Efficacy and safety of daptomycin for the treatment of infectious disease: a meta-analysis based on randomized controlled trials

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Objectives: A systematic review and meta-analysis based on randomized controlled trials (RCTs) of the efficacy and safety of daptomycin versus comparators.

Methods: Electronic databases (PubMed, Embase, Cochrane Central Register of Controlled Trials and clinical registered trials) were searched to identify RCTs that assessed the efficacy and safety of daptomycin versus therapy with comparators. Two reviewers independently applied selection criteria, performed a quality assessment and extracted the data. The $I^2$ statistic was calculated for heterogeneity, and a random-effects or fixed-effects model was used for estimates of risk ratio (RR). The primary outcome assessed was clinical treatment success among the intention-to-treat (ITT) population.

Results: Thirteen trials fulfilled the inclusion criteria. Daptomycin was as efficacious as comparator regimens among the ITT population (RR = 0.98, 95% CI 0.93 – 1.03) but had a lower efficacy among the clinically evaluable (CE) population (RR = 0.96, 95% CI 0.93 – 1.00). Subgroup analyses according to the quality of the trial, the type of antibiotic and the type of infection did not alter the outcomes. No significant difference was identified for all-cause mortality between the daptomycin and comparator groups (RR = 1.17, 95% CI 0.76 – 1.79) but daptomycin therapy did reduce the duration of treatment. Daptomycin caused a significantly lower incidence of renal impairment, nausea and headache but caused a reversible increase in creatine phosphokinase (CPK). Subgroup analysis indicated that daptomycin was significantly associated with a higher incidence of CPK elevation and fewer renal impairments among the population with a mean age $\leq$ 60 years and a dose of daptomycin $\geq$ 6 mg/kg/24 h.

Conclusions: Daptomycin showed efficacy similar to the comparator regimens among the ITT population but lower efficacy among the CE population. Fewer adverse effects in total, but more CPK elevation effects, were observed in patients treated with daptomycin.

Keywords: CPK elevation, renal impairment, lipopeptides

Introduction

With the emergence of an increasingly large number of multidrug-resistant pathogens, the treatment of infectious diseases can be difficult and challenging because of the need for a prolonged duration of administration, frequently combined with a lack of appropriate antimicrobial drugs, which also results in a high incidence of morbidity and mortality. Staphylococci, enterococci and streptococci are the most prevalent and relevant Gram-positive pathogens with a growing resistance pattern to various antibacterial drugs such as methicillin, vancomycin and occasionally linezolid. An increasing focus on hospital costs and pressure to free expensive hospital beds have motivated clinicians to seek alternative therapeutic approaches. Therefore, the development of new antibiotics with a high potency, stability against the mechanisms of resistance and favourable pharmacokinetic and pharmacodynamic characteristics has become an urgent priority.

Daptomycin is a novel cyclic lipopeptide that has in vitro bactericidal activity against most clinically relevant Gram-positive bacteria, including antibiotic-resistant pathogens such as Staphylococcus aureus, Enterococcus faecalis and Enterococcus faecium. Daptomycin seems to be a promising antimicrobial agent with once-daily use, proven safety, a low resistance profile, high levels of active drug in the blood, urine and joints, and good concentrations in the skin. It was approved by the US FDA for the treatment of patients with complicated skin and soft tissue infection (cSSTI) at a dose of 4 mg/kg once daily for 7 – 14 days in 2003 and for the treatment of patients with S. aureus bacteraemia and right-sided infective endocarditis at a dose of 6 mg/kg once daily for 14 – 42 days in 2006. Published studies, however, have shown results ranging from beneficial to no...
effect with respect to the treatment of cSSTIs, prosthetic joint infection (PJI), bacteraemia, community-acquired pneumonia (CAP) and complicated urinary tract infection (cUTI). A combination of the results of these trials can consolidate the efficacy and safety of daptomycin versus other antibiotics for infectious diseases.

**Methods**

**Inclusion criteria and outcomes**

We included randomized controlled trials (RCTs) that compared daptomycin with any other antibiotic treatment for the treatment of any infection among adults or children. The clinical success rate among the intention-to-treat (ITT) population was the primary efficacy outcome. The secondary outcomes included clinical success among the modified ITT (mITT) and clinically evaluable (CE) populations, microbiological success (defined as the eradication or presumed eradication of the pathogens present at baseline), adverse events (AEs) [headache, nausea, diarrhoea, constipation, renal impairment and creatine phosphokinase (CPK) elevation (CPK >500 U/L)], discontinuation of treatment related to AEs of the study drug, severe AEs (SAEs), drug-related SAEs and all-cause mortality.

