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Narrative review

# Management of Gram-positive multiresistant bacteria prosthetic joint infection: a narrative review on current and innovative strategies

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ABSTRACT

*Background:* Prosthetic joint infection (PJI) is a devastating complication of arthroplasty surgery, mostly caused by Gram-positive pathogens, including *Staphylococcus aureus* and coagulase-negative staphylococci. Multidrug resistance is of major concern in this setting: (a) it can negatively impact outcome, restricting the use of the most effective antimicrobials; (b) it may influence the choice of surgical strategies; and (c) it restrains the therapeutic options to newly labelled antimicrobials with limited experience in PJI.
*Objectives:* To provide a comprehensive overview of the clinical impact of antimicrobial resistance in Gram-positive PJI and on current and innovative therapeutic strategies.
*Sources:* The review is based on PubMed searches for relevant topics, including multiresistant staphylococci PJI and the discussed specific therapeutic approaches. Given the very few randomized trials in this setting, discussion is mostly based on observational studies and the experience and opinion of the authors.
*Content:* Methicillin resistance is an important concern in staphylococcal PJI, especially in coagulase-negative staphylococci. However, its impact on the outcome is controversial. Conversely, rifampicin and/or fluoroquinolone resistance are associated with worse prognosis and might be considered when defining difficult-to-treat pathogens in the PJI setting. There is very little experience with recently developed anti-Gram-positive antimicrobial in PJI, but evaluations of their antibiofilm activities are promising, and some of them might represent significant advances regarding antimicrobial tolerance (such as tedizolid) or pharmacokinetic profiles (such as dalbavancin) during long-term treatment required for PJI. Evaluation of innovative strategies in this setting is crucial, including repositioning of current surgical options using local antimicrobial delivery, pharmacokinetic monitoring and modelling to optimize antimicrobial therapy, suppressive antimicrobial treatment and/or phage-based approaches.
*Implications:* PJIs caused by resistant Gram-positive bacteria—including rifampicin- and/or fluoroquinolone-resistant staphylococci—may be associated with a poorer prognosis. It is therefore essential to optimize medical and surgical management, and to find new therapeutic alternatives.
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## Introduction

Prosthetic joint infection (PJI) is a major complication of arthroplasty, with an estimated incidence of 1% [1]. Gram-positive bacteria account for two-thirds of documented infections, mainly

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represented by *Staphylococcus aureus* and coagulase-negative staphylococci (CNS) [2]. The worldwide increase in antimicrobial resistance raises several concerns in the specific field of PJI. First, the impact of antimicrobial resistance on the outcome remains to be specifically evaluated. PJI management relies on antimicrobials chosen for their osteoarticular penetration and antibiofilm activity [3,4]. For instance, rifampicin is recognized as a cornerstone of staphylococcal device-associated infection because of its tissue penetration and activity against staphylococcal biofilms. Fluoroquinolones are considered as the best companion molecules of rifampicin for staphylococcal PJI because of their excellent bone penetration and lack of drug–drug interaction, and also display good biofilm activity against Gram-negative pathogens. However, these drugs are not commonly considered to define multidrug resistance (MDR). Second, antimicrobials recently marketed for the treatment of MDR Gram-positive have been approved for skin and soft-tissue infection (SSTI), with little information on their dosage, efficacy and tolerance upon prolonged treatment required for PJI, for which their use is more relevant. Third, apart from considerations related to antimicrobial resistance, current surgical strategies—mainly debridement, antibiotics and implant retention (DAIR), and one- or two-stage exchanges—are associated with a global risk of failure of 20% subject to carefully chosen indications [5], advocating for the implementation of innovative approaches in selected patients.

This review provides insights into the impact of antimicrobial resistance on Gram-positive PJI prognosis, and on innovative strategies to implement for a better outcome of these difficult-to-treat infections.

## Microbiological epidemiology, resistance and prognosis

In a large French cohort (2014–2019) using the national registry of complex bone and joint infection (BJI) reference centres to gather 11 812 documented PJI, *S. aureus* (26.3%) and CNS (25.1%) were the most frequently involved pathogens, streptococci (9.4%) and enterococci (5.7%) being less represented [2].

