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Oral antibiotic therapy in people who inject drugs (PWID) with bacteraemia

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Summary

Bacterial infections are a major cause of morbidity and mortality in people who inject drugs (PWID). Patients with bacteraemia have a particularly high risk of complications and are usually treated with intravenous antibiotics. Intravenous treatment is challenging in certain PWID because of difficult venous access and a high rate of catheter-associated complications. Therefore, oral treatment alternatives must be considered.

This review discusses the potential options for oral antimicrobial treatment of gram-positive and gram-negative bacteraemia in PWID and the evidence for them.

Data on oral antibiotic treatment of bacteraemia in PWID is scarce. Whenever possible, a course of intravenous antibiotic treatment should precede the switch to an oral regimen. For *Staphylococcus aureus* bacteraemia, there is growing evidence that initial intravenous antibiotics can be switched to oral treatment (e.g., a fluoroquinolone and rifampin or linezolid) when the patient is clinically stable and source control has been achieved. However, regimen selection remains challenging due to pharmacokinetic/pharmacodynamic issues, potential toxicity and drug-drug interactions of oral antibiotics. For some streptococcal bacteraemia, oral amoxicillin is probably a reasonable option. The best existing evidence for oral antibiotic treatment is for gram-negative bacteraemia, which, if susceptible, can be treated successfully with oral fluoroquinolones. Oral antibiotic options for fluoroquinolone-resistant gram-negative bacteraemia are very limited, although in selected patients oral trimethoprim-sulfamethoxazole can be considered.

In conclusion, treatment of bacteraemia in PWID remains very complex, and an interdisciplinary approach is essential in order to select the best therapy for this vulnerable group of patients.

Keywords: *people who inject drugs, PWID, intravenous drug user, IVDU, injection drug users, IDU, bacteraemia, bloodstream infection, oral antibiotics, endocarditis, suppurative thrombophlebitis, switch*

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Introduction

Infections are a leading cause of morbidity and hospitalisation in people who inject drugs (PWID) [1–6]. Among the most frequent infections in PWID are soft tissue infections, suppurative thrombophlebitis and endocarditis, which can all cause bacteraemia. In many cases, bacteraemia is treated with intravenous (IV) antibiotics for two or more weeks. IV antibiotic therapy requires a vascular catheter, with the potential risk of catheter-associated complications, and usually leads to higher costs and a longer hospital stay compared with oral therapy [7–9]. Prolonged IV treatment can be particularly challenging in some PWID due to difficult venous access and motivational problems. Many PWID need a central venous catheter (CVC) for adequate IV antibiotic treatment, but CVCs are prone to being manipulated and misused by PWID, who inject recreational drugs into them. This can lead to complications like central line thrombosis, secondary CVC-related infections, and de novo suppurative thrombophlebitis with nosocomial bacteria or fungi which are sometimes difficult to treat, as seen in our clinical practice and described in the literature [10, 11]. In some PWID, the rigid continuation of IV antibiotic therapy can endanger the patient's health, and treatment alternatives, e.g., oral antibiotic treatment, must be evaluated.

This review aims to give an overview of the available evidence on oral antibiotic treatment options for bacteraemia in PWID. Oral treatment should only be considered in patients in which standard IV antimicrobial therapy presents an unacceptably high risk to the patient's health. In our experience, this applies mainly to patients who have a history of multiple CVC-related complications. We emphasise that most bacteraemia in PWID can be treated with IV antibiotics [12], and that even outpatient parenteral antibiotic therapy can be a valid option in PWID [13, 14]. Whenever possible, a course of IV treatment should precede the switch to an oral regimen in cases where full-length IV treatment is not feasible.

Table 1 shows important aspects to consider when using oral antibiotics to treat bloodstream infections in PWID.

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General management considerations

Bacteraemia in PWID is most often caused by *S. aureus*, followed by *Streptococcus* spp., *Enterobacterales, Enterococci, Pseudomonas* spp., yeasts, and others [1, 2, 11, 12]. Like all patients with bacteraemia, PWID must be evaluated for persistent infectious foci. Particular attention must be paid to infectious complications such as endocarditis, suppurative thrombophlebitis, septic arthritis and vertebral osteomyelitis, which must be excluded by appropriate diagnostic measures. This is especially true for *S. aureus*, which is the leading pathogen of skin and soft tissue infections [15], endocarditis [11, 16], septic deep venous thrombosis [17] and septic arthritis [18] in PWID. Source control must be achieved, e.g., by incision and drainage of deep or superficial cutaneous abscesses.

Table 1: Checklist for using oral antibiotics in PWID with bacteraemia.

Prolonged intravenous treatment not possible due to high-risk circumstances (history of recurring CVC-related complications)
Multidisciplinary evaluation including expert in addiction medicine
Patient haemodynamically stable
Source control achieved
Species identification and susceptibility testing available
Availability of a valid oral antibiotic agent to which the targeted microorganism has tested susceptible and with favorable PK/PD characteristics (tables 2 and 3)
Gastrointestinal absorption is adequate
No serious drug-drug interactions between the selected agent and other medications or consumed recreational drugs (table 2)
No allergies or intolerances to the selected drug
Access and adherence to oral drug treatment after hospital discharge assured
Follow-up guaranteed

CVC = central venous catheter; PK/PD = pharmacokinetic/pharmacodynamic

Our review focuses on the most frequently detected microorganisms in PWID: *S. aureus*, *Streptococcus* spp. and gram-negative bacteria.

