Systematic review and meta-analysis: susceptibility-guided versus empirical antibiotic treatment for *Helicobacter pylori* infection

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**Background:** The cure rate of standard triple therapy for *Helicobacter pylori* infection is unacceptably low. Susceptibility-guided therapies (SGTs) have been proposed as an alternative to standard empirical treatments. The aim of this study was to perform a systematic review and meta-analysis evaluating the efficacy of SGTs.

**Methods:** A systematic search was performed in multiple databases. Randomized controlled trials comparing cure rates of SGTs versus those of empirical therapy were selected and analysed separately for first- and second-line treatments. A meta-analysis was performed using risk ratio (RR) and number needed to treat (NNT) to measure the effect.

**Results:** Twelve studies were included in the meta-analysis. In first-line treatment, SGT was more efficacious than empirical 7–10 day triple therapy (RR 1.16, 95% CI 1.10–1.23, \(I^2 = 33\%\), NNT = 8). Most studies used a 7–10 day triple therapy and randomized the patients after endoscopy and/or culture, thus precluding the comparison of SGT versus non-invasive testing and empirical treatment in clinical practice. For second-line therapy, only four studies were found. Results were highly heterogeneous and no significant differences were found (RR 1.11, 95% CI 0.82–1.51, \(I^2 = 87\%\)).

**Conclusions:** Once endoscopy and culture have been performed, SGT is superior to empirical 7 or 10 day triple therapy for first-line treatment. Further studies are needed to evaluate the effectiveness of SGT in clinical practice, especially when compared with currently recommended first-line quadruple therapies.

**Introduction**

*Helicobacter pylori* infection is one of the most frequent human infections. It is the major causative agent of chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma (MALT) and gastric cancer. Its worldwide prevalence is nearly 50%, although there are large differences between countries.1

Consensus conferences have recommended the combination of a proton pump inhibitor (PPI) and two antibiotics, mainly amoxicillin (1 g twice daily) and clarithromycin (500 mg twice daily) or metronidazole (500 mg twice daily) as first-line therapy for *H. pylori* infection.1 4 However, most recent data show that this combination has lost efficacy and that its cure rates are often <70%, well below the target rate of 80% set during the last decade.4 As resistance to clarithromycin is the most relevant factor predicting triple-therapy failure,3 the increase in primary *H. pylori* resistance to this antibiotic has probably been the most important factor in the decrease in the efficacy of first-line triple therapy.

The overall clarithromycin resistance rate in Europe increased from 9% in 1998 to 17.6% in 2008, reaching a prevalence >20% in many countries in Central, Western and Southern Europe.5 In these regions many alternative treatments have been proposed, among them bismuth quadruple therapy, recommended as first-line therapy by the Maastricht IV/Florence consensus.4 Other possible alternatives are non-bismuth quadruple...
therapies using amoxicillin, clarithromycin, metronidazole and a PPI as sequential or concomitant treatment. Finally, the Maastricht IV/Florence consensus suggests that a possible alternative may be susceptibility-guided treatment (SGT), adjusting the treatment schedule to antibiotic susceptibility in order to avoid resistance and increase cure rates.

The Maastricht IV/Florence consensus recommended culture plus antibiotic susceptibility testing in order to guide third-line treatment after failure of two previous schedules. The consensus did not regard this approach as mandatory before first- and second-line treatment. By contrast, a previous meta-analysis by Wenzhen et al. suggests that susceptibility-guided triple therapy is a more effective first-line treatment than standard triple therapy. However, their meta-analysis focused only on first-line treatment and found only a small number of studies. Furthermore, SGT requires endoscopy and susceptibility testing, either by culture or molecular analysis. Whether the need for invasive testing reduces the acceptability and effectiveness of SGT in clinical practice remains uncertain. Finally, the evidence regarding SGT for rescue treatment has not been systematically evaluated so far.

The aim of the present study was to perform a systematic review and meta-analysis evaluating the efficacy of SGT versus empirical therapy for both first-line and rescue H. pylori treatments.