### *MDR staphylococci*

Prevalence and evolution of staphylococcal resistance rates vary significantly across countries, with few international comparative data regarding specifically PJI isolates. For instance, 2021 data from the European surveillance of antimicrobial resistance revealed that among more than 60 000 invasive *S. aureus* isolates, overall methicillin-resistance rate was 15.8%, being stable or decreasing in most countries, but with major variations in prevalence ranging from 0.9% to 42.9% depending on countries [6]. Similarly, an important disparity of MRSA prevalence is noted towards PJI isolates depending on countries, with a global trend to diminution in Europe [7,8]. However, some observational studies showed an increase in MRSA prevalence in other countries, such as the United States [9]. Methicillin resistance is more frequent in CNS than in *S. aureus*, accounting for 59% and 16% of isolates, respectively, in our reported experience [10]. In a multicentric European study of *Staphylococcus epidermidis* PJI treated with DAIR (2007–2017), resistance rates were 82% for methicillin, 59% for levofloxacin, 57% for clindamycin, and 51% for cotrimoxazole [11]. Methicillin resistance was found to be more common in early postoperative infections [10,12].

The prognostic impact of methicillin resistance in staphylococcal PJI is debated. In a German retrospective study involving 74 chronic PJI with a two-stages surgical management caused by *S. aureus* and *S. epidermidis*, methicillin-resistant Staphylococcus epidermidis (MRSE) infection was associated with a lower eradication rate compared with MSSE [13]. However, this difference could rely on a baseline difference between patients in the two groups, MRSE-infected individuals have a significantly higher American Society of Anesthesiology score (ASA) score and a higher infection duration. Regarding Methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA), some studies showed no differences in PJI outcome [13,14], whereas others found a higher failure rate for MRSA infections [15,16]. Of note, the overall cost of treatment could also be higher in cases of methicillin resistance [17].

Beyond methicillin resistance, rifampicin resistance rate was found to be more frequent in CNS (24.4%) than *S. aureus* (7.8%) [7], and has been associated with a poorer outcome of staphylococcal PJI in several studies [18,19]. Rifampicin has been shown to improve the prognosis of staphylococcal PJI treated by DAIR, especially when used in combination with fluoroquinolones [20]. Similarly, quinolone resistance among *S. epidermidis* has been associated with a higher rate of failure in early PJI treated with DAIR [11]. Consequently, rifampicin and fluoroquinolone resistances might be considered when defining MDR pathogens in staphylococcal PJI (see Fig. 1).

### *Other resistant Gram-positive pathogens*

A Spanish study involving 444 patients with streptococci PJI treated by DAIR showed that reduced susceptibility to penicillin (MIC >0.125 mg/L) was not associated with a higher failure rate [21]. In an American study including 87 enterococcal PJI, vancomycin-resistant enterococci were not associated with a poorer outcome [22].

## Current antimicrobial options

### *Oxazolidinones*

With a spectrum comprising all Gram-positive pathogens and good bone penetration, oxazolidinones represent an alternative in MDR Gram-positive PJI. However, prolonged (>10 days) courses of linezolid are associated with a risk of haematological and neurological toxicities [23]. In a review pooling 372 PJI cases treated with linezolid from 16 studies, an infection control rate of 80% was reported, with a rate of adverse events of 33% [24]. Of note, the drug–drug interaction of linezolid with rifampicin is a source of conflicting data regarding tolerance (with a potential lower rates of anaemia—but not thrombocytopenia and neuropathy) and efficacy, some authors reporting a higher failure rate with this combination [25].

More recently approved for SSTI, tedizolid presents the advantage of a lower toxicity during long-term treatment. It has been successfully used in a rat model of MRSA and MRSE osteosynthesis-associated infection [26,27]. Patients with BJIs, a minority of them with PJI, have been treated with good tolerance, but differing degrees of success [28,29].

### *Long-acting lipoglycopeptides*

Dalbavancin and oritavancin are two lipoglycopeptides, active against most Gram-positive bacteria. Recently approved for SSTI, their long half-life of 15 and 10 days, respectively, makes them a more appropriate option for chronic MDR Gram-positive infections such as PJI.