The antimicrobial treatment should target the detected pathogen according to susceptibility testing and should achieve adequate drug concentrations in the blood and in the tissue at the site of infection (tables 2 and 3).

Treatment decisions in PWID with a severe infectious disease should be made by a multidisciplinary team, including specialists in internal medicine, infectious diseases, addiction medicine, psychiatry and nursing [35]. In PWID within a drug substitution program, adjustment of the substitution therapy may lower withdrawal symptoms and help to provide state-of-the-art IV antibiotic therapy.

Pharmacological considerations

Important factors to consider for oral antimicrobial therapy are (1) the susceptibility of the pathogen to the drug (measured by the minimum inhibitory concentration [MIC]), (2) antimicrobial pattern of activity (e.g., time-dependent killing, concentration-dependent killing), (3) oral bioavailability, (4) gastrointestinal tolerability, (5) distribution (blood and tissue concentration), (6) patient's adherence and (7) drug-drug interactions. In severe infections, adequate serum antibiotic drug concentrations are reached most reliably through parenteral application of antibiotics,

Table 2: Basic pharmacokinetic characteristics, side effects and interactions of oral antibiotics with a focus on PWID.

Antibiotic	Oral dosing	Oral bioavailability	Plasma half-life (h)	Peak serum concentration with oral dosing (mg/l)	EUCAST [19] breakpoint for S (mg/l)	Important side effects and interactions concerning PWID
Amoxicillin	1g tid – qid	80%	1.5	10.2 [20]	≤0.5 (*Streptococcus* spp.)	No particular side effects or interactions.
Ciprofloxacin	500 mg bid 750 mg bid	70%	4	2.97 3.9 [21]	≤0.25 (Enterobacterales)	Risk of QTc interval prolongation, especially when combined with other QTc-prolonging drugs such as methadone. Fluoroquinolones may enhance the CNS depressant effect of opioids. Fluoroquinolones decrease the seizure threshold.
Levofloxacin	500 mg bid	~100%	6–8	7.8 [22]	≤0.5 (Enterobacterales)	
Moxifloxacin	400 mg qd	90%	6–8	3.1	≤0.25 (Enterobacterales)	
Rifampin	450–600 mg bid	90–100%	Dose-dependent and inducible 1–4	9	≤0.06 (*Staphylococcus* spp.)	Rifampin may decrease the serum concentration of opioids, notably of methadone and morphine. Many drug-drug interactions due to cytochrome induction.
Linezolid	600 mg bid	100%	5.4	21.2	≤4 (*Staphylococcus* spp.)	Linezolid is a monoamine oxidase inhibitor. Opioids can enhance this effect. Simultaneous treatment with linezolid and opioids increases the risk of serotonin syndrome. High cost.
Trimethoprim-Sulfamethoxazole (TMP-SMX)	160/800 mg bid, up to 320/1600 mg tid	80–100%	10–11	TMP: 3, SMX: 80 TMP: 8.3, SMX: 181 [23]	≤2 (TMP concentration for *Staphylococcus* spp. and Enterobacterales)	No particular side effects or interactions.
Clindamycin	600 mg tid	90%	4.5–3.5	4.8 [24]	≤0.25 (*Staphylococcus* spp.)	No particular side effects or interactions.

bid = two times a day; CNS = central nervous system; EUCAST = European Committee on Antimicrobial Susceptibility Testing; qd = once daily; qid = four times a day; tid = three times a day All pharmacokinetic information is taken from the Swiss Compendium of Medicines (available at http://www.compendium.ch) unless otherwise stated

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as poor perfusion of the gut and liver limit the absorption of oral drugs [36].

Oral therapy requires antimicrobial agents with high oral bioavailability and few gastrointestinal side effects.

Among the penicillins, only amoxicillin has a high oral bioavailability (80–90%) [9] (table 2). Gastrointestinal side effects and a saturable absorption usually limit the maximal oral dose to 3–4 × 1 g per day [37, 38]. However, for some pathogens with low MICs, e.g., some *Streptococcus* spp., oral amoxicillin may reach serum drug levels which are sufficient to allow the successful treatment of bacteraemia with those pathogens. As an example, with an estimated peak concentration of 10 mg/l and a plasma half-life of 1.5 hours (see table 2), the amoxicillin blood concentration usually remains above the *Streptococcus* spp. EUCAST MIC breakpoint of 0.5 mg/l for more than 6 hours. Many *Streptococcus* spp. strains show even lower MICs [19]. The oral bioavailabilities of other oral beta-lactam antibiotics, such as penicillin V, anti-staphylococcal penicillins (e.g., flucloxacillin) and cephalosporins (e.g., cefuroxime), are too low for them to be used as reliable treatments for patients with bacteraemia.

Fluoroquinolones (including ciprofloxacin, levofloxacin and moxifloxacin) have good oral bioavailability, are well tolerated when taken orally at standard doses [39], and reach similar pharmacokinetic parameters when taken orally as when given intravenously [40]. The same applies to rifampin, which should always be given in combination with other antibiotics to avoid the development of resistance. Trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin and the oxazolidinone linezolid also have high bioavailabilities, but are bacteriostatic (except TMP-SMX for *S. aureus*) at standard doses compared to the bactericidal activity of the fluoroquinolones and rifampin. Linezolid has potentially serious side effects (mainly neurotoxicity and haematotoxicity), especially when taken for longer periods [39], and is expensive. Table 2 shows the basic pharmacokinetic characteristics, important side effects and potential interactions of antimicrobial agents used for oral treatment of bacteraemia.