Methods

The study was performed in accordance with the PRISMA statement. The PRISMA checklist is shown in Table S1 (available as Supplementary data at JAC Online) and the PRISMA flow chart of the meta-analyses is shown in Figure 1.

Search strategy

A systematic computerized literature search limited to full-text published articles was conducted in PubMed, Scopus, the Cochrane Library and the ISI Web of Knowledge from 1984 to March 2014 (Table S2). In addition, references of articles retrieved, significant reviews and the personal databases of the authors were also checked for eligible publications. Finally, all searches were repeated in February 2015 in order to include more recent articles.

Inclusion criteria

We included published full-text articles that fulfilled the following criteria: (i) they reported randomized clinical trials (RCTs) or quasi-RCTs comparing efficacy of SGT versus empirical therapy in the success of H. pylori eradication in adult patients; (ii) SGT and empirical therapy was used as first-, second- or third-line treatment; (iii) pre-treatment diagnostic tests for H. pylori detection comprised one or more of the common validated tests (urea breath test, histology, rapid urease test, stool antigen, PCR or culture); (iv) all these tests (except culture) were considered adequate as

![Figure 1. Flow of information through the different phases of selection of the studies.](https://academic.oup.com/jac/article-abstract/70/9/2447/721821)
Studies included

In the qualitative and quantitative analysis, a Chinese medical student helped to translate three articles, which were then carefully evaluated of the full texts, 12 were included in at least one of the meta-analyses (Figure 1). Details on excluded studies are given in Table S3.

Results

Twelve studies were finally included.42,44,46 Seven RCTs and three quasi-RCTs were available in the qualitative and quantitative analysis. A Chinese medical student helped to translate three articles, which were then carefully evaluated of the full texts, 12 were included in at least one of the meta-analyses (Figure 1). Details on excluded studies are given in Table S3.

Statistical analysis

The primary endpoint for the different meta-analyses was ITT cure rates, secondary endpoints were PP efficacy, adherence and adverse events.9

Risk of bias

Risk of bias was assessed independently by two reviewers (L.P., and M.B.) in accordance with the Cochrane Collaboration’s current recommendations.9,10 For each study, random sequence generation and allocation concealment were evaluated. To assess publication bias, funnel plot asymmetry was inspected for each comparison, eradication rates and risk ratios (RRs) were calculated with their corresponding 95% CIs and number needed to treat (NNT). For first- and second-line therapies, a meta-analysis was performed according to the case record number; (iii) method used to determine antibiotic susceptibility; (iv) percentage of successful cultures; (v) time of randomization (before or after endoscopy); (vi) ITT; (vii) PP cure rates and their 95% CI for the SGT group and for the control empirical treatment group; (viii) adherence to treatment; (ix) number and severity of side effects; and (x) rates of resistance to antibiotics.

