even soft tissue flaps with congestion. Leech therapy is further well known as a salvage option for tissue otherwise regarded impossible to save [1]. Despite the different potential complications with leech therapy like loss of blood and scaring, the main risk is still infection with a fatal outcome for congested tissue. The incidence of leech-born infections ranges from 2.4 to 36.2% with a delayed onset from 24 h to 26 days [2]. In a large systematic review of the efficacy of medicinal leeches in plastic and reconstructive surgery over a period from 1966 to 2009 with the inclusion of 67 papers, 79.05% of the included patients received antibiotics [3] to prevent or to treat infections of congested tissue. First report of a possible source of an infections by a leach-borne rod—identified as *Aeromonas hydrophila*—dated back until 1983 [4] and stated therefore the use of leeches as a contraindication. With the spreading of the benefits of leeches in the plastic surgery community, its use arose [5]. The first publication of a proven wound infection has been published in 1984 with

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Aeromonas hydrophila by using leeches to treat a congested flap [6]. Parallel to the slowly increasing number of reports of bacterial transmissions, more focus was placed on the source of infection [7, 8] and its resistance profile [9]. During the following decades, a growing numbers of reports of leech borne bacterial transmission and infections raised the question if there is an increase in drug resistance against common standard antibiotics and therefore do we have to adjust common treatment regimens like single use of gyrase inhibitors? The aim of this review is therefore to optimize the antibiotic treatment algorithm for leech borne infections in plastic surgery patients.

Methods

This review adheres to the PRISMA 2020 guidelines [10]. Prospero database was checked prior search for still existing reviews, but this protocol was refused to register because of overload by COVID-19 pandemic.

Search strategy and selection criteria

A systematic search through three different public databases, PubMed, Scopus, and Web of Science, was conducted from 1973, and the first data were extracted by search queries in June 2021 (Fig. 1). First search terms were "Aeromonas" AND "leech" OR "hirudo" AND "antibiotic resistance". Because of the limited number of results, we performed a second search query with extended search items. Second search term queries were "Resistance" AND "hirudo" OR "resistance" AND "leech" OR "resistant" AND "hirudo" OR "resistant" AND "leech" OR "infection" AND "leech" OR "infection" AND "hirudo" OR "infection" AND "aeromonas" OR "resistance" AND "aeromonas" OR "resistant" AND "aeromonas" OR "treatment" AND "hirudo" OR "treatment" AND "leech". Additional publications found by manually screening references and citations were also included in this publication. An additional repetitive search for recently published papers with the same search query was performed in September 2023 to be included in this review before publication. Additional studies found were also reviewed same way by the two independent reviewers. No language restrictions were included in the initial search, but by testing for inclusion, we discarded all studies other than written in English. Data extraction was guided by the previously prepared protocol conducted by the authors. Case reports or case series with low a number of patients were also included. No study was excluded based on the initial search by quality. A search for unpublished publications was not performed. We included studies which met the following criteria:

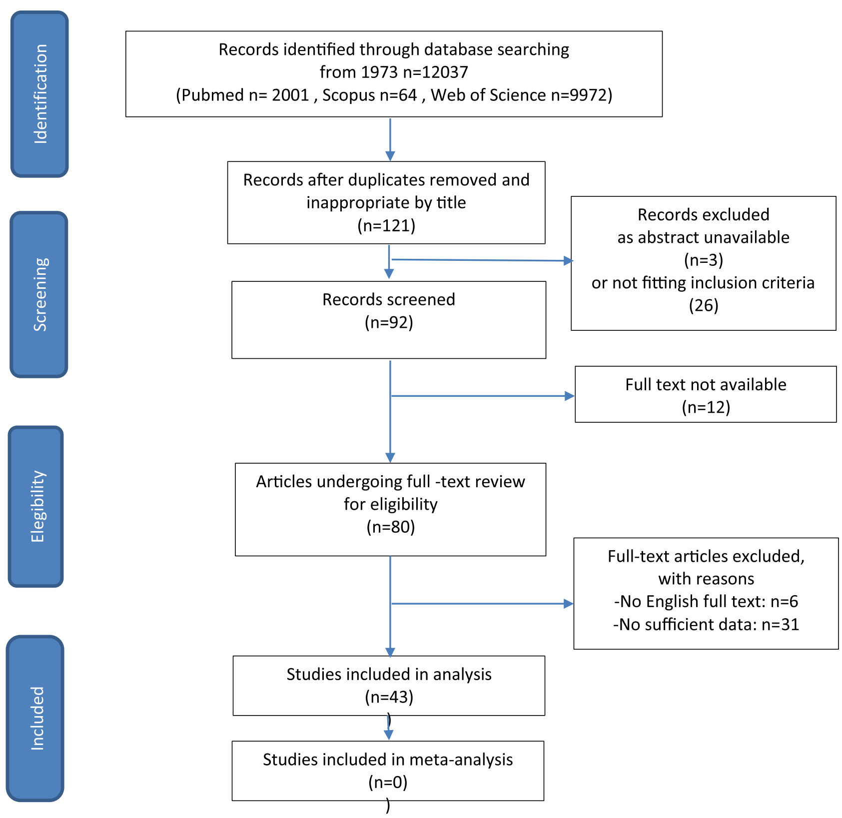

Fig. 1 Flow diagram of the study selection process

1. Medical leech gut samples or homogenates with bacterial identification and sensitivity or resistance testing
2. Wound infections samples caused by usage of a leech for medicinal treatment with bacterial rod identification of *Aeromonas* spp. and antibiotic treatment or resistance information

Two independent reviewers screened titles and abstracts to be sufficient for inclusion in this review. Disagreement was resolved by consensus with full text screening. Studies only available as abstracts or in a language other than English were not included in this review.

Quality of studies

Two independent reviewers assessed the quality of the included studies, and every study was overall rated in poor, fair, good, or not applicable. Disagreement was solved by consensus. The quality was assessed by the JBI critical appraisal tool for case series studies, the JBI critical appraisal checklist for case report, and Bias by the ROBIS tool.

Data extraction

The extraction protocol was based on data estimated as relevant for this review. Data were extracted based on the date of publication, title of the study, abstract, full text available in English, bacterial prevalence in leech gut or leech homogenates or wounds, and type of antibiotics tested and sensitivity/resistance.

Data analysis

For each included study, we calculated the presence of *Aeromonas* sup. percentage and the resistance of gut-born bacteria found against typically commonly used antibiotics. Data were collected in Microsoft Excel, and results were presented in tabular form.

Results

Flow of included studies

With the fist search strategy, we found 23 publications on Pubmed from 1973, 35 on Scopus, and 18 on Web of Science (both not earlier than 1988). Pubmed revealed with the second search query 1978 publications from 1973, Scopus 29 from 1988 (no earlier results), and Web of Science 9782 publications limited from 1973. A total of 12,037 publications could be found. After removing duplicates and screening titles, most of the studies we found were not appropriate in terms of inclusion. One hundred twenty-one studies remained for further processing. Of these studies, 3 were lacking an abstract and 26 were inappropriate after screening the abstract. Of the 92 publications, we found 12 were missing full text, six were written in a language other than English, and 31 had insufficient data. The remaining 43 publications were included in our survey.

Study characteristics

Study characteristics are summarized in Table 1. The studies—we included—were published between 1983 and 2022 (see Fig. 2). None of the studies was a randomized double-blinded control trial; only one was a retrospective multicenter cohort study. Most of the publications were case series or even case reports without controls. Inclusion criteria were the presence of *Aeromonas* spp. found in leech gut or leech homogenates and not in water samples with further determining of antibiotic sensitivity/resistance. Inclusion criteria of patients enrolled in case reports/case series were clinical signs of infection during leech therapy after surgical interventions.

Quality assessment

Quality assessment of the case series were based on the JBI critical appraisal tool [11] for case series and for case reports. Case series were rated by the JBI critical appraisal tool for case series (see Table 1) and for case reports with JBI critical appraisal checklist for case reports. Case series which were based on leech gut samples and were processed in a microbiological lab were rate good (13/43); case series based on different patient samples were rated poor (1/43) or rated fair (1/43). Case reports were most often rated good (24/28), fair (2/28), and poor (2/28) according to the JBI checklist. The poor and fair rated studies were also included in this review because of sufficient information related to the aim of the review. The only retrospective patient multicenter cohort study was rated in comparison to the case series good. Furthermore, most of the studies reported often a very limited number of patients or samples. Statistical analysis was therefore not performed even as meta-analysis caused by lack of RCT. Bias assessment was carried out by using the ROBIS tool [12]. We estimated the risk of selection bias low because of the high number of publications we found searching the most common public databases in the first instance and therefore the representativeness of the included paper is estimated high. Publication bias has been estimated high because of the fact of only published papers with stating increasing anti-microbiological resistance of *Aeromonas* spp. were included. The studies themselves were heterogenous, and therefor the risk of bias in the synthesis of findings was rated high.