Staphylococcus aureus

S. aureus is by far the most common pathogen detected in blood cultures from PWID [1, 2, 11, 12, 41]. *S. aureus* bacteraemia is traditionally classified as complicated or uncomplicated. The following criteria define uncomplicated *S. aureus* bacteraemia: (a) exclusion of endocarditis, (b) no implanted foreign body, (c) negative follow-up blood cultures 2–4 days after the initial set, (d) defervescence within 72 hours of initiating effective therapy and (e) no evidence of metastatic sites of infection (all criteria must be fulfilled) [42]. Uncomplicated *S. aureus* bacteraemia is typically treated with intravenous antibiotics for two weeks [43, 44]. Complicated *S. aureus* bacteraemia includes endocarditis, suppurative thrombophlebitis and metastatic infections. In these cases, the treatment is complex and frequently requires surgical intervention and prolonged IV antibiotic treatment, usually for 4–6 weeks [7, 45–47]. *S. aureus* is classified as methicillin-susceptible *S. aureus* (MSSA) if the isolate is susceptible to anti-staphylococcal beta-lactams like methicillin or oxacillin, and as methicillin-resistant *S. aureus* (MRSA) if it is resistant to these. MRSA cannot be treated with beta-lactams, except for the parenteral fifth generation cephalosporins (ceftaroline, ceftobibrole).

A recent propensity score-matched cohort study [27] investigated whether patients with uncomplicated *S. aureus* bacteraemia who were switched to oral linezolid after a

Table 3: Oral antimicrobial therapy options for bacteremic infections caused by important pathogens in PWID.

Pathogen	Oral option	Remarks
Staphylococcus aureus	Ciprofloxacin 750 mg bid + Rifampin 450 mg bid	In right-sided endocarditis and PWID [16]. Warning: increased risk of QTc interval prolongation with ciprofloxacin, especially in combination with methadone. Potential for drug-drug interactions with rifampin.
	Linezolid 600 mg bid	Switch to oral linezolid not inferior to IV vancomycin in two meta-analyses [25, 26] or compared to IV beta-lactam antibiotics in a retrospective study [27]. Warning: risk of bone marrow suppression and serotonin syndrome in conjunction with opioids.
	Further dual therapy options, according to susceptibility, with less evidence e.g.,: Amoxicillin* 1000 mg qid + Rifampin 600 mg bid Dicloxacillin** 1000 mg qid + Rifampin 600 mg bid Clindamycin + Rifampin (no information on dosage in [28])	In an RCT [29] and a retrospective study [28], various oral options were not inferior to standard treatment as a switch strategy in endocarditis. However, none of these options were used in a large number of cases. See the supplementary appendix of [29] for further options. * Only around 20% of *S. aureus* in Switzerland are amoxicillin susceptible. ** Dicloxacillin has a low bioavailability and is not available in Switzerland.
Streptococcus spp.	Amoxicillin 1000 mg tid to qid ± Rifampin 450–600 mg bid*	In an RCT [29] and a retrospective cohort study [28], non-inferior as a switch strategy compared to standard IV treatment in patients with endocarditis. Probably a safe option in pneumonia due to *Streptococcus pneumoniae* and in skin- and soft-tissue infections due to *Streptococcus pyogenes*. *Role of combination therapy unclear, used in endocarditis trials [28, 29]. See supplementary appendix of [29] for further options.
Gram-negative organisms	Ciprofloxacin 500–750 mg bid	Non-inferior in a randomised trial for gram-negative bacteraemia of various origins [30], and overall success rates >90% in a randomised [31] and a retrospective trial [32].
	Trimethoprim-Sulfamethoxazole (TMP-SMX) 160/800 bid/tid	Used in various retrospective studies with an overall success rate of >85% [32–34], but less effective than ciprofloxacin.

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mean of seven days of IV treatment had worse outcomes than patients who were treated with a standard IV regimen for a mean of 15 days. The study found no significant difference in the 90-day relapse rates in survivors, and no differences in the 14- and 30-day mortality rates. In this study, 15.8% of all *S. aureus* isolates were MRSA.

In a meta-analysis of five randomised controlled trials, Shorr et al. [25] found no significant differences in clinical cure rates between patients treated with IV vancomycin and patients switched to oral linezolid after a mean duration of IV treatment of 8.6 days and with a mean total duration of treatment of 12.1 days. Overall, 50.7% of the patients presented with MRSA infections. The most common sources of infection were pneumonia (41.7%) and skin and soft tissue infections (29.9%).

As for complicated *S. aureus* bacteraemia, only a few studies have investigated oral antibiotic treatment in patients with endocarditis or suppurative thrombophlebitis.

In a retrospective study of 36 PWID with suppurative thrombophlebitis due to *S. aureus* or *Streptococcus* spp., no relapse was observed if IV treatment was given for at least seven days before switching to the oral regimen [48].

A randomised controlled trial from 1996 compared oral treatment with ciprofloxacin (750 mg bid) and rifampin (300 mg bid) to standard IV treatment (oxacillin + gentamicin), both for 28 days, in PWID with right-sided endocarditis caused by *S. aureus* [16]. The authors found no significant difference in outcome between the two groups. Ever since, this study has been cited in various endocarditis guidelines [45, 46]. To our knowledge, it is the only study to have investigated the role and outcome of oral antibiotic treatment alone (i.e.,, without IV treatment) for *S. aureus* bacteraemia. However, the results should be interpreted with caution because of the high exclusion rate (only 44 out of 573 participants were included in the final analysis; most were excluded because they did not suffer from right-sided staphylococcal endocarditis or were lost to follow-up) and the questionable – espcecially from an ethical point of view – study protocol.