Table 1. Characteristics and cure rates of included studies

<table>
<thead>
<tr>
<th>Study author</th>
<th>n</th>
<th>Study design</th>
<th>Method for determining antibiotic susceptibility</th>
<th>Successful culture</th>
<th>ITT (%)</th>
<th>95% CI</th>
<th>PP (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawai29</td>
<td>70</td>
<td>RCT</td>
<td>faecal PCR</td>
<td>unknown</td>
<td>25/35 (71)</td>
<td>54–85</td>
<td>25/32 (78)</td>
<td>60–90</td>
</tr>
<tr>
<td>Marzio33</td>
<td>80</td>
<td>RCT</td>
<td>agar dilution</td>
<td>41/41</td>
<td>36/39 (92)</td>
<td>79–98</td>
<td>36/39 (92)</td>
<td>79–98</td>
</tr>
<tr>
<td>Neri36</td>
<td>242</td>
<td>RCT</td>
<td>Etest</td>
<td>unknown</td>
<td>78/121 (65)</td>
<td>55–73</td>
<td>78/116 (67)</td>
<td>55–79</td>
</tr>
<tr>
<td>Park45</td>
<td>114</td>
<td>RCT</td>
<td>Etest</td>
<td>14/9/237</td>
<td>41/57 (72)</td>
<td>60–83</td>
<td>41/56 (73)</td>
<td>61–85</td>
</tr>
<tr>
<td>Romano37</td>
<td>150</td>
<td>RCT</td>
<td>Etest</td>
<td>75/75%</td>
<td>58/75 (70)</td>
<td>70–80</td>
<td>58/73 (79)</td>
<td>69–87</td>
</tr>
<tr>
<td>Taracchio40</td>
<td>109</td>
<td>quasi-RCT</td>
<td>agar dilution</td>
<td>49/53</td>
<td>42/56 (75)</td>
<td>61–85</td>
<td>42/52 (81)</td>
<td>67–90</td>
</tr>
<tr>
<td>Wang62</td>
<td>120</td>
<td>quasi-RCT</td>
<td>dry plate</td>
<td>unknown</td>
<td>57/80 (71)</td>
<td>59–80</td>
<td>57/77 (74)</td>
<td>65–85</td>
</tr>
<tr>
<td>Zhou44</td>
<td>260</td>
<td>quasi-RCT</td>
<td>agar dilution</td>
<td>119/125</td>
<td>107/135 (79)</td>
<td>71–86</td>
<td>107/129 (83)</td>
<td>75–98</td>
</tr>
<tr>
<td>Zhuo46</td>
<td>813</td>
<td>RCT</td>
<td>agar dilution</td>
<td>313/500</td>
<td>405/500 (81)</td>
<td>77–84</td>
<td>405/472 (86)</td>
<td>82–89</td>
</tr>
</tbody>
</table>

*Successful culture rate was unknown in the studies that included only patients with positive culture.

Data extraction

Data were extracted independently by four reviewers (L.P., V.G., G.H., M.B.) and revised by a fifth investigator (A.V.). Data extraction was standardized using an additional investigator (X.C.). Variables compiled were: (i) number of patients; (ii) type of study (RCT or quasi-RCT—the latter if allocation was quasi-random, such as alternation, date of birth or number used.4 No language limitations were imposed.

Discussion

The primary endpoint for the different meta-analyses was ITT cure rates, secondary endpoints were PP efficacy, adherence and adverse events.9

Statistical analysis

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<table>
<thead>
<tr>
<th>Study author</th>
<th>C resistant strains, n/total (%)</th>
<th>Empirical therapy</th>
<th>Treatment duration (days)</th>
<th>Susceptibility-guided treatment</th>
<th>n</th>
<th>Treatment duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawai29</td>
<td>19/35 (54)</td>
<td>LA 30 mg, A 750 mg, C 400 mg bid</td>
<td>35</td>
<td>7</td>
<td>C resistant: RA 10 mg, A 750 mg, M 250 mg bid</td>
<td>19</td>
</tr>
<tr>
<td>Marzio33</td>
<td>9/41 (22)</td>
<td>E 20 mg, A 1 g, L 500 mg bid</td>
<td>39</td>
<td>10</td>
<td>A and L susceptible: E 20 mg, A 1 g, L 500 mg bid</td>
<td>36</td>
</tr>
<tr>
<td>Neri16</td>
<td>17/242 (7)</td>
<td>O 20 mg, C 500 mg, A 1 g bid</td>
<td>58</td>
<td>7</td>
<td>C susceptible: O 20 mg bid, C 500 mg bid A 1 g bid</td>
<td>29</td>
</tr>
<tr>
<td>Park45</td>
<td>38/114 (33)</td>
<td>P 40 mg/LA 20 mg, C 500 mg, A 1 g bid</td>
<td>57</td>
<td>7</td>
<td>C susceptible: P 40 mg/LA 20 mg, C 500 mg, A 1 g bid</td>
<td>57</td>
</tr>
<tr>
<td>Romano37</td>
<td>11/75 (15)</td>
<td>O 20 mg, C 500 mg, M 500 mg bid</td>
<td>75</td>
<td>7</td>
<td>C susceptible: O 20 mg, C 500 mg, M 500 g bid</td>
<td>48</td>
</tr>
<tr>
<td>Toracchio40</td>
<td>17/101 (17)</td>
<td>O 20 mg, TI 500 mg, C 500 mg bid</td>
<td>56</td>
<td>10</td>
<td>C and TI susceptible: O 20 mg, TI 500 mg, C 500 mg bid</td>
<td>29</td>
</tr>
<tr>
<td>Wang42</td>
<td>4/39 (10)</td>
<td>O 20 mg, A 1 g, M 400 mg bid</td>
<td>40</td>
<td>7</td>
<td>O 20 mg, A 1 g, M 400 mg bid</td>
<td>10</td>
</tr>
<tr>
<td>Zhou44</td>
<td>38/248 (15)</td>
<td>O 20 mg, C 500 mg, M 400 mg bid</td>
<td>135</td>
<td>10</td>
<td>C and M susceptible: O 20 mg, C 500 mg, M 400 mg bid</td>
<td>71</td>
</tr>
<tr>
<td>Zhuo46</td>
<td>108/313 (34)</td>
<td>E 20 mg, A 1 g, C 500 mg, RBC 400 mg bid</td>
<td>500</td>
<td>14</td>
<td>E 20 mg, A 1 g, C 500 mg, RBC 400 mg bid</td>
<td>259</td>
</tr>
</tbody>
</table>