Table 1 Study characteristics

First author and publication year	Study design	*Aeromonas* spp. prevalence in leech gut and/or homogenates and/or wound infections in %	Antibiotic resistance percentage *Aeromonas* spp.	Other results	JBI quality tool result for case reports and series
Whitlock et al. (1983)	Case report	100%	100% resistant to penicillin, ampicillin, streptomycin	Leech gut culture	Good
Dickson et al. (1984)	Case report	100%	100% resistant to ampicillin, trimethoprim, erythromycin, cephaline	Sample from flap-hematoma and wound	Good
Hermansdorfer et al. (1988)	Case series	80%	Resistant to ampicillin 100% (16/16) of samples and 1st generation cephalosporins 18.75% (3/16) of samples	Leech gut cultures	Good
Lucht et al. (1988)	Case report	100%	Not reported	Sensitive to cefotaxime and netilmicin, loss of free flap	Good
Snower et al. (1989)	Case report	50%	3/5 strains resistant to ampicillin, 1/5 strain resistant to ampicillin and cephalotin	Sample from failed flap, *S. aureus* also found, 1/5 strain sensitive to all antibiotics tested	Good
Evans et al. (1990)	Case report	50%	Resistant to cephradine and metronidazole	Sensitive to gentamicin	Good
Dabb et al. (1992)	Case report	100%	Not reported	Sensitive to ceftriaxone, cefoxitin, ceftazidime, tetracycline, aminoglycosides, SSI with loss of myocutaneous lat. dorsi flap	Good
Lineaweaver et al. (1992)	Case series	100%	Resistant to cefazolin (5/7), resistant to cefalexin (1/7) and cefoxitin (1/7)	Sensitivity not reported, SSI	Poor
Wilken et al. (1993)	Case series	82%	100% (60/60) resistant to penicillin, ampicillin, vancomycin, and clindamycin	Sensitive to co-trimoxazol, cefotaxime, and amikacin, leech gut samples	Good
Varghese et al. (1996)	Case report	0%	Not reported	100% *Vibrio fluvialis*, treated with doxycycline for 10 days, most probably missclassification and well *A. hydrophila*	Good
Nonomura et al. (1996)	Case series	100%	Resistant to ampicillin and 1st generation cephalosporins 100% (7/7)	Leech homogenates	Good
Mackay et al. (1999)	Case series	70%	Resistant to ampicillin 100%, oxacillin, and chloramphenicol	Leech gut samples, sensitive to co-trimoxazol	Good
Eroglu et al. (2001)	Case series	35%	Resistant to ampicillin 100% and 1st generation cephalosporins 36% and chloramphenicol 16%	Multiple other bacterial species found, all susceptible to ciprofloxacine, leech gut sample	Good
Aydin et al. (2004)	Case series	90%	100% resistant to ampicillin, sulbactam/ampicillin, amoxicillin/clavulanate, 66% (6/9) resistant to cefalozin	Leech gut samples	Good

Table 1 (continued)