Dalbavancin demonstrated an acceptable activity against staphylococcal biofilms especially in combination with rifampicin [30], and good efficacy in a rat model of sternal MRSA osteomyelitis [31]. A two-dose regimen of dalbavancin of 1500 mg 1 week apart provides satisfying bone concentrations for at least 4–6 weeks [32]. A randomized clinical trial compared this two-dose regimen of dalbavancin with standard of care in osteomyelitis, with similar

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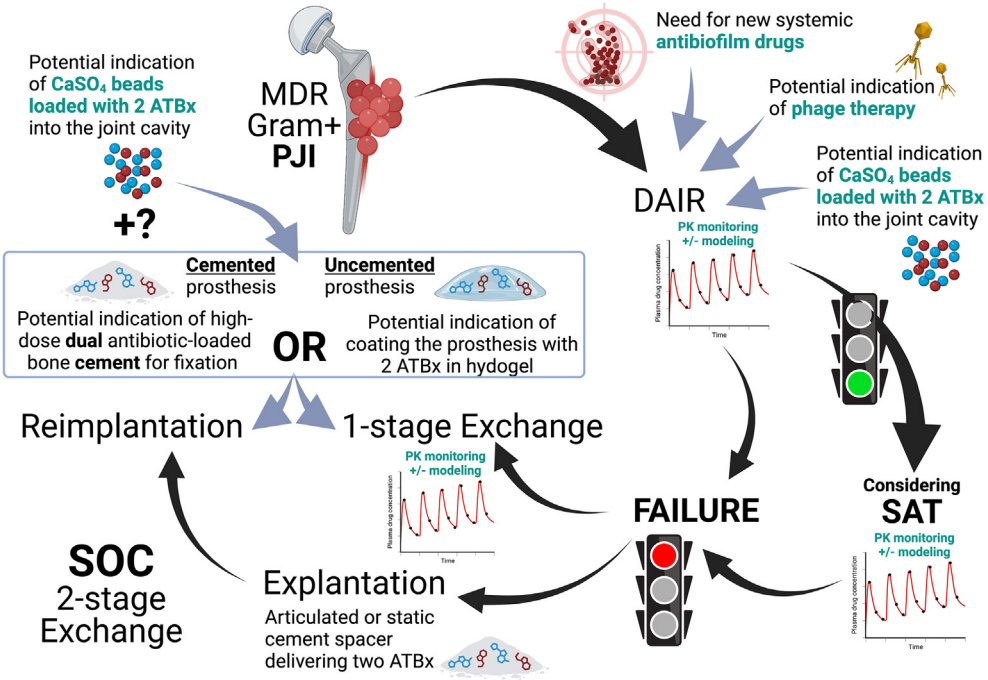


**Fig. 1.** Management strategies in patients with acute, late acute or haematogenous PJI with an unloosened prosthesis and for whom DAIR is the primary surgical approach. ATBx, antibiotics; $CaSO_4$, calcium sulphate; DAIR, debridement, antibiotics and implant retention; PJI, prosthetic joint infection; PK, pharmacokinetic; SAT, suppressive antimicrobial therapy SOC, Standard of Care.

clinical response at 1 year (96%) and an acceptable tolerance [33]. Turning especially to PJI, data are more limited, but pooled results of cohort studies showed a clinical cure rate of 73% [34]. In situations necessitating more than 6 weeks of treatment, two injections of 1500 mg 1 week apart with trough concentration monitoring and pharmacokinetic (PK) modelling allow for individualized intervals and doses of subsequent injections [35].

In addition to the spectrum of dalbavancin, oritavancin has potential activity against vanA + *Enterococcus faecium* [36]. Its activity against staphylococcal and enterococcal biofilms has been described [37,38]. However, the use of multidose oritavancin in PJI is less documented [39], and PK guidelines are missing for individualized long-term administration. To date, the largest series gathered 134 BJI, including 17.9% with prosthetic material, receiving one dose of 1200 mg followed by 3 or 4 weekly doses of 800 mg [40]. The rate of clinical success was 80%, but was evaluated at 6 months post-therapy, only.