A, amoxicillin; B, bismuth subcitrate; bid, twice a day; C, clarithromycin; E, esomeprazole; F, furazolidone; L, levofloxacin; LA, lansoprazole; M, metronidazole; O, omeprazole; qds, four times a day; RA, rabeprazole; RBC, ranitidine bismuth citrate; RI, rifabutin; TE, tetracycline; TI, tinidazole.
Six RCTs and three quasi-RCTs compared cure rates of SGT versus empirical treatment in first-line therapy. Two RCTs were found for second-line treatment. No RCTs comparing SGT versus empirical treatment in third-line therapy were found.

The characteristics of the studies are shown in Table 1 and the treatment administered is shown in Tables 2 and 3. The risk of bias was moderate to high in most of the studies, and is summarized in Figure 2. As all the comparative studies but one allocated the patients after endoscopy had been performed, the effectiveness and applicability of SGT in clinical practice could not be compared.

First-line treatment

Six RCTs and three quasi-RCTs compared cure rates of SGT versus empirical treatment with non-invasive testing and empirical treatment with non-invasive testing and endoscopy. All RCTs were performed in patients with endoscopy and 34% of patients allocated the treatment after endoscopy was performed. The effectiveness and applicability of SGT in clinical practice could not be compared.

In untreated patients, while only four RCTs were found for first-line treatment, the effectiveness and applicability of SGT in clinical practice could not be compared.

### Table 3. Antimicrobial therapies used in second-line therapy studies

<table>
<thead>
<tr>
<th>Study author</th>
<th>Previous treatment</th>
<th>N (total)</th>
<th>Treatment duration (days)</th>
<th>Susceptibility-guided treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avidan</td>
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<tr>
<td>Lamouliatte</td>
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<tr>
<td>Marzio</td>
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<td>Miwa</td>
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<td>Toracchio</td>
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<td>Wang</td>
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<td>Kawai</td>
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<td>Zhou</td>
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<td>Zhuo</td>
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<td>Gotto</td>
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<td>Konno</td>
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Figure 2. Risk of bias of the studies. This figure appears in colour in the online version of this paper and in black and white in the print version of this paper.

### Table 2. Characteristics of the studies

<table>
<thead>
<tr>
<th>Study author</th>
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<th>N (total)</th>
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<tr>
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studies except one, 46 in which a bismuth-containing quadruple therapy was used. Treatment was notably more heterogeneous in the SGT arm. Most studies tested for clarithromycin resistance. However, patients with susceptible strains received triple therapy that included clarithromycin; those harbouring resistant strains were often treated with a combination of a PPI, amoxicillin and a nitroimidazole.