**Search strategy and selection criteria**

To retrieve relevant randomized trials, we undertook a search of PubMed, the Cochrane Central Register of Controlled Trials and Embase with search terms that included ‘daptomycin’ and ‘randomized clinical trials’. Specific search terms for each database are available in the Supplementary data at JAC Online. No language restrictions were used. A methodological filter was used to select controlled trials. To identify relevant completed studies that were unpublished, we searched clinical trial registries (ISRCTN Register, Nederlands Trial Register, UMIN Clinical Trials Registry, Australian New Zealand Clinical Trials Registry and ClinicalTrials.gov) and ClinicalStudyResults.org up to 30 May 2014. We obtained the results of these studies by contacting the manufacturer via one of their expert opinion leaders. References were also identified from the bibliographies of studies retrieved from the literature search. The final search for inclusion in the meta-analysis was completed on 30 May 2014.

**Study selection and data extraction**

Two reviewers carried out the search independently, applied the inclusion criteria and extracted the data. The following variables were collected in a standardized form: authors, publication year, study design, age, sex, type

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**Figure 1.** Flow diagram displaying the number of publications identified in the literature search. *These studies (23, 24 and 34) were included in the meta-analysis. **Hospital stay and economic variables. †Published trials 9, 24, 30 and 33–35 identified through database searching were included in the meta-analysis.
<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Daptomycin dose (mg/kg/24 h)</th>
<th>Control regimen dose</th>
<th>Treatment duration (days)</th>
<th>Time of TOC visit after the EOT (days)</th>
<th>Number of patients (ITT population)</th>
<th>Allocation concealment</th>
<th>Allocation generation</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aikawa et al. (2013)</td>
<td>SSTI 4</td>
<td>vancomycin 1 g/12 h</td>
<td>7–14</td>
<td>88</td>
<td>69.5 (12.5)</td>
<td>ND</td>
<td>ND</td>
<td>open label</td>
</tr>
<tr>
<td>Arbeit et al. (2004)</td>
<td>cSSTI 4</td>
<td>vancomycin 1 g/12 h, PRP 4–12 g/24 h</td>
<td>7–14</td>
<td>534</td>
<td>51.7 (12.5)</td>
<td>601</td>
<td>ND</td>
<td>A</td>
</tr>
<tr>
<td>Byren et al. (2012)</td>
<td>PJI 6–8</td>
<td>vancomycin 1 g/12 h, teicoplanin 6 mg/kg/24 h, SSP 2 g/4 h</td>
<td>up to 42</td>
<td>49</td>
<td>61.7 (13.2)</td>
<td>39</td>
<td>ND</td>
<td>A</td>
</tr>
<tr>
<td>Evers et al. (2013)</td>
<td>SSTI 4</td>
<td>teicoplanin 10 mg/kg/24 h</td>
<td>10–14</td>
<td>20</td>
<td>67 (—)</td>
<td>18</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Fowler et al. (2006)</td>
<td>bacteraemia with or without endocarditis 6</td>
<td>low gentamicin plus vancomycin 1 g/12 h, ATP 2 g/4 h</td>
<td>10–42</td>
<td>124</td>
<td>52.7 (11.0)</td>
<td>141</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Katz et al. (2008)</td>
<td>cSSTI 10</td>
<td>vancomycin 1 g/12 h, SSP 2 g/4 h</td>
<td>4–14</td>
<td>48</td>
<td>42.2 (10.6)</td>
<td>66</td>
<td>ND</td>
<td>A</td>
</tr>
<tr>
<td>Konychev et al. (2013)</td>
<td>cSSTI 4 or 6</td>
<td>vancomycin 1 g/12 h, SSP 2 g/4 or 6 h</td>
<td>5–28</td>
<td>81</td>
<td>74.8 (5.74)</td>
<td>47</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Naber et al. (2004)</td>
<td>cUTI 4</td>
<td>ciprofloxacin 400 mg/12 h</td>
<td>5–14</td>
<td>34</td>
<td>57.9 (14.4)</td>
<td>30</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Pertel et al. (2008)</td>
<td>CAP 4</td>
<td>ceftriaxone 2 g/24 h</td>
<td>5–14</td>
<td>413</td>
<td>55.2 (12.7)</td>
<td>488</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Pertel et al. (2009)</td>
<td>cSSTI 4</td>
<td>vancomycin 1 g/12 h</td>
<td>7–14</td>
<td>50</td>
<td>51.4 (10.2)</td>
<td>37</td>
<td>ND</td>
<td>A</td>
</tr>
<tr>
<td>Quist et al. (2012)</td>
<td>cSSTI 4</td>
<td>vancomycin 1 g/12 h, teicoplanin 400 mg/12 h</td>
<td>4–10</td>
<td>97</td>
<td>—</td>
<td>—</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>NCT01287832 (2013)</td>
<td>bacteraemia 8</td>
<td>vancomycin 15–20 mg/mL</td>
<td>—</td>
<td>6</td>
<td>64.7 (17.5)</td>
<td>9</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>NCT00695903 (2011)</td>
<td>bacteraemia 10</td>
<td>vancomycin 15 mg/kg</td>
<td>2–43</td>
<td>19</td>
<td>64.7 (17.5)</td>
<td>26</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

