The Use of Mupirocin in the Preoperative Eradication of Staphylococcus Aureus

Matthias Trautmann, Jens Stecher, Klaus Luz, Wolfgang Hemmer, Thomas Hupp, Paul Alfred Grützner

SUMMARY
Introduction: Mupirocin is a natural antibiotic derived from Pseudomonas fluorescens, and is available as an ointment for external use. The drug is used mainly for nasal decolonization in patients colonized with Staphylococcus aureus. Methods: In a selective literature review, 13 comparative prospective studies were analyzed. Results: 5 randomized trials showed no influence of mupirocin on the overall rate of post-operative wound infections or S. aureus infections. 5 out of 8 „before and after“ studies showed a significant reduction of all wound infections, and 4 out of 8 a significant reduction of infections caused by S. aureus. 3 open interventional „before and after“ studies examining the influence of mupirocin on wound infections due to methicillin-resistant S.-aureus (MRSA) demonstrated a significant reduction. Discussion: Based on the literature data, routine preoperative prophylaxis with mupirocin before elective surgery cannot be recommended. This holds also true for special indications such as cardiac surgery. Independently from literature data, preoperative decolonization and decontamination of MRSA-positive patients is recommended.

Key words: Staphylococcus aureus, methicillin-resistant S. aureus (MRSA), surgical site infection, prophylaxis

If preventive hygienic measures are strictly adhered to the rate of postoperative surgical infections after aseptic elective procedures is usually below 5% (e5, e14, e18, e22). But even low rates of infection should prompt quality improvement measures because any infection entails additional risks for the patients and incurs costs for the healthcare system that could be avoided.

Many studies since the 1950s have shown that nasal colonization with Staphylococcus aureus in surgical patients increases the risk of postoperative infection of the surgical site significantly (1, 3, 9, 11, e21, e24; overviews in e2, e12, 20, e23). This effect is quantifiable: colonization with a large number of bacteria was associated with double the infection rate compared with low grade colonization (9). For this reason, several working groups have attempted to lower the rate of postoperative infections by using preoperative nasal decolonization treatment with mupirocin. The following literature review evaluates the results of comparative prospective studies.

Materials and methods
The authors searched Medline using the search terms “Staphylococcus aureus AND surgical site infection AND mupirocin”. Further studies were identified from the bibliographies of the selected studies and through personal suggestions. The authors included studies that meet the following inclusion criteria:

- Prospective study
- Surgical patients
- Comparison of a mupirocin group with a historical or parallel control group
- Statistical evaluation.

The end points were the rate of all postoperative infections affecting the surgical site, the rate of infections caused by S. aureus, and the rate of infections caused by methicillin resistant S. aureus (MRSA) strains of the surgical site.
Results

Literature search

The authors identified a total of 32 studies through Medline and 6 studies thanks to suggestions from others. 13 studies met the inclusion criteria (table 1). Because of the notable heterogeneity of the studies, no formal meta-analysis was possible. The results are therefore presented in a purely descriptive fashion.

Study design, mupirocin regimen, and accompanying preoperative measures

5 studies were randomized studies and 8 studies were open interventional (“before and after” studies). In 4 studies, mupirocin was administered to all patients in the treatment group without investigating whether they were nasal S. aureus (4, 22, 23, 24). One study investigated only a part of the population for nasal colonization with S. aureus but the treatment was administered regardless of the finding (3). In 7 studies, a nasal swab was taken at the start of treatment and the treatment was started immediately afterwards (5, 6, 10, 12, 18, 19, 25). If a swab turned out a negative result treatment was stopped, if the result was positive, treatment was continued. Altogether the duration of treatment with mupirocin ranged from 3 doses (6) to 7 days (13, 18). Control swabs after the end of treatment were taken in 7 studies; they showed eradication rates between 74% (3) and 95% (13). The timing of the control swab ranged from a few days after treatment (5, 10, 12, 13) to several months (3) after treatment; pertinent data were not provided in a couple of publications (6, 19). A clear association between the duration of therapy and frequency of administration on the one hand and successful eradication on the other hand was not shown.

In only one study, prophylaxis was not started immediately after the swab but only after the results from the culture had been obtained. This made it possible to include only carriers of S. aureus in the study and randomize them to either mupirocin or placebo. Prophylactic treatment was stopped 3 days before the operation. Immediately before the procedure, another nose swab was taken to document successful eradication. The eradication rate in this study was about 95% (13).

The accompanying preoperative measures in the studies were relatively similar. Patients mostly received prophylactic antibiotics with a second generation cephalosporin and a preoperative whole body wash or shower; in some cases antiseptic preparations were used.