### *Anti-methicillin-resistant staphylococci cephalosporins*

Ceftaroline and ceftopibrole possess a high affinity to penicillin-binding proteins associated with methicillin resistance (including penicillin-binding protein 2a (PBP2a)), making them the only β-lactams active against methicillin-resistant staphylococci. Ceftaroline showed good efficacy in a rabbit model of MRSA PJI in comparison to vancomycin [41]. However, the experience of these molecules in PJI is limited to a few case reports. Additionally, their broad spectrum including non-Extended-spectrum β-lactamase (ESBL) Enterobacterales—and *Pseudomonas aeruginosa* for ceftobiprole—might be associated with a significant ecologic impact. Thus, their use should probably be restricted to polymicrobial infections.

### *Delafloxacin*

Delafloxacin is a new fluoroquinolone that may retain activity against fluoroquinolone-resistant staphylococci thanks to its dual targeting of DNA topoisomerase IV and DNA gyrase. In addition, the expected excellent bone diffusion of fluoroquinolone and the activity of delafloxacin against staphylococcal biofilm make it a potential alternative in MDR staphylococci PJI [42]. We recently compared levofloxacin and delafloxacin minimum biofilm eradication concentration (MBEC) among two pairs of levofloxacin susceptible/resistant *S. aureus* isolates and a collection of ten clinical strains isolated from BJIs (five *S. aureus*, five *S. epidermidis*), showing significantly lower delafloxacin MBEC, including against most levofloxacin-resistant isolates (34th European Congress of Clinical Microbiology and Infectious Diseases, 2024, Barcelona; Abstract P1131). However, there are no delafloxacin Minimum inhibitory concentration (MIC) interpretation guidelines for CNS, and two different breakpoints for *S. aureus* in SSTI (0.25 mg/L) and other infections (0.016 mg/L). Using these two breakpoints to screen collections of levofloxacin-resistant staphylococci BJI isolates, susceptibility rate drops from 89.1% to 3.9%, only, despite MICs significantly lower than other fluoroquinolones [43]. To date, very few clinical cases of PJI treated with delafloxacin-based therapies have been published [44]. Pending for specific breakpoints and more extensive data regarding bone penetration, antibiofilm activity, tolerance and risk of resistance selection during prolonged treatment, it can be considered as an alternative in combination therapy for PJI caused by pathogens resistant to other fluoroquinolones and without any other therapeutic options.

### *'Anti-biofilm' molecules*

The use of molecules able to penetrate and to remain active in staphylococcal biofilm is believed to be a determinant of PJI treatment outcome [45]. Rifampicin and daptomycin are the most potent molecules active against staphylococcal biofilms [3]. Of note, some *in vitro* data suggested that other rifamycins, and especially rifabutin, might even have a better activity against staphylococcal biofilms [46], and are currently under evaluation in a clinical trial

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(NCT04672525). Regarding daptomycin, its use in combination with fosfomycin is of growing interest in severe MRSA infections, and has been positively evaluated in a biofilm infection model and a retrospective cohort of PJI [47,48]. Afabicin, by targeting the staphylococcal FabI enzyme, is the first-in class anti-staphylococcal drug with antibiofilm activity *in vitro* [49]. A clinical trial (NCT03723551) evaluating its safety and efficacy in staphylococcal BJI is ongoing.

## Innovative approaches

### *Current surgical strategies combined with local antimicrobials*

Acute postoperative and acute late haematogenous infections with unloosened prosthesis are currently managed by DAIR, with complex determinants of outcome, for which prognostic scores—such as KLIC and CRIME-80 scores—have been established without considering antimicrobial resistance [50]. On the other hand, patients with chronic infections, prosthesis loosening and/or at high risk of DAIR failure usually benefit from one-stage or two-stage exchanges. As discussed previously, *S. aureus* itself, especially in case of MDR, might be associated with an increased risk of failure, especially if rifampicin cannot be used. Thus, the identification of MDR Gram-positive pathogen advocates for additional non-surgical intervention to improve the prognosis of DAIR-treated patients, and might support a two-stage exchange procedure if the pathogen is identified before surgery [51]. Some common antibiotics (particularly vancomycin and gentamicin) have shown antibiofilm effects *in vitro* and in animal models at high doses. Reaching such local concentrations with systemic treatment is hampered by the risk of toxicity but can be obtained through local administration [52]. In this setting, the SOLARIO clinical trial aims to assess a treatment strategy that may enable the reduction of systemic antibiotic use to less than 7 days for patients with orthopaedic infection for whom local antibiotics are used, in comparison with standard surgical treatment with prolonged antimicrobial. Partial results of the trial have been presented, showing no difference in infection recurrence between the two arms, suggesting a good efficacy of this local approach [53]. This strategy needs to be evaluated more specifically in patients with MDR Gram-positive PJI, as there are most of time fewer treatment options and these infections are frequently more difficult to treat.

