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

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 unacceptable 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.
General management considerations

Bacteraemia in PWID is most often caused by *S. aureus*, followed by *Streptococcus* spp., *Enterobacteriales*, *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, suppurrative 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.

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,

| 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 | 70%                  | 4                   | 2.97 [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] | s2 (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.
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, suppurrative 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 (ceftriaxone, cefotibobrole). A recent propensity score-matched cohort study [27] investigated whether patients with uncomplicated S. aureus bacteraemia who were switched to oral linezolid after a

| Pathogen | Oral option | Remarks |
|----------|-------------|---------|
| Staphylococcus aureus | Ciprofloxacin 750 mg bid + Rifampin 450 mg bid | In right-sided endocarditis and PWID [10]. 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.: | 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 a 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 [29, 28]. 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) 180/800 bid/tid | Used in various retrospective studies with an overall success rate of >85% [32–34], but less effective than ciprofloxacin. |
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 – especially 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.

**Streptococcus spp.**

Among streptococcal bacteraemia in PWID, group A streptococcal (GAS) infections are particularly frequent [58]. In PWID, invasive GAS infections typically present...
Infectious complications in drug addicts: W. Scheidegger

Aemia of other origins [125]. Evidence comes from studies of urogenital bacteraemia, especially 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 bacteremia, 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 bacteremia 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.

Bacteremia 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 bacteremia 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 bacteremia for 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 bacteremia with susceptible gram-negative pathogens [30–33]. Although most evidence comes from studies of urogenital bacteremia, there are also some studies from gram-negative bacteremia of other origins [30, 32]. Fluoroquinolones have good bioavailability and usually reach adequate serum drug concentrations for successfully treating gram-negative bacteremia.

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

**Conclusion**

Data on oral antibiotic treatment of bacteremia 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 bacteremia.

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

In gram-positive bacteremia, 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* bacteremia 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.
53 Gillman PK. Monomeric oxidase inhibitors, opioid analgesics and seroton- 
toxicity. Br J Anaesth. 2005;95(4):434–41. doi: http://dx.doi.org/ 10.1093/bja/aei210. PubMed.

54 Gupta V, Kamik ND, Deshpande R, Patil MA. Linezolid-induced sero- 
toin toxicity. J Anaesth. 2013;57:231–3. doi:10.1007/s10639-013-9705-7. PubMed.

55 Van Hise NW, Anderson M, McKeiny D, McKeiny J, Harting B, Bel- 
nares J, et al. The Use of Dalbavancin for Staphylococcus aureus Bac- 
teria in Persons Who Inject Drugs (PWID). Open Forum Infect Dis. 
2018;5(Suppl 3):S722. doi:10.1093/ofid/ofy352.1923.

Bork JT, Heil EL, Berry S, Lopes E, Davie R, Gillilan BL, et al. Dalba- 
vancin Use in Vulnerable Patients Receiving Outpatient Parenteral An-
tibiotic Therapy for Invasive Gram-Positive Infections. Infect Dis Ther. 
2019;8(2):217–84. doi: http://dx.doi.org/10.1007/s40121-019-00247-0. PubMed.

56 Bryson-Cahn C, Beiler 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.

57 Curtis SJ, Tanna A, Russell HJ, Elson J, Cuningham 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.

58 Alwan M, Davis JS, Dantzner N, Fowler R, Shahabi Y, Rogers D. Du-
ration of treatment for methicillin-resistant Staphylococcus aureus 
infections varies widely among clinicians. Int J Antimicrob Agents. 
2019;54(2):184–8. doi: http://dx.doi.org/10.1016/j.ijantimicag.2019.05.011. PubMed.

59 Jorup-Rönström C, Britton S, Gavlevik A, Gunnarsson K, Redman AC. 
The course, costs and complications of oral versus intravenous penicillin 
therapy for community-acquired pneumonia in adults. Clin Infect Dis. 
2014;59(4):50–52. doi: Correction in: Clin Infect Dis. 2014;69(3):566. 
http://dx.doi.org/10.1093/cid/ciu429. PubMed.

60 de Wazières R, Ramirez JA, Borton JD. Early switch from intrave-
rous 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.38893.56984.BE. PubMed.

61 Ansueto A, Aguirre KJ, Baddour LM, García JA, Cremonesi R, 
Campbell SD, 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 Car-
diovascular Surgery and Anesthesia, and Stroke Council. Infective endo-
carditis 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/CIRCULATIONAHA.115.020069. PubMed.

62 Habhi G, Lancellotti P, Antunes MJ, Bongioni MG, Casalta JP, Del 
Zotti F, et al. Ghid de management al endocarditei infectioase 2015. Rev Rom Cardiol. 2016;62(3):343–405. Available from: 
https://academic. 
63 Pagani F, Cristani A, Ricotta S, Tumianni C, Zanotti A, et al. Endo-
carditis in nonvalvular atrial fibrillation: A multicentre randomised trial 
[Clin Infect Dis. 2015;60(9):1448. doi: http://dx.doi.org/10.1093/cid/ciu296. 
PubMed.

64 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 Car-
diovascular Surgery and Anesthesia, and Stroke Council. Infective endo-
carditis 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/CIRCULATIONAHA.115.020069. PubMed.

65 Mertz D, Khanali B, Viktorin N, Battegay M, Flueckiger U. Less than 
28 days of intravenous antibiotic treatment is sufficient for supportive 
thrombophlebitis in injection drug users. Clin Infect Dis. 
2008;46(5):741–4. doi: http://dx.doi.org/10.1086/527445. PubMed.

66 Casalta JP, Zarzarian C, Huber S, Thuny F, Gouriet F, Habhi 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.

67 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.

68 Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxa-
zeole compared with vancomycin for the treatment of Staphylococcus au-
reus infection. Ann Intern Med. 1992;117(5):390–8. doi: http://dx.doi.org/10.1086/317030. PubMed.

69 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: ran-
donised controlled trial. BMJ. 2015;355(may14 24):h2219. doi: 
http://dx.doi.org/10.1136/bmj.h2219. PubMed.

70 Gillman PK. Monomeric oxidase inhibitors, opioid analgesics and sero-
toxicity. Br J Anaesth. 2005;95(4):434–41. doi: http://dx.doi.org/ 10.1093/bja/aei210. PubMed.

71 Gupta V, Kamik ND, Deshpande R, Patil MA. Linezolid-induced sero-
toxicity. J Anaesth. 2013;57:231–3. doi:10.1007/s10639-013-9705-7. PubMed.

72 Van Hise NW, Anderson M, McKeiny D, McKeiny J, Harting B, Bel-
nares J, et al. The Use of Dalbavancin for Staphylococcus aureus Bac-
teria in Persons Who Inject Drugs (PWID). Open Forum Infect Dis. 
2018;5(Suppl 3):S722. doi:10.1093/ofid/ofy352.1923.

Bork JT, Heil EL, Berry S, Lopes E, Davie R, Gillilan BL, et al. Dalba-
vancin Use in Vulnerable Patients Receiving Outpatient Parenteral An-
tibiotic Therapy for Invasive Gram-Positive Infections. Infect Dis Ther. 
2019;8(2):217–84. doi: http://dx.doi.org/10.1007/s40121-019-00247-0. PubMed.