First author and publication year	Study design	*Aeromonas* spp. prevalence in leech gut and/or homogenates and/or wound infections in %	Antibiotic resistance percentage *Aeromonas* spp.	Other results	JBI quality tool result for case reports and series
Ouderkirk et al. (2004)	Case report	100%	Not reported	Meningitis after leech therapy for venous flap congestion, treated with gatifloxacin/aztreonam, followed by ceftriaxone and cefipime-tobramycin	Good
Ardehali et al. (2006)	Case report	100%	Not reported, resistant to imipenem and gentamicin	Sensitive to ciprofloxacin, tazocin, and ceftazidime	Good
Bauters et al. (2007)	Case series	8.5%	Resistant to co-trimoxazol 75% (3/4)	Mostly resistant to co-trimoxazole, multiple other bacterial species, isolates from SSI	Good
Mumcuoglu et al. (2010)	Case series	71.25%	Not reported	100% sensitive to ciprofloxacin (56/56), leech gut samples	Good
Schnabl et al. (2010)	Case series	100%	Not reported	100% sensitive to fluroquinolone (5/5), SSI	Fair
Whitaker et al. (2011)	Case series	14.2%	Not reported	100% sensitive to ciprofloxacin (5/5)	Good
Wang et al. (2011)	Case report	100%	Resistant to ciprofloxacin and co-trimoxazol 100% (1/1)	First report of resistant to fluroquinolone	Good
Maetz et al. (2012)	Case reports	100%	Resistant to amoxicillin/clavulanate 100% (2/2)	Sensitive to fluroquinolone 100% (2/2)	Good
Sartor et al. (2013)	Case reports	100%	Resistant to ciprofloxacin 100% (2/2)		Good
Patel et al. (2013)	Case report	100%	Resistant to ciprofloxacin 100% (1/1)	Multidrug resistance and also to ciprofloxacin	Fair
Giltner et al. (2013)	Case report	100%	Resistant to ampicillin, cefazolin, and ciprofloxacin 100% (1/1)	Other bacterial species found	Good
Bibbo et al. (2013)	Case report	100%	Resistant to ciprofloxacin and levofloxacin (1/1)	Leech gut sample with additional *Proteus vulgaris* and *Morganella morganii*	Good
Wilmer et al. (2013)	Case report	100%	Resistant to ciprofloxacin 100% (1/1)	Sensitive to co-trimoxazol and gentamicin	Fair
Litwinowicz et al. (2014)	Case series	100%	Not reported	100% sensitive to ciprofloxacine and cefotaxime (7/7) and (7/7, leech gut samples	Good
Whitaker et al. (2014)	Case series	100%	Resistant to amoxicillin and sensitive to ciprofloxacin	Multiple other bacterial species found on sample	Good

Table 1 (continued)

First author and publication year	Study design	*Aeromonas* spp. prevalence in leech gut and/or homogenates and/or wound infections in %	Antibiotic resistance percentage *Aeromonas* spp.	Other results	JBI quality tool result for case reports and series
Van Alphen et al. (2014)	Case reports	100%	Resistant to ampicillin (100%) (2/2), resistant to ciprofloxacin and levofloxacin (50%), ertapenem (50%), Co-trimoxacol (50%) and cefazolin (50%)	Sample from failed replantation	Good
Kruer et al. (2015)	Retrospective multicenter cohort study	57.1%	75% resistant to ciprofloxacin (3/4), 25% resistant to piperacillin-tazobactam (1/4)	75% sensitive to co-trimoxazol (3/4)	Good
Verriere et al. (2016)	Case reports	66%	Resistant to fluoroquinolones (33%) in wounds (1/3)	Samples from failed replantation or breast reconstruction	Poor
Berger et al. (2018)	Case report	100%	Resistant to co-trimoxazole 60% (3/5), sensitive to cefuroxime and fluoroquinolones (5/5)	SSI/wound sample	Good
Ruppe et al. (2018)	Case report	100%	Resistant to amoxicillin 0% (0/1) and sensitive to cipro/levofloxacin	Samples from wound	Good
Beka et al. (2018)	Case series	100%	Resistant to ciprofloxacin after 2012 (77%)	No resistance to ciprofloxacine prior 1999, samples from wound infections after leech therapy	Good
Bykowski et al. (2018)	Case report	100%	Resistant intermediate to ciprofloxacin, resistant to amoxicillin, co-trimoxazol, and ceftriaxone 100% (1/1)		Good
Floug et al. (2019)	Case report	100%	Resistant to ciprofloxacin, co-trimoxazol, and ESBL	Sensitive to ceftazidime, meropenem and imipenem, multidrug resistance	Good
Mokhtar et al. (2020)	Case reports	100%	Resistant to ciprofloxacin/levofloxacin 100% (3/3), Co-trimoxacol 66% (2/3), ampicillin 100% (3/3)		Poor
Barraud et al. (2020)	Case report	100%	Resistant to fluoroquinolones 100%	2 distinct strains with one multidrug resistant (ESBL) and resistant to aminoglycosides	Good
Segatore et al. (2020)	Case reports	100%	Resistant to levofloxacin 90% (9/10)	Resistant to all tested antibiotics 90% (9/10), extremely resistant strain found, leech gut samples	Good
Masters et al. (2020)	Case report	100%	Resistant to ciprofloxacin 100% (1/1), co-trimoxazol, ceftriaxone	Sensitive to meropenem and piperacillin, multidrug resistant	Good
McCracken et al. (2022)	Case report	100%	Resistant to fluoroquinolones, co-trimoxazol, tetracycline, and cefazolin	Sensitive to piperacillin/tazobactam, meropenem, ceftriaxone, amikacin	Good