EOT, end of test; ND, no description; PRP, penicillinase-resistant penicillin; SSP, semi-synthetic penicillin; ATP, antistaphylococcal penicillin.
of infection, antimicrobial agents and their doses, treatment duration, time of test of cure (TOC) visit, number of patients (ITT population if available) and outcomes (clinical, microbiological and AE). Efficacy analyses were conducted on four patient populations defined as follows: ITT, all patients receiving at least one dose of the study medication; mITT, those ITT patients with a Gram-positive pathogen infection; CE, those ITT patients who met all the protocol criteria for a valid clinical outcome at each of the assessment visits; and microbiologically evaluable (ME), those CE patients who had an infecting Gram-positive organism isolated at baseline.

The quality of every randomized trial was judged using an individual component approach assessing the generation of the allocation sequence, allocation concealment, blinding, ITT analysis and number of patients excluded from the outcome assessments.\footnote{9} Allocation concealment and generation were graded as adequate (A), unclear (B) or inadequate (C) according to the criteria in the Cochrane handbook. To assess the effect of the study quality on outcomes, sensitivity analyses were performed on four patient populations defined as follows: ITT, all patients receiving at least one dose of the study medication; mITT, those ITT patients with a Gram-positive pathogen infection; CE, those ITT patients who met all the protocol criteria for a valid clinical outcome at each of the assessment visits; and microbiologically evaluable (ME), those CE patients who had an infecting Gram-positive organism isolated at baseline.

The search strategy is shown in Figure 1. A total of 643 potential articles were identified; 36 studies met the inclusion criteria according to their titles and abstracts, 23 of which were excluded.\footnote{11–27} Thirteen RCTs were included in our meta-analysis: 11 published trials\footnote{6–8,28–35} and two unpublished trials (NCT00695903 and NCT01287832).

Table 1 summarizes the characteristics of the 13 included RCTs. The mean age of the participants was 42.2–74.8 years and most were men (about 73%) and white (about 88%), except for those in one study that included only Asians. Eight studies gave pooled risk ratios (RRs) and 95% CIs were calculated using a Mantel–Haenszel fixed-effects or random-effects model according to heterogeneity analysis. Subgroup analysis was performed according to the type of infection, types of comparator, dose of daptomycin (<6 mg/kg/24 h and ≥6 mg/kg/24 h) and patients’ mean age (≤60 years and >60 years). Statistical significance was defined as the 95% CI excluding zero. Publication bias was assessed by the visual inspection of a funnel plot.

Results

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information about clinical success among the ITT population, while clinical success among the mITT and CE populations was compared in nine and six studies, respectively. Ten studies compared microbiological success between daptomycin and other antimicrobial agents among the TOC visit population, and only five trials described microbiological success among the ME population.

In the ITT and mITT populations, clinical efficacy in the daptomycin group was statistically equivalent to standard therapy (RR = 0.98, 95% CI 0.93–1.03; RR = 1.00, 95% CI 0.95–1.06, respectively) (Figures 2 and 3). Sensitivity analyses (Table 2) showed no significant difference for treatment with vancomycin versus other comparators (vancomycin treatment RR 1.03, 95% CI 0.91–1.17), or adequate versus unclear allocation concealment, among studies reporting clinical success by ITT studies.

A total of 1899 participants were included in the CE samples, and the overall clinical treatment success rate in the comparator group was significantly higher than in the daptomycin group (RR = 0.96, 95% CI 0.93–1.00, $I^2 = 47\%$, $P = 0.09$) (Figure 3). Subgroup analysis indicated that daptomycin treatment in the group with a mean age $\leq 60$ years was significantly less efficient than comparator treatment (RR = 0.95, 95% CI 0.92–0.99). However, these conclusions could not be safely drawn from the data in the individual trials. It is evident that the higher clinical success observed among the CE population in the comparator group should be attributed to a trial that investigated the comparative efficacy for the treatment of patients with CAP. Data from the study revealed that daptomycin was less efficacious than ceftriaxone for CAP therapy, especially when excluding patients who had received prior effective antibacterial therapy.