In a French retrospective cohort study, the authors compared 212 patients (mostly non-PWID) with endocarditis receiving a full course of IV antimicrobial treatment to 214 patients who were switched to an oral regimen [28]. For *S. aureus* endocarditis, different oral regimens were used. Combination therapy. mainly one of (a) clindamycin + either rifampin, a fluoroquinolone or amoxicillin, (b) a fluoroquinolone + either rifampin or amoxicillin, or (c) amoxicillin + rifampin), was given in 72% of cases, and monotherapy (amoxicillin, fluoroquinolone, clindamycin or linezolid) was used in the remaining patients. After correcting for various risk factors, the authors found no significant difference in all-cause mortality between the IV and the oral groups with a mean follow-up of five months. However, the mean duration of IV treatment before switching to oral treatment was 21 days.

A two time periods (i.e., before/after) intervention study of patients with *S. aureus* endocarditis compared a standard intravenous protocol (oxacillin or vancomycin for six weeks combined with gentamycin for five days) with an early oral switch protocol (high dose (960 mg/4800 mg per day) oral TMP/SMX after seven days of IV treatment with a combination of TMP/SMX and clindamycin). Length of hospital stay and mortality rate were both reduced in the oral TMP/SMX group [49, 50]. This treatment regimen is included as an alternative therapy in the 2015 European Society of Cardiology Endocarditis guidelines [46]. However, two randomised trials that compared oral TMP/SMX to IV vancomycin for various *S. aureus* infections, including bacteraemia, showed inferior outcomes for patients treated with TMP/SMX [51, 52], although they used lower dosages (320 mg/1600 mg bid). One of these trials included only PWID [51].

Finally, the recent POET study randomised patients with endocarditis to standard IV treatment or a switch to dual oral treatment after a minimum of 10 days of IV treatment [29]. The authors used a multitude of different oral regimens for *S. aureus* bacteraemia, including (a) dicloxacillin combined with either rifampin or fusidic acid, (b) amoxicillin combined with either rifampin or fusidic acid, or (c) moxifloxacin combined with either rifampin or fusidic acid. Considering the composite primary outcome (all-cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteraemia with the primary pathogen) six months after completion of treatment, non-inferiority criteria were met. Moreover, the authors showed that in almost all patients, oral regimens reached serum antibiotic drug levels which are considered effective for treating bacteraemia.

In conclusion, there is growing evidence that a switch from initial IV antimicrobial treatment to oral treatment can be an option in uncomplicated, and even in selected cases of complicated, *S. aureus* bacteraemia. Several studies have shown good results with linezolid or various (mainly rifampin-containing) dual regimens (table 3). Monotherapy with agents other than linezolid (e.g., TMP/SMX) seems to be less favorable. However, treatment with linezolid is problematic in PWID because of the high risks of serotonin syndrome in conjunction with opioids [53, 54] and of bone marrow toxicity. Another disadvantage is the high cost of linezolid. Rifampin interacts with a multitude of drugs, including methadone, and can therefore lead to withdrawal symptoms. Unfortunately, data on the treatment of *S. aureus* bacteraemia with oral antibiotics other than linezolid and rifampin are scarce. Other options may be considered in situations where rifampin and linezolid cannot be given (table 3).

The new lipoglycopeptide antibiotic dalbavancin, which is not yet available in Switzerland, might be an interesting treatment option in the future. Dalbavancin has a very long half-life (147–258 hours) and can be given intravenously once weekly. Dalbavancin is FDA approved for skin and soft-tissue infections (SSTI) and has in vitro activity against many gram-positive pathogens, including MSSA, MRSA and streptococci. A few studies, some of which included PWID, have shown promising results for patients with bacteraemia [55–57]. However, most of these studies were small, with a heterogeneous study population, and their findings should be confirmed by larger studies.

Streptococcoccus spp.

Among streptococcal bacteraemia in PWID, group A streptococcal (GAS) infections are particularly frequent [58]. In PWID, invasive GAS infections typically present

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as an SSTI, often with an abscess at the injection site [58]. There is no consensus, either among clinicians or in the literature, on the best management of GAS bacteraemia in SSTI [59]. At least one trial with oral treatment excluded patients with positive blood cultures [60]. However, guidelines do not recommend drawing blood cultures routinely in immunocompetent patients with cellulitis and erysipela [44]. Penicillin is the drug of choice to treat GAS infections. The switch to oral therapy must be discussed on a case-by-case basis once source control has been achieved. A potential candidate for oral therapy is amoxicillin – as GAS remain invariably susceptible to penicillin, usually with low MICs (see paragraph "pharmacological considerations"). Other highly bioavailable agents are levofloxacin, moxifloxacin, clindamycin and linezolid. However, supporting data for all oral options is lacking because, to the best of our knowledge, no clinical trials have compared these agents with IV therapy in bacteremic GAS infections.

For *Streptococcus pneumoniae,* studies [61–63] of community-acquired pneumonia (CAP), including bacteraemia, did not show worse outcomes when patients were switched from IV to oral antimicrobial treatment (mostly beta-lactam antibiotics). This is reflected in the ATS/IDSA 2007 guidelines [64], which encourage a switch to oral treatment of pneumococcal bacteraemia in the setting of CAP once the patient has improved clinically. It is of note that the 2019 ATS/IDSA guidelines [65] do not recommend drawing blood cultures in CAP without specific risk factors.