Table 1 (continued)

First author and publication year	Study design	*Aeromonas* spp. prevalence in leech gut and/or homogenates and/or wound infections in %	Antibiotic resistance percentage *Aeromonas* spp.	Other results	JBI quality tool result for case reports and series
Sproll et al. (2022)	Case report	100%	Resistant to ampicillin + sulbactam, amoxicillin	Sensitive to fluoroquinolone, cephalosporin, co-trimoxazol	Good

Outcomes

Outcomes of the studies were included by percentage of *Aeromonas* spp. and anti-microbiological resistance. First study showing possible upcoming issues by using leeches for solving surgical problems was in 1983 by Whitlock et al. [4] with showing *Aeromonas* as the dominant rod in leech guts (see Table 1). First report of a confirmed surgical site infection was by Dickson et al. [6] in 1984.

Addressing the issue of resistance of leech gut-borne infections included in our review was of Hermansdorfer et al. in 1988 [8]. He dissected 20 leech guts and found in 16 of 20 specimen *Aeromonas hydrophila* (80%), which were all resistant to ampicillin (100%). In one of the 20 specimen, authors found *Pseudomonas* species other than aeruginosa, which also might have been a water-borne organism that was resistant to ampicillin and chloramphenicol. Lucht et al. reported a case of surgical site infection with loss of a free flap by *Aeromonas*, which was sensitive to cefotaxime and netilmicin without further resistance reporting [13]. Snower et al. [14] demonstrated a case of infection with flap failure caused by *Aeromonas hydrophila* which was susceptible to all common antibiotics. Further, water tank and leech sampling showed predominantly five different strains of *Aeromonas* spp. whereas three of five were resistant to ampicillin. Evans et al. [15] published a case of septicemia during leech therapy in an attempt to salvage a replanted arm by *Aeromonas*. In the patient sample, 50% of *Aeromonas* was resistant to cephradine and metronidazole but sensitive to gentamicin. Dabb et al. [16] presented a surgical site infection (SSI) in a 48-year-old women with breast reconstruction with *Aeromonas* without reporting any resistance. Lineaweaver et al. [17] demonstrated seven cases with SSI caused by *Aeromonas* with resistance to cephalosporins and in most cases loss of replants (5/7). Wilken et al. [18] did leech gut sampling of the potential Southern African leech and revealed 82% positivity for *Aeromonas* and resistance to penicillin, ampicillin, vancomycin, and clindamycin. Varghese et al. [19] reported a case of *Vibrio fluvialis* infection after leech therapy, which was treated with 10 days of doxycycline. Most probably was this a misclassification caused by unproperly bacterial culture testing [20, 21]. Nonomura et al. [22] tested homogenates of five leaches *Hirudo medicinalis* all positive for *Aeromonas* (four strains *A. sobria* and three strains *A. hydrophila/caviae*) and less susceptible for ampicillin and first-generation cephalosporins. Mackay et al. [23] found in 70% of leech gut samples *Aeromonas* spp., which were resistant to ampicillin, oxacillin, and chloramphenicol but sensitive to Co-trimoxacol. Eroglu et al. [24] found in leech gut samples from 16 leeches (*Hirudo medicinalis*) besides 81.25% *Aeromonas* spp. (13 × *Aeromonas hydrophila*, one *Aeromonas sobria*) also *Ochrobacter anthropi*, *Serratia* sp., *Proteus* sp. and *Vibrio* sp. All were