For the surveillance of postoperative infections of the surgical site, 8 studies used the definitions of the US Center for Disease Control and Prevention (CDC) (4, 5, 6, 10, 12, 22, 23, 25), 2 studies used modified CDC definitions (3, 19), and 3 studies other published (13, 18) or their own internal definitions (24).

Influence of mupirocin prophylaxis on the rate of all postoperative infections of the surgical site

The target criterion of a reduction of all postoperative infections of the surgical site was evaluated in all 13 studies (table 1). In the randomized studies shown with blue underlay in the table no influence of mupirocin treatment on the rate of postoperative infections of the surgical site was seen. By contrast, 5 of 8 before and after studies showed a significant drop in infections (relative risk 0.33 to 0.48) in the subsequent mupirocin group (table 1).

Influence on the rate of surgical site infections due to S. aureus

12 of 13 studies evaluated this target criterion (table 2). None of the randomized studies (again in blue tint) showed a significantly reduced rate of infection in the mupirocin group. 4 of 7 before and after studies describe a significant reduction, with a relative risk of 0.35 to 0.06 (table 2).

Influence on the rate of surgical site infections with MRSA

Infections of the surgical site with MRSA strains were considered separately in 1 study from Japan (25), 1 study from the British Midlands (24), and 1 study from Turkey (4). All 3 studies were before and after studies. Neither the Japanese study nor the Turkish study contained any data on the prevalence of MRSA in the hospital or the patients’ MRSA carrier rate. The English study reported a high MRSA prevalence of 38%. All 3 studies showed a significant reduction on infections of the surgical site with MRSA (table 3).
<table>
<thead>
<tr>
<th>Study No</th>
<th>Authors (citation)</th>
<th>Study type</th>
<th>Type of surgical procedure</th>
<th>Treatment</th>
<th>Postoperative infection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kluytmans et al., 1996 (12)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Cardiopulmonary surgeries</td>
<td>Historical controls: no treatment, n = 928; Treatment group: intranasal mupirocin, n = 868</td>
<td>2.8% 2.0%&lt;sup&gt;1*&lt;/sup&gt; 0.38 (p &lt; 0.001)&lt;sup&gt;1*&lt;/sup&gt; 0.28 (0.0023)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Gernaat van der Sluijs et al., 1998 (6)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Orthopedic surgery</td>
<td>Historical controls: no treatment, n = 1260; Treatment group: intranasal mupirocin, n = 1044</td>
<td>1.3% 2.7% 0.48 (p = 0.02)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Yano et al., 2000 (25)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Gastrointestinal surgery</td>
<td>Historical controls: no treatment, n = 128; Treatment group: intranasal mupirocin, n = 141</td>
<td>11.3% 18.0% 0.63 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Cimochowski et al., 2001 (3)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Cardiac surgery</td>
<td>Historical controls: no treatment, n = 992; Treatment group: intranasal mupirocin, n = 854</td>
<td>0.9% 2.7% 0.33 (p = 0.005)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Perel et al., 2002 (19)</td>
<td>Randomized, placebo-controlled, double-blinded study</td>
<td>Elective cardiothoracic general, tumor, gynecological, or neurological surgery</td>
<td>Group 1: placebo, n = 1931; Group 2: intranasal mupirocin, n = 1933</td>
<td>7.9% 8.5% 0.93 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Kalmeijer et al., 2002 (10)</td>
<td>Randomized, placebo-controlled, double-blinded study</td>
<td>Elective orthopedic surgery, including implantation</td>
<td>Group 1: placebo, n = 299; Group 2: intranasal mupirocin, n = 315</td>
<td>3.8% 4.7% 0.81 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Usry G et al., 2002 (23)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Cardiopulmonary surgery</td>
<td>Historical controls: no treatment, n = 2595; Treatment group: intranasal mupirocin, n = 1205</td>
<td>1.24% 2.62% 0.47 (p = 0.007)&lt;sup&gt;1*&lt;/sup&gt; 0.75% 1.66% 0.45 (p = 0.025)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Suzuki et al., 2003 (22)</td>
<td>Randomized, controlled study</td>
<td>Gastrointestinal surgery</td>
<td>Group 1: no placebo, n = 202; Group 2: intranasal mupirocin, n = 193</td>
<td>8.8% 6.9% 1.27 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Wilcox et al., 2003 (24)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Elective orthopedic surgery, including implantation</td>
<td>Historical controls: no treatment, n = 420; Treatment group: intranasal mupirocin, n = 1758</td>
<td>no data no data ns&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Garcia et al., 2003 (5)</td>
<td>Randomized, controlled, prospective study</td>
<td>Cardiac surgery</td>
<td>Group 1: no treatment, n = 95; Group 2: intranasal mupirocin, n = 96</td>
<td>10.4% 11.6% 0.89 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Coskun &amp; Aytac, 2004 (4)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Orthopedic surgery</td>
<td>Historical controls: no treatment, n = 920; Treatment group: intranasal mupirocin, n = 2329</td>
<td>1.4% 3.0% 0.47 (p &lt; 0.001)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Nicholson &amp; Huesman, 2006 (18)</td>
<td>Open interventional study, comparison with historical control group</td>
<td>Cardiac surgery</td>
<td>Historical controls: no treatment, n = 954; Treatment group: intranasal mupirocin, n = 1077</td>
<td>1.1% 1.89% 0.58 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>Konvalinka et al., 2006 (19)</td>
<td>Prospective, randomized, double-blinded, placebo-controlled study</td>
<td>Cardiac surgery</td>
<td>Control group: placebo, n = 127; Treatment group: intranasal mupirocin, n = 130</td>
<td>5.4% 4.7% 1.15 (ns)&lt;sup&gt;1*&lt;/sup&gt; 0.8% 0.3% 1.0 (ns)&lt;sup&gt;1*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ns, non-significant; 1*top row, left column: infection rate in all patients in the intervention group (n = 868, of which 116 were accidentally not treated). Top row, right column: historical controls not treated with mupirocin. Bottom row, left column: infection rate in all patients effectively treated with mupirocin (n = 752). Bottom row, right column: infection rate in patients accidentally not treated with mupirocin (n = 116); 2*top row: all postoperative sternotomy infections, bottom row: only deep sternotomy infections; 3*study contains only the statement that the number of postoperative infections remained the same.
Discussion