Bacteraemia with streptococci from other groups (e.g., oral *Streptococcus* spp. *and Streptococcus bovis* group) are often associated with endocarditis. Some of these streptococci may show increased MICs to penicillin. To our knowledge, there are no studies that have investigated oral therapies for bacteraemia with these pathogens in diseases other than endocarditis. In streptococcal endocarditis (including different groups of streptococci), the switch to oral treatment (mostly amoxicillin monotherapy, and in a small proportion amoxicillin combined with either clindamycin or rifampin) was not associated with a significant difference in all-cause mortality or relapse in a retrospective French cohort [28]. In the POET study [29], streptococcal endocarditis was successfully treated with oral combination therapy (mostly amoxicillin and rifampin or amoxicillin and moxifloxacin) after an initial course of IV treatment.

In summary, we suggest that a switch to an oral treatment, especially with amoxicillin, is a reasonable option in PWID with streptococcal bacteraemiafor whom an alternative to IV treatment is warranted (table 3). In complicated infections such as endocarditis, combination oral therapy can be considered

Gram-negative bacteria

Several studies have shown that oral fluoroquinolones can be a valid option for the treatment of bacteraemia with susceptible gram-negative pathogens [30–33]. Although most evidence comes from studies of urogenital bacteraemia, there are also some studies from gram-negative bacteraemia of other origins [30, 32]. Fluoroquinolones have good bioavailability and usually reach adequate serum drug concentrations for successfully treating gram-negative bacteraemia.

The risk of cardiac QTc interval prolongation and torsade de pointes ventricular arrhythmias must be kept in mind when using fluoroquinolones in PWID, especially in combination with other QTc interval-prolonging drugs such as methadone [66].

Other oral treatment options, including oral beta-lactam antibiotics and TMP/SMX, are less convincing [32, 67] and seem to be inferior to fluoroquinolones, although reported cure rates were still above 85% for patients switched to an oral beta-lactam after initial IV treatment [32–34]. However, these trials were not powered to show non-inferiority in comparison to oral fluoroquinolones.

In patients with more resistant gram-negative infections, e.g., due to fluoroquinolone-resistant *Pseudomonas aeruginosa* or many ESBL-producing Enterobacterales, there are usually no good options for oral treatment. Although there is limited data for intramuscular or even subcutaneous treatment with broad-spectrum beta-lactam antibiotics [68–70], caregivers must balance the benefits of such therapy against its risks (soft tissue infection, haematoma, pain).

In summary, gram-negative bacteraemia can be treated successfully with oral fluoroquinolones if susceptible. Oral TMP/SMX is less favourable, but can be considered in fluoroquinolone-resistant gram-negative bacteraemia.

Conclusion

Data on oral antibiotic treatment of bacteraemia in PWID is scarce. Most data originate from retrospective studies and a non-PWID population. Only a few randomised controlled trials have investigated oral treatment options for bacteraemia.

The best existing evidence for oral antibiotic treatment in PWID is for gram-negative bacteraemia in the setting of urinary tract infections, which can be treated successfully with oral fluoroquinolones. Oral treatment options for fluoroquinolone-resistant gram-negative bacteraemia are very limited, with TMP/SMX a possible second choice.

In gram-positive bacteraemia, most clinical data on oral antimicrobial treatment comes from switch studies, in which antimicrobial therapy was started intravenously before a switch to oral treatment. The selection of an oral regimen in PWID with *S. aureus* bacteraemia seems particularly challenging, as the best-documented regimens, including fluoroquinolones, linezolid and rifampin, also have the highest risk of toxicity and interactions.

The very limited number of good and well-studied oral antimicrobial treatment options in this very complex patient population highlights the importance of adequate source control and an interdisciplinary approach, encompassing all persons involved in the treatment and care, to select the best therapy and to ensure follow-up.

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References

1 Scheidegger C, Zimmerli W. Infectious complications in drug addicts: seven-year review of 269 hospitalized narcotics abusers in Switzerland.