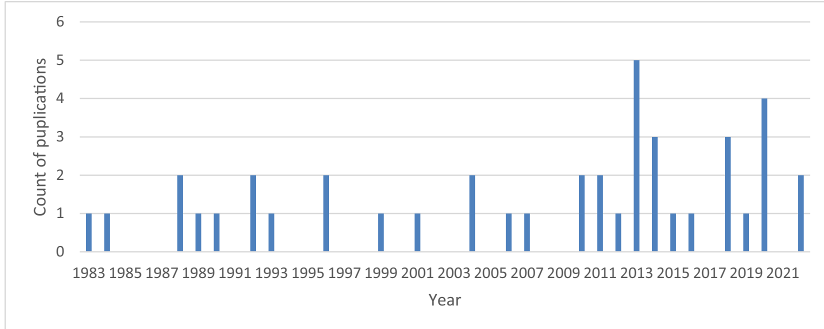

Fig. 2 Distribution per year after removing duplicates from Scopus/Pubmed/Web of Science of the relevant publications. Increase after 2010

sensitive to ciprofloxacin, trimethoprim/sulfamethoxazole, and resistant to ampicillin. Aydin et al. [25] reported in a case series of leech gut samples a percentage of 90% of *Aeromonas* of which all were resistant to ampicillin/sulbactam or amoxicillin/clavulanate and 66% resistant to cefalozin. Ouderkirk et al. [26] published a case of SSI in combination with meningitis caused by *Aeromonas*. Treated in first instance with gatifloxacin and aztreonam and secondary with ceftriaxone and cefipime and tobramycin for a total of 21 days, this might be the first documented resistant strain of *Aeromonas* to gyrase inhibitors at all. Ardehali et al. presented a case of SSI after usage of leeches for venous congestion caused by *Aeromonas hydrophila*, which was resistant to imipenem and gentamicin but sensitive to ciprofloxacin. Bauters et al. [27] found in a retrospective analysis of 47 patients treated with leeches during their clinical course 17 cultures were suspected of postoperative wound infection. Of these 47 patients, four (8.51%) tested positive for *Aeromonas* spp. (two *Aeromonas hydrophila*, one *Aeromonas sobria* and one with both strains). All were susceptible to ofloxacin and partially resistant to trimethoprim/sulfamethoxazole (three out of four). During sample testing from postoperative wound infections, multiple other strains like *Morganella morganii*, *Escherichia coli*, *Klebsiella pneumonii*, *Staphylococci* spp., *Pseudomonas aeruginosa*, *Proteus* spp., and *Serratia* spp. were found, but these samples were not specifically sampled directly from leeches. Mumcuoglu et al. [28] did leech gut sampling, showing 71.25% positive for *Aeromonas* in the control group and 0% in the test group after ciprofloxacin feeding. Schnabl et al. [29] presented five cases of SSI with *Aeromonas* spp. after using leeches for venous congestion, which where all sensitive to ciprofloxacin. Whitaker et al. [30] published a case series of SSI after the use of leeches whereas 14.2% of the specimen was positive for *Aeromonas*, but all strains were sensitive to ciprofloxacin (5/%). Wang [31] reported the first proven case of ciprofloxacin-resistant *Aeromonas* infection which was also resistant to trimethoprim/sulfamethoxazole. Investigation revealed most likely resistance before arriving at the institution of use. Maetz et al. [32] reported two cases of infection with *Aeromonas veronii* biovar sobria which were only resistant to amoxicillin/clavulanic acid. Sartor et al. [33] reported two cases of *Aeromonas hydrophila* infection, which where resistant to ciprofloxacin and sensitive to trimethoprim/sulfamethoxazole. Next was Patel et al. [34] who described a patient treated with *Hirudo medicinalis*, which was positive for ciprofloxacin-resistant *Aeromonas hydrophila* infection and treated with aztreonam. Giltner et al. published [35] a case report of *Aeromonas hydrophila* strain in a 9-year-old patient, which found to be resistant to ciprofloxacin and sensitive to trimethoprim/sulfamethoxazole. Bibbo et al. [36] presented a case of wound infection caused by an *Aeromonas hydrophila* strain nonsusceptible to fluoroquinolones but sensitive to trimethoprim/sulfamethoxazole. Wilmer et al. [37] also reported a case of *A. hydrophila* infection which was resistant to ciprofloxacin but susceptible to gentamicin and trimethoprim/sulfamethoxazole. Further leech water sampling revealed *Aeromonas* spp. which were 100% sensitive to trimethoprim/sulfamethoxazole, 61.9% to gentamicin, and 71.4% to ciprofloxacin. Litwinowicz et al. [38] presented a case series of leech gut samples (ten) from the control group which were 100% positive for *Aeromonas* as well 100% of the study group (seven). All samples of the test group were sensitive to ciprofloxacin and co-trimoxazol. Whitaker et al. [39] processed seven *Hirudo orientalis* and