*S. aureus* is still the leader among causative agents of postoperative infections of the surgical site. In the context of surgery to primarily sterile regions of the body, 30 to 50% of all postoperative infections are caused by *S. aureus* (15, e5, e14). The strain has a dominant role especially in orthopedic surgery as well as in heart surgery or vascular surgery. In the context of gastrointestinal surgery, urological procedures, or gynecological surgery, the rate drops to 10 to 15% (e6, e10). In these procedures, enterobacteria, enterococci, obligatory anaerobes, and, to a very small proportion, non-fermenters predominate, which are part of patients’ intestinal or vaginal/urethral flora. Studies into prophylaxis with mupirocin were therefore mostly conducted in surgical environments with an emphasis on cardiovascular or orthopedic procedures, because these disciplines offer the greatest potential for prevention.

The studies found and analyzed by the authors were methodologically heterogeneous in terms of inclusion criteria, frequency of administration, and duration of use of mupirocin, as well as eradication control after the end of treatment. It was therefore not possible to conduct a formal meta-analysis. Mupirocin or placebo prophylaxis focused on the relevant target group of *S. aureus* carriers in merely 1 study (13). 5 studies had a prospective randomized design, 2 of these used placebo controls. None of these studies showed an effect of mupirocin, not even below the significance level. The fact that 5 of 8 open interventional (before and after) studies showed a significant reduction in infections subsequent to mupirocin use has to be interpreted with caution. Such studies entail the risk

### TABLE 2

Nasal carrier rate and influence of nasal mupirocin treatment on the rate of *Staphylococcus aureus* related surgical site infections