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Rev Infect Dis. 1989;11(3):486–93. doi: http://dx.doi.org/10.1093/clinids/11.3.486. PubMed.
2 Bassetti S, Hoffmann M, Bucher HC, Fluckiger U, Battegay M. Infections requiring hospitalization of injection drug users who participated in an injection opiate maintenance program. Clin Infect Dis. 2002;34(5):711–3. doi: http://dx.doi.org/10.1086/338876. PubMed.
3 Louria DB, Hensle T, Rose J. The major medical complications of heroin addiction. Ann Intern Med. 1967;67(1):1–22. doi: http://dx.doi.org/10.7326/0003-4819-67-1-1. PubMed.
4 World Health Organization. Management of common health problems of drug users. Geneva: World Health Organization; 2009. 131 p.
5 Hope VD, Ncube F, Parry JV, Hickman M. Healthcare seeking and hospital admissions by people who inject drugs in response to symptoms of injection site infections or injuries in three urban areas of England. Epidemiol Infect. 2015;143(1):120–31. doi: http://dx.doi.org/10.1017/S0950268814000284. PubMed.
6 Scheidegger C, Zimmerli W. Incidence and spectrum of severe medical complications among hospitalized HIV-seronegative and HIV-seropositive narcotic drug users. AIDS. 1996;10(12):1407–14. doi: http://dx.doi.org/10.1097/00002030-199610000-00014. PubMed.
7 Zou H, Li G. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Chinese J Infect Chemother. 2010;10(2):81–4. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/599376
8 Scarborough M, Li HK, Rombach I, Zambellas R, Walker AS, McNally M, et al. Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT. Health Technol Assess. 2019;23(38):1–92. doi: http://dx.doi.org/10.3310/hta23380. PubMed.
9 Cunha BA. Oral antibiotic therapy of serious systemic infections. Med Clin North Am. 2006;90(6):1197–222. doi: http://dx.doi.org/10.1016/j.mcna.2006.07.009. PubMed.
10 Gardner EM, Kestler M, Beieler A, Belknap RW. Clostridium butyricum sepsis in an injection drug user with an indwelling central venous catheter. J Med Microbiol. 2008;57(Pt 2):236–9. doi: http://dx.doi.org/10.1099/jmm.0.47578-0. PubMed.
11 Rodger L, Shah M, Shojaei E, Hosseini S, Koivu S, Silverman M. Recurrent Endocarditis in Persons Who Inject Drugs. Open Forum Infect Dis. 2019;6(10):ofz396. doi: http://dx.doi.org/10.1093/ofid/ofz396. PubMed.
12 Mertz D, Viktorin N, Wolbers M, Laifer G, Leimenstoll B, Fluckiger U, et al. Appropriateness of antibiotic treatment in intravenous drug users, a retrospective analysis. BMC Infect Dis. 2008;8(1):42. doi: http://dx.doi.org/10.1186/1471-2334-8-42. PubMed.
13 Hill A, Wai A, Marsh D, Stiver H, Sakakibara T. Pilot assessment of Intravenous Antibiotic Therapy in Live-in Street-based Clinic, for Infections in Intravenous Dur Users [Internet]. IDWeek. Idsa; 2006 [cited 2019 Dec 10]. Available from: https://idsa.confex.com/idsa/2006/webprogram/Paper22373.html
14 Ho J, Archuleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother. 2010;65(12):2641–4. doi: http://dx.doi.org/10.1093/jac/dkq355. PubMed.
15 Summanen PH, Talan DA, Strong C, McTeague M, Bennion R, Thompson JE, Jr, et al. Bacteriology of skin and soft-tissue infections: comparison of infections in intravenous drug users and individuals with no history of intravenous drug use. Clin Infect Dis. 1995;20(Suppl 2):S279–82. doi: http://dx.doi.org/10.1093/clinids/20.Supplement_2.S279. PubMed.
16 Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996;101(1):68–76. doi: http://dx.doi.org/10.1016/S0002-9343(96)00070-8. PubMed.
17 Fäh F, Zimmerli W, Jordi M, Schoenenberger RA. Septic deep venous thrombosis in intravenous drug users. Swiss Med Wkly. 2002;132(27-28):386–92. PubMed.
18 Peterson TC, Pearson C, Zekaj M, Hudson I, Fakhouri G, Vaidya R. Septic arthritis in intravenous drug abusers: a historical comparison of habits and pathogens. J Emerg Med. 2014;47(6):723–8. doi: http://dx.doi.org/10.1016/j.jemermed.2014.06.059. PubMed.
19 Nathan AJ, Scobell A. How China sees America. Foreign Aff. 2012;91:1689–99. Available from: http://www.eucast.org
20 Spyker DA, Rugloski RJ, Vann RL, O'Brien WM. Pharmacokinetics of amoxicillin: dose dependence after intravenous, oral, and intramuscular administration. Antimicrob Agents Chemother. 1977;11(1):132–41. doi: http://dx.doi.org/10.1128/AAC.11.1.132. PubMed.