noted the type of strains and resistant patterns. All *Aeromonas* spp. he found were sensitive to ciprofloxacin and resistant to amoxicillin, but also different other species were found not otherwise described. Van Alphen et al. [40] described two cases, whereas case one showed an infection after leech therapy with an *Aeromonas* strain resistant to ciprofloxacin, levofloxacin, ampicillin/sulbactam and prior administered ertapenem, but sensitive to trimethoprim/sulfamethoxazole. Case two revealed resistance to trimethoprim/sulfamethoxazole and moderate sensitivity to ciprofloxacin/levofloxacin. Kruer et al. [41] published a retrospective multicenter cohort study which showed 57.1% of *Aeromonas* in all SSI samples. Of the tested strains were 75% resistant to ciprofloxacin, 25% resistant to piperacillin-tazobactam, but 75% sensitive to cotrimoxazol. Verriere et al. [2] reported case series over a period of 24 months with three infections out of 28 patients treated with leeches, whereas only one showed resistance to fluroquinolones. Further, leech water tank sampling revealed similar bacterial strains of *Aeromonas* spp. between crushed leeches and simple water tank samples. All of them showed 100% sensitivity (21/21) to fluroquinolone and trimethoprim/sulfamethoxazole. Berger et al. [42] published a case of SSI with *Aeromonas veronii* complex, whereas all tested strains were sensitive to fluroquinolones and cefuroxime, but 60% were resistant to co-trimoxazol. Ruppe et al. [43] were the first to report a case of multidrug resistance *Aeromonas salmonicida* after medicinal leech therapy, whereas the primary *Aeromonas veronii* strain showed wildtype sensitivity (susceptible to ciprofloxacin and trimethoprim/sulfamethoxazole). This case was rated as colonization. Beka et al. [44] was the first who could link the rise in ciprofloxacin-resistant *Aeromonas* strains to low levels of ciprofloxacin concentrations in environment after 1999. Bykowski et al. [45] reported the first case of ceftriaxone-resistant *Aeromonas hydrophila* infection following postoperative leech therapy. This strain was resistant to trimethoprim/sulfamethoxazole, intermediate to ciprofloxacine and also resistant to 3rd generation cephalosporins. Next was Floug et al. [46], who presented a case of ESBL and extensively drug-resistant *Aeromonas hydrophila* infection after the use of leech therapy. This strain was also resistant to ciprofloxacin and trimethoprim/sulfamethoxazole. Mokhtar et al. [47] reported three cases of post-medical leech therapy infection with *Aeromonas hydrophila* (two patients) and one with *Aeromonas veronii* (one patient). *Aeromonas hydrophila* was resistant to trimethoprim/sulfamethoxazole and cipro/levofloxacin whereas *Aeromonas veronii* was resistant to ciprofloxacin but sensitive to trimethoprim/sulfamethoxazole. Barraud [48] presented a case report of infection with two distinct strains of *Aeromonas veronii* in one patient, one ESBL positive, resistant to fluoroquinolones and aminoglycosides, and the other resistant to fluoroquinolones only. Segatore et al. [49] found in samples of *Dina lineata* (leeches) from environment in Italy in nine out of ten samples of multidrug resistance of *Aeromonas hydrophila* and *A. veronii*. Masters et al. [50] reported recently also a case of multidrug-resistant *Aeromonas* species, which was resistant to ciprofloxacin, ceftriaxone, and trimethoprim/sulfamethoxazole. McCracken et al. [51] recently showed a case of *Aeromonas* infection after the use of medical leech therapy after surgical functional flap reconstruction with a relative broad spectrum of resistance to fluroquinolones, co-trimoxazole, tetracycline, and cefazolin. Most recently, Sproll et al. [52] most recently reported a case of a lethal *Aeromonas veronii* sepsis after the surgical use of medical leeches with a strain only resistant to ampicillin/sulbactam and amoxicillin, but sensitive to fluoroquinolone, co-trimoxazol, piperacillin, cefuroxime, ceftzidime, ertapenem, and gentamicin.