Table 2. Sensitivity analysis (ITT analysis)

<table>
<thead>
<tr>
<th>Study/patient characteristics</th>
<th>No. of studies</th>
<th>Population (n)</th>
<th>Statistical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of comparator antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin</td>
<td>2</td>
<td>112</td>
<td>RR 1.03, 95% CI 0.91–1.17</td>
</tr>
<tr>
<td>other</td>
<td>6</td>
<td>2428</td>
<td>RR 0.97, 95% CI 0.93–1.03</td>
</tr>
<tr>
<td>Randomization generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adequate</td>
<td>6</td>
<td>1695</td>
<td>RR 1.01, 95% CI 0.95–1.08</td>
</tr>
<tr>
<td>unclear</td>
<td>2</td>
<td>845</td>
<td>RR 0.92, 95% CI 0.85–0.99</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adequate</td>
<td>2</td>
<td>366</td>
<td>RR 1.11, 95% CI 0.91–1.34</td>
</tr>
<tr>
<td>unclear</td>
<td>6</td>
<td>2174</td>
<td>RR 0.96, 95% CI 0.92–1.01</td>
</tr>
<tr>
<td>Blinding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>double-blind</td>
<td>2</td>
<td>845</td>
<td>RR 0.92, 95% CI 0.85–0.99</td>
</tr>
<tr>
<td>single-blind</td>
<td>4</td>
<td>1329</td>
<td>RR 1.00, 95% CI 0.91–1.34</td>
</tr>
<tr>
<td>open</td>
<td>2</td>
<td>366</td>
<td>RR 1.11, 95% CI 0.91–1.34</td>
</tr>
</tbody>
</table>

RR $> 1$ is in favour of daptomycin treatment.

The removal of this trial from the analysis led to a result with no difference in clinical success between daptomycin and comparators (RR = 0.99, 95% CI 0.95–1.04 and RR = 0.99, 95% CI 0.94–1.20, respectively, in the subgroup with a mean age $\leq 60$ years).
Microbiological success in the TOC population was evaluated in 10 trials with a total of 1780 patients, and daptomycin therapy was similar to comparator therapy (RR = 0.99, 95% CI 0.93–1.04) (Figure 3). Data from 1220 ME patients indicated that the microbiological success of comparator therapy was higher than that of daptomycin, although it was not statistically significant (RR = 0.96, 95% CI 0.92–1.01). Subgroup analysis indicated that daptomycin was less efficient than comparators in the group with a mean age ≤60 years (RR = 0.95, 95% CI 0.91–1.00).

Regarding the eradication of pathogens, no difference was found between the daptomycin and comparator groups (Figure 3). Treatment-related AEs attributed to daptomycin were similar to those observed with comparator agents (RR = 0.88, 95% CI 0.74–1.04). SAEs were more common in the comparator group.

We could not compare the duration of therapy between daptomycin and its comparators statistically, but the duration of therapy was shorter in the daptomycin group (75% of patients required

### Figure 4.
The safety of daptomycin versus comparator antibiotics. The vertical line indicates no difference between the two treatment groups. Pooled RRs were calculated from random-effects models using the Mantel–Haenszel method.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Daptomycin</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Aikawa et al. (2013)</td>
<td>1</td>
<td>88</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Arbeit et al. (2004)</td>
<td>8</td>
<td>534</td>
<td>8</td>
<td>558</td>
</tr>
<tr>
<td>Byren et al. (2012)</td>
<td>0</td>
<td>49</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Flower et al. (2006)</td>
<td>13</td>
<td>120</td>
<td>13</td>
<td>115</td>
</tr>
<tr>
<td>Konychev et al. (2013)</td>
<td>0</td>
<td>80</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Pertsel et al. (2008)</td>
<td>21</td>
<td>457</td>
<td>12</td>
<td>462</td>
</tr>
<tr>
<td>Pertsel et al. (2009)</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1378</td>
<td>1273</td>
<td>100.0%</td>
<td>1.17 (0.76–1.79)</td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 5.16$, df = 3 ($P = 0.16$); $I^2 = 42%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.72$ ($P = 0.47$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 5.
4–10 days of therapy versus 62% in the comparator group;32 63% required only 4–7 days of therapy versus 33% in the comparator group (P < 0.001), with a median duration of 4 days in daptomycin group versus 8 days in the comparator group.7,28

Discussion

This systematic review and meta-analysis compared the efficacy and safety of daptomycin with those of comparator therapy. Treatment groups were well balanced with respect to demographics, comorbidity and type of infection.