No studies reported the number of patients who did not accept endoscopy or were lost to follow-up before randomization at the time the results of culture and antibiotic susceptibility analysis were available. Only one study randomized patients before endoscopy; even in this study, patients had to accept the possibility of undergoing an endoscopy in order to be randomized. Furthermore, the study did not report how many patients refused invasive methods and had to be excluded. In consequence, there were no data on the acceptability and applicability of SGT. In summary, as no study reported the number of patients excluded for not accepting endoscopy, the effectiveness of SGT has never been evaluated either in clinical practice or in RCTs.

ITT efficacy analysis, including seven RCTs/quasi-RCTs (1958 patients), showed that SGT cure rates were superior to those of empirical treatment (RR 1.16, 95% CI 1.10–1.23, P<0.0001, I² = 33%); NNT was 8 (Figure 3). The sub-analysis excluding quasi-RCTs (489 patients) showed similar results (RR 1.15, 95% CI 1.07–1.24, P<0.00001, I² = 47%, NNT = 9). PP efficacy was also significantly higher in the SGT group (RR 1.18, 95% CI 1.10–1.23, P<0.0001, I² = 52%) and NNT was 8 (Figure S1). PP efficacy excluding quasi-RCTs showed similar significant results (RR 1.14, 95% CI 1.06–1.22, P=0.0006, I² = 54%, NNT = 9). The sub-analysis including only studies in which triple therapy was given as empirical therapy (excluding one study29 in which quadruple therapy containing bismuth was administered) showed similar results (ITT: RR 1.18, 95% CI 1.11–1.26, P<0.00001, I² = 26%, NNT = 7; PP: RR 1.18, 95% CI 1.12–1.25, P<0.00001, I² = 23%, NNT = 7).

The heterogeneity in all the analyses was mild to moderate (I² = 23%–54%). The notable heterogeneity of treatments and the reduced number of studies prevented any subgroup analyses. The funnel plot showed moderate asymmetry in all the analyses, with larger studies being less favourable to SGT, thus suggesting a possible publication bias. Figure S2 shows the funnel plot for the ITT analyses of included studies.

Mild to moderate adverse events were reported in 6%–38%20,31,33,45,46 of patients. Two studies reported dropout rates of 1%30 and 3%36 due to side effects. Adverse events for the empirical treatment and SGT were rarely reported separately. In consequence, no meta-analysis could be carried out.

**Second-line treatment**

Four RCTs,23,30,33,34 compared SGT with empirical treatment as second-line therapy. The characteristics of the studies are shown in Table 1 and the treatment administered in Table 3.
The meta-analysis of ITT efficacy, including 455 patients, did not show significant differences between the two therapy strategies (RR 1.11, 95% CI 0.82–1.51, \( P = 0.5, I^2 = 87\% \); Figure 4). PP efficacy analysis, including 388 patients, showed similar results (RR 1.13, 95% CI 0.86–1.50, \( P = 0.38, I^2 = 86\% \); Figure 53). There was considerable heterogeneity in the analyses; this fact, along with the limited number of patients, ruled out the performance of sub-analyses. Adverse events were generally mild to moderate and were reported in 65%,\(^{30} \) 26%,\(^{34} \) and 34% of cases.\(^{38} \) Only one study\(^{34} \) reported severe adverse events in 4% of patients.

**Discussion**

The main result of the present study is that, once endoscopy and susceptibility testing are performed, SGT achieves better cure rates than 7–10 day empirical triple therapy as first-line therapy. The study also revealed no significant differences between SGT and empirical second-line therapy. However, few studies and high heterogeneity in rescue treatments prevent us from drawing any conclusion.

Another important finding is that the evidence regarding SGT is very limited. We identified only 12 studies suitable for review—a very low figure, especially bearing in mind that a search for \( H. pylori \) treatment trials performed at the time of writing identified nearly 3000 citations. What is more, the quality of the studies was not high, and funnel plots suggest the possibility of publication bias.