Discussion

This systemic review is the first to answer the question of growing drug resistance during leech therapy. During reviewing process, we were confronted with several limitations, most of them were inherent to the studies themselves like a small number of samples, different sample materials or included patients, publishing bias with overreporting of case reports, or possible underestimating of the problem by underreporting this issue or incoherent antibiotic testing. We most often found only case reports which were impossible to rate in means of quality, but they show well an increasing percentage of quinolone resistance or even multidrug resistance in leeches, especially over the last two decades. But this conclusion is influenced by publication bias. Thus, clear advice on how to treat patients during leech therapy is not possible to give based on the studies we found, even the overview of different regimes published recently by McCracken is inconclusive [51]. Brambullo et al. [53] still advise ciprofloxacin or in case of allergies or increased risk of resistance Co-timoxazol. Conclusively in the late 1980s and early 1990s of the twentieth century, first descriptions of leech-associated infections by *Aeromonas* spp. were published. During this period, almost all samples were susceptibly to common antibiotics like ciprofloxacin [24], tetracycline, and trimethoprim/sulfamethoxazole [54], or gentamicin, chloramphenicol, or 3rd generation cephalosporins [8]. Resistance to ciprofloxacin—of other quinolone—derived gyrase inhibitors was virtually absent [4, 8, 16, 18, 55] whilst intrinsic resistance to ampicillin or amoxicillin was well known by *Aeromonas* spp. With increasing use—especially of the easy-to-handle quinolone-derived antibiotics—the number of reported resistant strains rose [47]. One of the most putative reason is the misusage of quinolone antibiotics and others in large scale farm industry, especially in the feeding of poultry whose blood is use to feed medical leeches before inset instead of cattle blood caused by putative risk of prion transmission [56] or even in fish farm industries [57]. With the increasing awareness of potential infection risks with *Aeromonas* spp. and other species, which often have to be treated with potent antibiotics, the number of cases reported rose within the last two decades. *Aeromonas* species are nowadays susceptible in different degrees to second and third degree cephalosporins, fluoroquinolones, sulfamethoxazole-trimethoprim, tetracycline, and aminoglycosides [8, 58] and resistant to penicillin and derivates [35]. More up-to-date publications show a further expanding multidrug resistance for 3rd generation cephalosporin-like ceftriaxone [45] or even ESBL resistance [46]; thus, microbiological leech gut testing—regularly of every batch used—seems to get more important than ever, and the whole delivery pathway from supplier to the patient should be assessed. In most recent publications, there is also a growing number of reports regarding ciprofloxacin-resistant or 3rd degree cephalosporin-resistant (ceftriaxone) *Aeromonas* infections following leech therapy [34, 35, 37, 40, 45]. Taking the growing numbers of resistant strains of *Aeromonas* spp. into account and the misusage of quinolone-derived anti-microbiological drugs in the past, blind administration of a single antibiotic seems to be nowadays most probably insufficient, even because of the increasing numbers of other bacterial species found in the digestive tracts of leeches. Thus, it is recommendable to start antibiotics at least before leech therapy with a combination of ciprofloxacin and sulfamethoxazole-trimethoprim [35, 59, 60] because most of the *Aeromonas* samples were still susceptible to at least one of them, whilst constantly adjusting antibiotic therapy based on resistance testing. The advantage of both types of antibiotics is sufficient oral uptake and soft tissue penetration thus iv-antibiotics as 3rd generation cephalosporin, or others are not necessary and therefore potentially less hospitalization and costs [61].

Author contribution TW and DU designed this systematic review. TW conducted the systematic review, data extraction, and data analysis. DU participated in screening process and extraction analysis. TW wrote the draft of the manuscript whilst DU did data checking and proofreading. The final version of the manuscript was approved after critically appraisal by both authors.

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Data Availability Data are available by the authors.

Declarations

Ethical approval For this type of study, formal consent from a local ethics committee is not required.

Consent to participate Not required.

Conflict of interest Till Wagner and Dietmar Ulrich declare no competing interests.

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