21 Catchpole C, Andrews JM, Woodcock J, Wise R. The comparative pharmacokinetics and tissue penetration of single-dose ciprofloxacin 400 mg i.v. and 750 mg po. J Antimicrob Chemother. 1994;33(1):103–10. doi: http://dx.doi.org/10.1093/jac/33.1.103. PubMed.
22 Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet. 1997;32(2):101–19. doi: http://dx.doi.org/10.2165/00003088-199732020-00002. PubMed.
23 Chin TWF, Vandenbroucke A, Fong IW. Pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients. Antimicrob Agents Chemother. 1995;39(1):28–33. doi: http://dx.doi.org/10.1128/AAC.39.1.28. PubMed.
24 Dan M, Yampolsky E, Poch F. Serum concentrations and ex vivo inhibitory/bactericidal activity of clindamycin after administration of two oral dosages. Chemotherapy. 1997;43(4):227–31. doi: http://dx.doi.org/10.1159/000239571. PubMed.
25 Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother. 2005;56(5):923–9. doi: http://dx.doi.org/10.1093/jac/dki355. PubMed.
26 Beibei L, Yun C, Mengli C, Nan B, Xuhong Y, Rui W. Linezolid versus vancomycin for the treatment of gram-positive bacterial infections: meta-analysis of randomised controlled trials. Int J Antimicrob Agents. 2010;35(1):3–12. doi: http://dx.doi.org/10.1016/j.ijantimicag.2009.09.013. PubMed.
27 Willekens R, Puig-Asensio M, Ruiz-Camps I, Larrosa MN, González-López JJ, Rodríguez-Pardo D, et al. Early Oral Switch to Linezolid for Low-risk Patients With Staphylococcus aureus Bloodstream Infections: A Propensity-matched Cohort Study. Clin Infect Dis. 2019;69(3):381–7. doi: http://dx.doi.org/10.1093/cid/ciy916. PubMed.
28 Mzabi A, Kernéis S, Richaud C, Podglajen I, Fernandez-Gerlinger M-P, Mainardi J-L. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. Clin Microbiol Infect. 2016;22(7):607–12. doi: http://dx.doi.org/10.1016/j.cmi.2016.04.003. PubMed.
29 Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med. 2019;380(5):415–24. doi: http://dx.doi.org/10.1056/NEJMoa1808312. PubMed.
30 Amodio-Groton M, Madu A, Madu CN, Briceland LL, Seligman M, McMaster P, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. Ann Pharmacother. 1996;30(6):596–602. doi: http://dx.doi.org/10.1177/106002809603000605. PubMed.
31 Dinh A, Davido B, Etienne M, Bouchand F, Raynaud-Lambinet A, Aslangul-Castier E, et al. Is 5 days of oral fluoroquinolone enough for acute uncomplicated pyelonephritis? The DTP randomized trial. Eur J Clin Microbiol Infect Dis. 2017;36(8):1443–8. doi: http://dx.doi.org/10.1007/s10096-017-2951-6. PubMed.
32 Kutob LF, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. Int J Antimicrob Agents. 2016;48(5):498–503. doi: http://dx.doi.org/10.1016/j.ijantimicag.2016.07.013. PubMed.
33 Rieger KL, Bosso JA, MacVane SH, Temple Z, Wahlquist A, Bohm N. Intravenous-only or Intravenous Transitioned to Oral Antimicrobials for Enterobacteriaceae-Associated Bacteremic Urinary Tract Infection. Pharmacotherapy. 2017;37(11):1479–83. doi: http://dx.doi.org/10.1002/phar.2024. PubMed.
34 Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al.; Antibacterial Resistance Leadership Group. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019;179(3):316–23. doi: http://dx.doi.org/10.1001/jamainternmed.2018.6226. PubMed.
35 Rapoport AB, Beekmann SE, Polgreen PM, Rowley CF. Injection Drug Use and Infectious Disease Practice: A National Provider Survey. Open Forum Infect Dis. 2017;4(suppl1):S340. doi: http://dx.doi.org/10.1093/ofid/ofx163.810.
36 De Paepe P, Belpaire FM, Buylaert WA. Pharmacokinetic and pharmacodynamic considerations when treating patients with sepsis and septic shock. Clin Pharmacokinet. 2002;41(14):1135–51. doi: http://dx.doi.org/10.2165/00003088-200241140-00002. PubMed.
37 Dajani AS, Bawdon RE, Berry MC. Oral amoxicillin as prophylaxis for endocarditis: what is the optimal dose? Clin Infect Dis. 1994;18(2):157–60. doi: http://dx.doi.org/10.1093/clinids/18.2.157. PubMed.
38 de Velde F, de Winter BCM, Koch BCP, van Gelder T, Mouton JW; COMBACTE-NET consortium. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical break-