Daptomycin was as efficacious as standard therapy for clinically successful treatment among the ITT population. The eradication of pathogens (methicillin-susceptible S. aureus, methicillin-resistant S. aureus, Streptococcus pyogenes, E. faecalis and Streptococcus pneumoniae) was similar between daptomycin and comparator therapy. Our concern is that daptomycin-resistant strains have been reported. The prevalence of resistance to daptomycin de novo among S. aureus strains without prior exposure is extremely low; a large survey study found that only 0.4% of the S. aureus clinical isolates had an MIC of 2 mg/L.36 However, 6% of patients receiving this drug had isolates that developed an increase in daptomycin MICs to ≥2 mg/L in one RCT.8 It has been speculated that non-susceptibility to daptomycin was associated with a high inoculum and/or subtherapeutic dosing of the drug. Hence, daptomycin should be administered at an appropriate dose and for an appropriate duration.

In this study, vancomycin was used in the comparator group in most of the trials.7,28,29,31–34 Our meta-analysis elucidated that daptomycin was statistically equivalent to vancomycin for clinical success among the ITT population. It has been proven that daptomycin is safe with a long duration of treatment or a high dose,7,37,38 while vancomycin is associated with nephrotoxicity and ototoxicity with long-term use, regardless of its serum concentration.39 As noted, the longer duration of treatment in the comparator arm may have provided opportunities for additional medical interventions (e.g. surgery) that may influence clinical outcomes. Daptomycin significantly reduced the treatment duration in our study. A subsequent study also found that daptomycin resulted in a faster clinical improvement, a shorter duration of intravenous antibiotic therapy, a shorter antibiotic-associated length of hospital stay and decreased total hospital costs compared with matched controls treated with vancomycin.40 Accordingly, daptomycin is a convincing alternative antibiotic to vancomycin.

Our study indicated that the overall incidence of treatment-related AEs was similar between daptomycin and comparator therapy. This result was consistent with the RCTs included in our meta-analysis and in previous published studies.7,37,44 Renal impairment, although relatively rare, is one of most feared AEs of vancomycin and is associated with an increased risk of poor outcome, while daptomycin appears to be effective and well tolerated in patients with S. aureus bacteraemia and mild to moderate renal insufficiency.52 It has been reported that moderate renal impairment is a characteristic of an elderly population, and no significant difference was identified between daptomycin and the comparators in the >60 years old group in our study. Daptomycin administered at the same dose as for younger patients was well tolerated with no new or unexpected safety findings compared with the pivotal Phase III trials for bacteraemia and cSSTI.7 Our subgroup analysis was consistent with this conclusion that the incidence of renal impairment in the comparator group was greater than that in the daptomycin group with a mean age ≤60 years.

Our study confirmed that daptomycin was associated with CPK elevation, especially with CPK >500 U/L and a daptomycin dose ≥6 mg/kg/24 h. Clinical symptoms of myalgia and/or muscle weakness and significantly elevated CPK levels resolved rapidly and completely after the discontinuation of daptomycin therapy.43 All-cause mortality was higher with daptomycin than with the comparator regimens but the difference was not significant. Numerous caveats exist with regard to these data. The patient populations investigated were heterogeneous and difficult to compare, both within and across studies. In another two non-RCTs, daptomycin was found to be associated with decreased 30 day44 or 60 day45 mortality and fewer instances of persistent bacteraemia.44 Hence, long-term RCTs are needed to confirm whether patients can benefit from daptomycin with lower mortality.

Our study had several limitations. First, missing data from some trials led to the meta-analysis of fewer than the 13 originally identified studies for some outcomes of interest. When we contacted the researchers directly for missing data they did not provide us with them. Second, the majority of trials included were for the treatment of cSSTI; there were only two trials for bacteremia and one trial each for PJL, CAP and cUTI. Finally, all trials included were funded by the pharmaceutical company producing the branded form of daptomycin, which might have introduced bias into our results.

Conclusions

Daptomycin may be a promising alternative antimicrobial agent for various infectious diseases, with a short treatment of duration, despite the reversible CPK elevation. Large studies are needed to corroborate these preliminary results.

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Transparency declarations

All authors: no conflicts of interest to declare.

Complementary data were requested from the pharmaceutical companies that sponsored the studies included. None of the companies provided additional data.

Supplementary data

Specific search terms for each database are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).
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