In case of two-stage exchange, the use of articulated or static spacers with antibiotic-loaded polymethylmethacrylate cement is usually proposed [54]. For cost reasons, vancomycin is frequently added manually to gentamicin cement, but the required dose, local PK and mechanical impact of this practice are not well known, whereas commercial Polymethylmethacrylate (PMMA) cement delivering gentamicin plus clindamycin or vancomycin is available [55]. In case of gentamicin and vancomycin resistance, daptomycin or linezolid impregnated cements could be an alternative for the spacer, but only commercially available cements can be used for the prosthesis fixation during the second stage.

In patients with PJI without loosening but with joint effusion as exclusive clinical sign, a DAIR procedure is frequently proposed. In such patients, filling the joint cavity with local anti-infectious agents at the end of the procedure can locally complement the extensive debridement. To achieve significant concentration over time in the joint fluid, local antibiotics must be injected locally several times, or need a carrier that facilitates local delivery [56]. Some authors reported positive experiences of repeated intra-articular antibiotic infusion following DAIR, using the post-operative drainage tube or a dedicated catheter placed during surgery [57]. However, those procedures are theoretically associated with a risk for catheter crushing and superinfection. There is also a growing interest in biodegradable calcium sulphate beads loaded with antibiotics. However, the major indication of such devices is osteomyelitis, as they fill the dead space and promote bone modelling, but as they are biodegradable and do not contain hydroxyapatite, they could also be used as antibiotic carriers in the joint cavity after a DAIR [58].

### *Bacteriophages and lysins*

Phage therapy consists in the use of bacteriophages that are natural viruses specifically targeting a bacterial species. They could be purified and produced as a medication for clinical use [59]. Phages have synergistic activity with antibiotics and antibiofilm effect *in vitro* [60]. Some patients with complex *S. aureus* PJI have been treated recently as compassionate use [61,62]. Few pharmaceutical-grade phages targeting other Gram-positive species are available, and experience is rapidly growing, particularly in France [62]. Some clinical trials are ongoing, especially using staphylococcal phages during DAIR procedure (NCT05369104). Of note, phage therapy can also be administrated intravenously or locally under scopy or sonography after the surgery [62].

Lysins are phage-derived enzymes that could be used as a new medication. Some engineered enzymes are in development, and interestingly, their spectrum of action includes more largely CNS. Few patients were treated as compassionate use with such type of enzymes [63].

### *Pharmacokinetics (PK) monitoring and modelling to optimize drug exposure*

Therapeutic drug monitoring (TDM) consists in measuring antibiotic concentration to adjust drug dosage and ensure sufficient concentration at the infection site while limiting overexposure. TDM is relevant in PJI, especially in the case of high MICs, to take into account parameters altering antibiotic PKs, including: (a) the low antibiotic bone penetration, with median bone/serum concentration ratios ranging from 0.2 (β-lactams) to 0.5 (quinolones, linezolid) [4]; and (b) the high prevalence of older patients with comorbidities, including renal impairment and obesity, and who are co-administered other drugs. In addition, PKs modelling improves the interpretation of measured concentrations, permitting to derive quantities such as the area under the curve (AUC), and compute an individualized dosage. This approach is known as modelled-informed precision dosing [64]. However, this approach is limited by the absence of consideration of specific pathophysiological features of PJI, including antibiofilm activity (MBEC) that is not routinely accessible, even if it has not been correlated with clinical success to date [45].