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points. J Antimicrob Chemother. 2016;71(10):2909–17. doi: http://dx.doi.org/10.1093/jac/dkw226. PubMed.
39 Hale AJ, Snyder GM, Ahern JW, Eliopoulos G, Ricotta D, Alston WK. When are oral antibiotics a safe and effective choice for bacterial bloodstream infections? An evidence-based narrative review. J Hosp Med. 2018;13(5):328–35. doi: http://dx.doi.org/10.12788/jhm.2949. PubMed.
40 LeBel M. Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. Pharmacotherapy. 1988;8(1):3–33. doi: http://dx.doi.org/10.1002/j.1875-9114.1988.tb04058.x. PubMed.
41 Hartnett KP, Jackson KA, Felsen C, McDonald R, Bardossy AC, Gokhale RH, et al. Bacterial and fungal infections in persons who inject drugs - Western new york, 2017. MMWR Morb Mortal Wkly Rep. 2019;68(26):583–6. doi: http://dx.doi.org/10.15585/mmwr.mm6826a2. PubMed.
42 Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al.; Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18–55. doi: http://dx.doi.org/10.1093/cid/ciq146. PubMed.
43 Holland TL, Arnold C, Fowler VG, Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014;312(13):1330–41. doi: http://dx.doi.org/10.1001/jama.2014.9743. PubMed.
44 Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al.; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10–52. doi: Correction in: Clin Infect Dis. 2015;60(9):1448 http://dx.doi.org/10.1093/cid/ciu296. PubMed.
45 Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr, Tleyjeh IM, Rybak MJ, et al.; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132(15):1435–86. doi: http://dx.doi.org/10.1161/CIR.0000000000000296. PubMed.
46 Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. Ghid de management al endocarditei infecţioase 2015. Rev Rom Cardiol. 2016;26(3):343–405. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehv319
47 Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al.; Infectious Diseases Society of America. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015;61(6):e26–46. doi: http://dx.doi.org/10.1093/cid/civ482. PubMed.
48 Mertz D, Khanlari B, Viktorin N, Battegay M, Fluckiger U. Less than 28 days of intravenous antibiotic treatment is sufficient for suppurative thrombophlebitis in injection drug users. Clin Infect Dis. 2008;46(5):741–4. doi: http://dx.doi.org/10.1086/527445. PubMed.
49 Casalta JP, Zaratzian C, Hubert S, Thuny F, Gouriet F, Habib G, et al. Treatment of Staphylococcus aureus endocarditis with high doses of trimethoprim/sulfamethoxazole and clindamycin-Preliminary report. Int J Antimicrob Agents. 2013;42(2):190–1. doi: http://dx.doi.org/10.1016/j.ijantimicag.2013.05.002. PubMed.
50 Tissot-Dupont H, Gouriet F, Oliver L, Jamme M, Casalta JP, Jimeno MT, et al. High-dose trimethoprim-sulfamethoxazole and clindamycin for Staphylococcus aureus endocarditis. Int J Antimicrob Agents. 2019;54(2):143–8. doi: http://dx.doi.org/10.1016/j.ijantimicag.2019.06.006. PubMed.
51 Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann Intern Med. 1992;117(5):390–8. doi: http://dx.doi.org/10.7326/0003-4819-117-5-390. PubMed.
52 Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial. BMJ. 2015;350(may14 24):h2219. doi: http://dx.doi.org/10.1136/bmj.h2219. PubMed.
53 Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth. 2005;95(4):434–41. doi: http://dx.doi.org/10.1093/bja/aei210. PubMed.
54 Gupta V, Karnik ND, Deshpande R, Patil MA. Linezolid-induced serotonin syndrome. BMJ Case Rep. 2013;2013:bcr2012008199. PubMed.
55 Van Hise NW, Anderson M, McKinsey D, McKinsey J, Harting B, Belmares J, et al. The Use of Dalbavancin for Staphylococcus aureus Bacteremia in Persons Who Inject Drugs (PWID). Open Forum Infect Dis. 2019;6(Suppl2):S772. doi: http://dx.doi.org/10.1093/ofid/ofz360.1933.
56 Bork JT, Heil EL, Berry S, Lopes E, Davé R, Gilliam BL, et al. Dalbavancin Use in Vulnerable Patients Receiving Outpatient Parenteral Antibiotic Therapy for Invasive Gram-Positive Infections. Infect Dis Ther. 2019;8(2):171–84. doi: http://dx.doi.org/10.1007/s40121-019-0247-0. PubMed.
57 Bryson-Cahn C, Beieler AM, Chan JD, Harrington RD, Dhanireddy S. Dalbavancin as Secondary Therapy for Serious *Staphylococcus aureus* Infections in a Vulnerable Patient Population. Open Forum Infect Dis. 2019;6(2):ofz028. doi: http://dx.doi.org/10.1093/ofid/ofz028. PubMed.
58 Curtis SJ, Tanna A, Russell HH, Efstratiou A, Paul J, Cubbon M, et al. Invasive group A streptococcal infection in injecting drug users and non-drug users in a single UK city. J Infect. 2007;54(5):422–6. doi: http://dx.doi.org/10.1016/j.jinf.2006.10.004. PubMed.
59 Alwan M, Davis JS, Daneman N, Fowler R, Shehabi Y, Rogers B. Duration of therapy recommended for bacteraemic illness varies widely amongst clinicians. Int J Antimicrob Agents. 2019;54(2):184–8. doi: http://dx.doi.org/10.1016/j.ijantimicag.2019.05.011. PubMed.
60 Jorup-Rönström C, Britton S, Gavlevik A, Gunnarsson K, Redman AC. The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. Infection. 1984;12(6):390–4. doi: http://dx.doi.org/10.1007/BF01645222. PubMed.
61 Sutton JD, Sayood S, Spivak ES. Top Questions in Uncomplicated, Non-*Staphylococcus aureus* Bacteremia. Open Forum Infect Dis. 2018;5(5):ofy087. doi: http://dx.doi.org/10.1093/ofid/ofy087. PubMed.
62 Oosterheert JJ, Bonten MJM, Schneider MME, Buskens E, Lammers JWJ, Hustinx WMN, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ. 2006;333(7580):1193–5. doi: http://dx.doi.org/10.1136/bmj.38993.560984.BE. PubMed.
63 Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired Streptococcus pneumoniae pneumonia. Arch Intern Med. 2001;161(6):848–50. doi: http://dx.doi.org/10.1001/archinte.161.6.848. PubMed.
64 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al.; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72. doi: http://dx.doi.org/10.1086/511159. PubMed.
65 Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019;200(7):e45–67. doi: http://dx.doi.org/10.1164/rccm.201908-1581ST. PubMed.
66 Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. Addiction. 2008;103(12):2062–4. doi: http://dx.doi.org/10.1111/j.1360-0443.2008.02390.x. PubMed.
67 Sandberg T, Englund G, Lincoln K, Nilsson LG. Randomised double-blind study of norfloxacin and cefadroxil in the treatment of acute pyelonephritis. Eur J Clin Microbiol Infect Dis. 1990;9(5):317–23. doi: http://dx.doi.org/10.1007/BF01973737. PubMed.
68 Musson DG, Majumdar A, Birk K, Holland S, Wickersham P, Li SX, et al. Pharmacokinetics of intramuscularly administered ertapenem. Antimicrob Agents Chemother. 2003;47(5):1732–5. doi: http://dx.doi.org/10.1128/AAC.47.5.1732-1735.2003. PubMed.
69 Roubaud-Baudron C, Forestier E, Fraisse T, Gaillat J, de Wazières B, Pagani L, et al. Tolerance of subcutaneously administered antibiotics: a French national prospective study. Age Ageing. 2017;46(1):151–5. PubMed.
70 Walker P, Neuhauser MN, Tam VH, Willey JS, Palmer JL, Bruera E, et al. Subcutaneous administration of cefepime. J Pain Symptom Manage. 2005;30(2):170–4. doi: http://dx.doi.org/10.1016/j.jpainsymman.2005.03.007. PubMed.

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