An additional major limitation of the current evidence regarding SGT is that the studies evaluated SGT efficacy by randomizing patients to SGT after diagnostic endoscopy or even after successful culture. One study randomized the patients before endoscopy to empirical treatment versus SGT, but it did not report the number of patients who did not accept endoscopy and therefore were not included in the study. In clinical practice most dyspeptic patients are diagnosed with \( H. pylori \) infection in primary care by non-invasive tests and subsequently receive empirical treatment. Therefore, both burdensome additional exploration (namely endoscopy) and complex, time-consuming procedures such as culture or molecular techniques will be needed to determine antibiotic susceptibility.\(^{2} \) In this setting, the need for endoscopy and the practical barriers for routine and timely \( H. pylori \) culture or genotypic evaluation of resistances may reduce the applicability of SGT. Therefore, the comparative effectiveness of SGT versus the current non-invasive diagnosis and empirical treatment policy in patients with suspected \( H. pylori \) infection has not been evaluated in RCTs and remains unclear. Further evaluation of the acceptability and applicability of SGT in clinical practice is necessary before recommending widespread SGT use.

As stated above, regarding first-line therapy, the meta-analysis of nine RCTs showed that once endoscopy and culture are performed, the efficacy of SGT is significantly higher than that of empirical 7–0 day triple therapy, which was the standard treatment at the time that most of the studies were conducted. However, 7 or 10 day clarithromycin-containing triple therapies are currently known to achieve poor cure rates and, therefore, are suboptimal comparators. Only one study compared SGT versus bismuth-containing quadruple therapy,\(^{30} \) and also showed a significantly higher efficacy in the SGT group. However, this is a further limitation of the evidence regarding SGT: there is not enough evidence comparing this approach with 14 day triple therapies or with the highly effective bismuth- and non-bismuth-containing quadruple therapies currently recommended by the Maastricht consensus.\(^{2} \)

The evidence supporting SGT is even more limited in rescue treatment. The meta-analysis of the four RCTs comparing SGT with empirical treatment did not find significant differences. However, these results are inconclusive, because the lack of significance may have been due to the limited power of the comparison and the reduced number of patients. Furthermore, treatment schedules in the different studies were extremely heterogeneous and the evidence regarding second-line SGT is very limited. Therefore, the conclusions of this particular meta-analysis should be interpreted with extreme care.

Regarding third-line or mixed second- and third-line treatments, no randomized controlled trials were found and most of the studies were non-comparative. In general, the cure rates with third-line therapies were not especially good with SGT and do not seem to be superior to those previously published for empirical therapies.\(^{48}–{56} \) A separate meta-analysis of non-comparative studies reporting cure rates of SGT in third-line treatment showed a mean cure rate of 72% (95% CI 56–87, \( I^2 = 92\% \)) (data not shown).

The meta-analysis highlights the need for well-designed studies evaluating the effectiveness of SGT either as a first-line therapy or as a rescue therapy. A study evaluating SGT effectiveness as a first-line treatment should randomize patients with uninvestigated dyspepsia to non-invasive testing or endoscopy plus culture. For second- or third-line treatment, the study should randomize patients with a positive control test to endoscopy and culture versus empirical treatment.

In conclusion, the currently available evidence suggests that SGT is superior to 7–10 day triple therapies as first-line treatment in patients who have already undergone endoscopy and culture. There is lack of strong evidence to support SGT in rescue treatment. There is an urgent need for data regarding the effectiveness and acceptability of SGT in clinical practice. Data are also needed on its efficacy in comparison with the highly effective quadruple therapies, which are currently recommended. Overall, the evidence is too limited to support the generalized use of SGT for \( H. pylori \) treatment, either as first-line or as rescue treatment; more studies will be needed to reach an evidence-based conclusion. However, once endoscopy and culture are performed, the use of SGT seems to increase cure rates and may therefore be effective in specific situations. As for rescue treatments, the efficacy of more intensive schedules, such as long quadruple therapies, either associated with SGT or not, deserves further study.

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Transparency declarations
None to declare.

Supplementary data
Tables S1–S3 and Figures S1–S3 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