<table>
<thead>
<tr>
<th>Study No</th>
<th>Authors (citation)</th>
<th>Mupirocin group</th>
<th>Control group</th>
<th>Postoperative infection rate with <em>S. aureus</em></th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kluytmans et al., 1996 (12)</td>
<td>16.0%</td>
<td>15.1%</td>
<td>1.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>Gernaat van der Sluis et al., 1998 (6)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.67%</td>
<td>1.11%</td>
</tr>
<tr>
<td>3</td>
<td>Yano et al., 2000 (25)</td>
<td>12.1%</td>
<td>15.6%</td>
<td>0.71%</td>
<td>11.7%</td>
</tr>
<tr>
<td>4</td>
<td>Cimochowski et al., 2001 (3)</td>
<td>n.a.</td>
<td>19%</td>
<td>0.47%</td>
<td>1.11%</td>
</tr>
<tr>
<td>5</td>
<td>Perl et al., 2002 (19)</td>
<td>22.9%</td>
<td>23.1%</td>
<td>2.3%</td>
<td>3.7%</td>
</tr>
<tr>
<td>6</td>
<td>Kalmieijer et al., 2002 (10)</td>
<td>30.3%</td>
<td>28.8%</td>
<td>1.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>8</td>
<td>Suzuki et al., 2003 (22)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>9</td>
<td>Wilcox et al., 2003 (24)</td>
<td>MSSA: 27%</td>
<td>MSSA: 42%;</td>
<td>MSSA: 16%;</td>
<td>MSSA: 1.96%</td>
</tr>
<tr>
<td>10</td>
<td>Garcia et al., 2003 (5)</td>
<td>32.3%</td>
<td>35.8%</td>
<td>1%</td>
<td>6.3%</td>
</tr>
<tr>
<td>11</td>
<td>Coskun &amp; Aytaç, 2004 (4)</td>
<td>Not examined</td>
<td>0.4%</td>
<td>1.5%</td>
<td>0.26 (p &lt; 0.001)</td>
</tr>
<tr>
<td>12</td>
<td>Nicholson &amp; Huesman, 2006 (18)</td>
<td>MSSA: 17.8%</td>
<td>0.37%</td>
<td>1.68%</td>
<td>0.22 (p &lt; 0.0087)</td>
</tr>
<tr>
<td>13</td>
<td>Konvalinka et al., 2006 (13)</td>
<td>MSSA: 100%**4</td>
<td>3.1%</td>
<td>3.2%</td>
<td>0.97 (ns)</td>
</tr>
</tbody>
</table>

n.a.: not available; ns: non-significant;

**1 Top row, left column: *S. aureus* infection rate in all patients in the intervention group (n = 868, of which 116 were accidentally not treated). Bottom row, left column: *S. aureus* infection rate in all patients effectively treated with mupirocin (n = 752).

**2 Top row: all patients; bottom row: only confirmed *S. aureus* carriers;

**3 2 consecutive treatment periods with mupirocin of 6 months’ duration each were investigated in this study. 2 figures are therefore reported for the mupirocin group.

**4 Only patients with confirmed nasal colonization with *S. aureus* were included.
that other influential factors changed in an uncontrolled fashion during the intervention period. The continuous capture and documentation of surgical wound infections ("surveillance") is known to be a per se factor that is accompanied by a reduction in postoperative infection rates (e4, e18). Further, architectural or staff related changes, changes of surgical technique, or more stringent adherence to hygiene guidelines can reduce the rate of infection. In one study, continual surveillance and an increased operating room presence of the hospital hygiene team in a cardiovascular hospital resulted in a drop in the rate of deep sternal wound infections from 10% to 2.8% (p = 0.007) (2). The statistical phenomenon of "regression to the mean" also has to be taken into consideration (e7). This means that after a period of raised measurements, a drop in subsequent measurements is to be expected on the basis of statistical probability alone. Such a phenomenon should not be underestimated in studies about hospital acquired infections because hygiene interventions are typically always implemented when raised infection rates produce a pressure to act (e7).

Owing to these limitations, several authors of before and after studies have emphasized in the discussion of their data that their results are merely indicative and should be tested in randomized studies (3, 12), or that the conclusion of the study has its limitations (18). Altogether, not enough studies have been conducted to date that favor the routine preoperative use of mupirocin in surgical patients. The fact that the authors of earlier reviews gave a more positive rating to mupirocin – at least for certain disciplines such as cardiac surgery – can be explained with the results of before and after studies were evaluated without the limitations mentioned earlier (8, 14, 20, 21). Further, the study by Konvalinka et al. (13) was too recent to be included in these reviews.

The question why no effect of mupirocin has been identified in randomized studies can currently not be answered unequivocally. It is possible that the effect could not be shown because of the methodological limitations of most studies.

The proportion of the study populations that would potentially benefit from mupirocin was small even in the large studies. 4 studies included all patients, regardless of their nasal carrier status. In 7 studies, nasal carrier status was ascertained subsequently; only 20 to 30% of patients in these studies were carriers of S. aureus (table 2). Since the rate of postoperative infections was usually in single-figure percentages, only some of the infections were caused by S. aureus, and endogenous genesis is to be expected in only some of those infections (1, 16, e1, e9, e17), the target variable affected too few patients.