The primary objective of TDM is to avoid underexposure and minimize the risk of failure. In the absence of specific PKs target for PJI, reaching therapeutic concentrations in plasma while considering the MIC of the pathogen and bone/serum concentration ratio might be appropriate. For example, a trough concentration $\geq 4-5 \times$ MIC in plasma may be adequate for β-lactams, considering their average bone penetration of 20%. PK targets defined as unbound concentration can also be used, when available. For example, as daptomycin PK target is free AUC over the MIC (*f*AUC/MIC), achieving the PK target in plasma should be associated with effective concentrations in bone tissue as bone/serum ratio and free fraction of the drug in blood are similar (about 10%).

The other objectives of TDM are: (a) to avoid overexposure and toxicity, especially in case of high MCIs, with drugs with narrow therapeutic margin and concentration-dependent adverse reactions; (b) to manage drug–drug interactions, especially for rifampicin which decreases concentrations of co-administered antibiotics such as clindamycin or linezolid [25,65]; (c) to design

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individualized dosage regimens with adjustment of the dose and dosing interval of parenteral suppressive therapy, such as Subcutaneous (SC) β-lactams for which modelled-informed precision dosing permitted to increase the dosing interval from daily to thrice or twice weekly, or for dalbavancin [66]; and (d) to help monitoring patients' adherence to treatment, even if trough concentrations only reflects the intake of the last doses, and may be low even when adherence is good for drugs with short half-life.

*Suppressive antimicrobial therapy*

Suppressive antimicrobial therapy (SAT), consisting in extended—and sometimes life-long—antibiotic treatment, is increasingly used in reference centres. The indication must be driven by the risk of failure related to: (a) the general outcome determinants, eventually guided by clinical scores [50]; (b) the presence of a difficult-to-treat pathogens; (c) a surgical strategy unlikely to achieve complete infectious source control (such as DAIR for a chronic infection), chosen because of the anaesthesiology risk or for functional reasons; and (d) the treatability and consequences of a potential relapse. The heterogeneity of the literature makes recommendations difficult, but reported rates of favourable outcomes range between 60% and 93% [67]. There are few data regarding the use of recently developed antimicrobials as SAT. The TediSAT cohort described 17 patients using tedizolid as SAT with a median duration of 6 months, with no severe adverse event [68]. The use of long-acting lipoglycopeptides guided by TDM is of particular interest in this indication [69].

## Conclusions

MDR Gram-positive PJIs are mainly represented by methicillin-resistant staphylococci, but resistance to rifampicin and/or fluoroquinolones should also be included to define difficult-to-treat pathogens. Antimicrobial resistance significantly impacts the prognosis, and future prognostic scores should include resistance in algorithms to guide medico-surgical strategies, including DAIR and SAT indications. In DAIR-treated patients, additional interventions are needed to improve the success rate, including TDM and SAT, that are the first options that could be easily implemented. Additional local antibiotics delivery and phage therapy also need to be evaluated in this setting. A two-stage exchange is often proposed for patients with documented MDR Gram-positive PJI, for which a combination of antibiotics in a spacer is largely used in addition to systemic antimicrobials. At the time of reimplantation, local delivery of antimicrobial with commercially available antibiotic-loaded cements or coating with a particular hydrogel need to be evaluated, especially for the prevention of subsequent infection. The low level of evidence and the complexity of these intertwined medical and surgical strategies prevent providing more specific guidance, and all cases must be discussed individually in dedicated multidisciplinary meetings in expert centres.

## Author contributions

F.V. and T.F. coordinated the review. All authors contributed to the literature review, writing and critical review for the manuscript, and agreed to the submission.

## Transparency declaration

*Potential conflict of interest*

T.F. was the principal investigator of the 'PhagoDAIR I' clinical study funded by Phaxiam, is a member of the IDMC that was set up for a clinical trial funded by Debiopharm, and if punctual expert for HERAEUS. All contracts were signed with EZUS University Lyon 1 and T.F. has not received any direct funding. S.G. participated in advisory boards (Menarini, Shionogi, Advanz Pharma) and symposia (MSD, Pfizer, Correvio), without personal fee. F.V. participated in the advisory board (Pfizer) and symposia (MSD, Pfizer). All contracts were signed with EZUS University Lyon 1 and F.V. has not received any direct funding.

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