school. Second-year students were entirely based at a single campus. Third-year students were distributed among hospitals in 5 communities throughout the state. Swabbing was done at the end of the academic year to ensure that third-year students had significant patient exposure. Results were analyzed using the χ² test and the Fisher exact test, with 95% confidence intervals calculated using the modified Wald method.

Separate swab specimens (BactiSwab; Remel) were obtained from both the nares and the pharynx of students who provided verbal consent. Swabs were streaked onto mannitol salt agar plates (BD Diagnostic Systems) and incubated overnight at 37°C. Both the nasal and pharyngeal swabs were streaked on the same plate. Samples that screened positive for S. aureus were then streaked on MRSA oxacillin screen agar plates (BD Diagnostic Systems) and incubated overnight at 37°C. Positive samples were streaked onto mannitol salt agar plates to ensure a pure culture and were then frozen in Mueller Hinton media plus 20% glycerol and stored at −70°C.

There were 182 students in the study, including 95 second-year students and 87 third-year students. This represented 90% and 82% of the second- and third-year classes, respectively. Of second-year students, 5% reported an inpatient rotation in the previous 3 months, compared with 98% of third-year students.

There were 62 cultures that were positive for S. aureus (34% of the population), which is similar to the rate of 29% for the general US population [1]. Five participants (2.7%) had cultures positive for MRSA (95% confidence interval, 1.6–6.5%); this is similar to the rate for the general US population, for which the reported carriage rate is 1.5% on the basis of nasal cultures alone [1]. Of the 5 persons with MRSA carriage, 2 were second-year students who had not had a clinical inpatient rotation. Three were third-year students with inpatient experience (each from a different community campus). Thus, the prevalence of MRSA carriage was 2.1% for second-year students and 3.4% for third-year students (P = .67).

This study provides the first estimate, to our knowledge, of MRSA carriage among US medical students in the era of community-associated MRSA infection. It is also the first to compare carriage rates in the preclinical and clinical years. The results showed that nasopharyngeal MRSA carriage was not an occupational hazard of patient care exposure in third-year medical students.

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Are Statins Applicable for the Prevention and Treatment of Zygomycosis?

To the Editor—A recent article by Sun and Singh [1] summarized the antimicrobial and immunomodulatory attributes of statins. Among other things, they detailed the antifungal effects of statins on Zygomycetes, suggesting their possible application for protection against zygomycosis. Here, we should like to point out some aspects pertaining to this application that have previously been only partially discussed: the minimum inhibitory concentration (MIC) values of statins, their attainable serum concentrations, and their possible combinations with other antifungal agents.

Published data on statins’ antifungal activities against Zygomycetes are available only for lovastatin, simvastatin, rosuvastatin, and atorvastatin [2–4]. These statins displayed significant in vitro effects, completely blocking the growth of Zygomycetes at concentrations of 8–64 μg/mL, depending on the test method applied, the organisms involved, and the drugs studied [2–4]. Our investigations on the antifungal action of fluvastatin recently furnished similar results: MICs were found in the range of 3.125–100 μg/mL, depending on the sensitivity of the species investigated [5]. Atorvastatin seems less effective against Zygomycetes; it blocks sporangiospore germination at concentrations of 50–100 μg/mL (L.G., T.P., and Cs.V., unpublished data).

The MICs of statins are much higher than the concentrations attainable in the human serum; the differences are about 1 order of magnitude (table 1) [6–11]. In consequence, the combined application of statins and antifungal agents may be of practical importance. In particular, drugs that can act synergistically with statins, allowing substantial decreases in their therapeutic concentration, should be investigated. Indeed, lovastatin and voriconazole have proved to be synergistically effective against Zygomycetes in a range of clinically achievable concentrations of both drugs [3]. Our in vitro studies have revealed that amphotericin B acts synergistically with atorvastatin and fluvasatin at concentrations that can be achieved in the plasma. Their MIC₅₀ values (with regard to the minimum statin concentration in the studied combinations) were 390 ng/mL amphotericin B with 6 ng/mL atorvastatin and 48 ng/mL amphotericin B with 6 ng/mL fluvasatin (L.G., I.Ny., T.P., and Cs.V., unpublished data). Another study has revealed a synergistic interaction between fluvasatin and a non-antifungal agent, suramin, on the growth of different
Zygomycetes [5]. Theoretically, some of the examined statin concentrations can be reached in the human plasma via administration of high oral doses (e.g., a daily dosage of 40–80 mg).

The administration of statins together with antifungals that are predominantly metabolized by the same cytochrome P450 (CYP450) isoenzymes in the liver is contraindicated, because such drug interactions with the CYP system may cause serious adverse effects (e.g., myopathy). Thus, even if combinations of lovastatin and voriconazole may well be effective against Zygomycetes in clinically available concentrations, their possible application would involve considerable risks, because both compounds are metabolized by CYP3A4. Table 1 presents examples of statins and antifungal drugs (and their CYP inhibitions) that could possibly be coadministered with fluvastatin, pitavastatin, or rosuvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, miconafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system). The following antifungal drugs (and their CYP inhibitions) could possibly be coadministered with atorvastatin, cerivastatin, lovastatin, pravastatin, or simvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, miconafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system). Cmax, maximum plasma concentration.

Table 1. Pharmacokinetic Properties of Statins

<table>
<thead>
<tr>
<th>Property</th>
<th>Atorvastatin</th>
<th>Cerivastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Pitavastatin</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>27–66</td>
<td>2</td>
<td>10–20</td>
<td>45–56</td>
<td>10–34</td>
<td>448</td>
<td>65</td>
<td>37</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>10</td>
<td>&gt;60</td>
<td>5</td>
<td>18</td>
<td>5</td>
<td>19–29</td>
<td>&gt;60</td>
<td>20</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4</td>
<td>CYP3A4, CYP2C8</td>
<td>CYP3A4</td>
<td>CYP3A4, CYP3A5</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP2C9, CYP2C8</td>
<td>CYP3A4, CYP2C19</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>

NOTE. Data are based on a 40 mg oral dose of the above-mentioned statins, with the exception of cerivastatin (0.2 mg) and pitavastatin (2 mg). The following antifungal drugs (and their CYP inhibitions) could possibly be coadministered with atorvastatin, cerivastatin, lovastatin, pravastatin, or simvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, miconafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system). The following antifungal drugs (and their CYP inhibitions) could possibly be coadministered with atorvastatin, cerivastatin, lovastatin, pravastatin, or simvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, miconafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system). Cmax, maximum plasma concentration.

References


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Reply to Galgóczi et al

To the Editor—We thank Galgóczi et al [1] for their interest in our work [2] and for sharing their unpublished and in press data regarding the use of statins for the prevention and treatment of zygomycosis. The prophylactic and even therapeutic effects of pharmacologic agents may be evident despite their subinhibitory activity, such as echinocandins against Aspergillus and Zygomycetes [3, 4]. However, we agree that, given a relatively high minimal inhibitory concentration of statins for the Zygomycetes, their efficacy may be best realized when used in conjunction with antifungal agents. We also note that statins modulate key host defenses by modification of signal transduction and cytokine transcriptional pathways, and they may exert a mediating effect on fungal infections independent of their anti-

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