Alternatively it is possible that the negative study results are real and can be explained with the absence of an effect of mupirocin in this particular field of indication. Nasal colonization with S. aureus in surgical patients would thus only be a marker of an increased risk of infection but would not have a role in the chain of cause and effect in the development of infection. 3 main conceivable endogenous infectious pathways for S. aureus in surgical patients are postulated:

- Nasal colonization with S. aureus is usually accompanied by colonization of the pharynx. Intubation trauma might result in lesions to the oropharyngeal mucosa and thus an ingress of S. aureus into the blood circulation. The colonization of the surgical wound would therefore be the result of hematogenic spread of the causative strain. An

<table>
<thead>
<tr>
<th>Study No</th>
<th>Authors (citation)</th>
<th>Carrier rate of nasal MRSA</th>
<th>Postoperative infection rate with MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mupirocin group</td>
<td>Control group</td>
</tr>
<tr>
<td>3</td>
<td>Yano et al., 2000 (25)</td>
<td>No data</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>Wilcox et al., 2003 (24)</td>
<td>General prevalence 38%</td>
<td>0.33%; 0.4%</td>
</tr>
<tr>
<td>11</td>
<td>Coskun &amp; Aytac, 2004 (4)</td>
<td>Not investigated</td>
<td>0.13%</td>
</tr>
</tbody>
</table>

*1 2 consecutive treatment periods with mupirocin of 6 months' duration each were investigated in this study.
2 figures are therefore reported for the mupirocin group.

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increased risk of spread of S. aureus into the bloodstream in nasal carriers has been described several times, but not specially in association with surgical procedures (e16, e20).

- S. aureus might spread into the surrounding air and colonize the wound via the airborne route.
- Nasal carriers of S. aureus often have cutaneous colonization with the same strain. In cardiac surgical patients this has been shown especially for the sternal area (e9). Parts of the cutaneous flora that reside in deeper locations might escape the effect of skin disinfectants and penetrate into the wound from the wound margin.

Although formulated as a hypothesis several times (e11, 20) neither of these methods has been proved in any way. The absence of a significant effect of mupirocin in the described randomized studies should prompt basic research in order to primarily ascertain the endogenous transmission pathway of the strain.

The 3 comparative studies that showed a significant reduction of MRSA infections are without exception before and after studies and thus do not provide a basis for evidence based recommendations (4, 24, 25). Further, these studies were conducted in countries with a substantially higher prevalence of MRSA in the general population than Germany, so that the results do not translate.

Several aspects, however, prompt the authors to assess positively the use of mupirocin in MRSA patients in the preoperative phase in the sense of an expert recommendation. It is known on the one hand that nasal colonization with MRSA is associated with a notably higher risk of subsequent invasive infection than is the case for methicillin susceptible strains (MSSA). Pujol et al., for example, showed in the context of an infection outbreak on an intensive care ward that the risk of S. aureus bacteremia was 38% for MRSA carriers compared to only 9.5% for MSSA carriers and 1.7% for non-carriers (e16). Davis et al. reported that patients who were found to be colonized with MRSA at admission, or acquired infection during their hospital stay, developed invasive MRSA infection in 19 and 25% of cases, respectively. By comparison, the corresponding risk for MSSA patients was only 1.5 or 2%, respectively; the MRSA associated risk was thus higher by a factor of 13 (e3).

It should not be forgotten that, in addition to the individual risk for the MRSA carrier, MRSA-positive patients are a potential source of infection for fellow patients and neighboring patients, especially within the same surgical unit. In the context of risk minimization it seems therefore sensible to ascertain MRSA carrier status by nasal swab before planning a surgical procedure and to treat MRSA-positive patients before the procedure. In view of the still low prevalence of 0.7% in Germany's general population (17), MRSA screening is not recommended in all patients but in defined risk groups, according to the recommendations of the Robert Koch Institute (e13). These risk groups include, among others, patients with chronic cutaneous ulcers or wounds; chronically care dependent patients; or patients transferred from hospitals with a known high prevalence of MRSA. The decolonization treatment in MRSA-positive patients should include nasal administration of mupirocin, but also further measures, such as antiseptic pharyngeal rinses and body washes. It seems sensible to complete decontamination treatment for MRSA and use control swabs to confirm its success before embarking on elective surgery. Cohort studies and observational studies from Japanese authors have shown that such an approach significantly reduces the risk of post-intervention MRSA infection (7, e19). All in all, decolonization treatment before surgical procedures seems sensible.

The use of mupirocin recommended in this review – that is, limited to MRSA patients – should also contribute to avoid resistance as a risk associated with widespread use (e15) since short, targeted mupirocin treatment regimens were not associated with an increased risk of resistance (8).

Conflict of Interest Statement
Professor Trautmann received a speaker’s honorarium from GlaxoSmithKline in 2001. The other authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES
For e-references please refer to the additional references listed below.


ADDITIONAL REFERENCES


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