Concise report

Persistence of Staphylococcus aureus colonization among individuals with immune-mediated inflammatory diseases treated with TNF-α inhibitor therapy

Cara D. Varley¹, Atul A. Deodhar¹, Benjamin D. Ehst¹, Antony Bakke¹, Andrew Blauvelt¹, Robert Vega², Shellie Yamashita¹ and Kevin L. Winthrop¹

Abstract

Objective. We investigated the relationship between Staphylococcus aureus colonization and the use of immunosuppressive therapies in patients with immune-mediated inflammatory diseases (IMIDs).

Methods. We prospectively enrolled IMID patients from the rheumatology and dermatology departments of Oregon Health & Science University. At enrolment, we surveyed patients for S. aureus infection risk factors and those using immune-modulating therapies, and evaluated their colonization status with bilateral nares and inguinal fold cultures. Patients were asked to follow up 6–12 months later for reassessment of colonization status by repeat culture. S. aureus isolates were tested for the presence of methicillin resistance by PCR.

Results. We enrolled a total of 548 IMID patients. At enrolment, 219 (40.0%) patients were colonized with S. aureus, of which 27 (12.3%) were methicillin-resistant S. aureus (MRSA). Baseline colonization rates were similar between TNF-α inhibitor users and non-users (40.5% and 39.4%, P = 0.79), but were significantly higher for psoriasis patients compared with those with RA (43.5% and 31.8%, P = 0.02). A total of 384 patients were available for follow-up. Patients who were colonized at enrolment were more likely to be colonized at follow-up if they were treated with TNF-α inhibitors during the study as compared to patients without TNF-α inhibitor exposure [odds ratio (OR) = 2.2 (95% CI 1.1, 4.2), P = 0.02].

Conclusion. Patients with psoriasis are more likely to be colonized with S. aureus than patients with RA. Patients who are colonized with S. aureus are more likely to remain colonized if exposed to TNF-α inhibitors.

Key words: Staphylococcus aureus, biologic therapy, tumour necrosis factor-alpha, rheumatoid arthritis, psoriasis.

Introduction

Patients with immune-mediated inflammatory diseases (IMIDs) are often at increased risk for infection due to their underlying disease, associated co-morbidities and immunosuppressive therapies [1, 2]. RA patients are five-times more likely to die of pneumonia, have a 10–15 times greater risk for bone and joint infections and are three times more likely to suffer skin infections than the general public [2–4]. Observational studies suggest that the infectious risks of RA can be increased further by biologic therapies, specifically TNF inhibitors [4, 5]. TNF-α is an important part of the innate immune response to both intracellular and extracellular infections including Staphylococcus aureus [3, 6, 7].

In parallel with the rise of biologic therapies, the infectious disease community has witnessed increasing S. aureus and methicillin-resistant S. aureus (MRSA) infections in the last decade. In the USA, ~30% of persons in...
the community are nasal carriers of \( S. \) \( aureus \), and 1–2% are MRSA [8]. The recent emergence of community-acquired MRSA strains has been associated with an increasing number of severe infections. MRSA now accounts for >50% of soft tissue infections and \( Staphylococcus \) is one of the leading causes of healthcare-acquired pneumonia in the USA [8, 9].

Studies of hospitalized patients in the pre-surgical and pre-intensive care unit (ICU) settings, in addition to HIV positive and continuous peritoneal dialysis populations, have demonstrated that colonized patients are at increased risk for subsequent staphylococcal infections [10–12]. This is particularly relevant with the greater risk of serious infections in the IMID population [13, 14]. Given the increased infection risk posed by TNF inhibitors, \( S. \) \( aureus \) colonization could theoretically further increase the risk of serious infections in this population.

The burden of \( S. \) \( aureus \) colonization and infection in subjects with IMIDs and the modifying role of immuno-suppressive therapies are relatively unknown. The rare studies that have been completed in the RA population have shown higher or equal rates of colonization (50–56%) compared with controls, however, sample sizes were limited [14, 15]. The purpose of this study was to determine the prevalence of \( S. \) \( aureus \) colonization in subjects with IMIDs, assess whether colonization risks vary according to disease-modifying therapies and evaluate the risk for remaining colonized after the baseline study visit.

**Patients and methods**

**Baseline assessment**

The Oregon Health & Science University (OHSU) Institutional Review Board approved this study. All participants provided informed consent. We prospectively identified IMID patients \( \geq 18 \) years of age who were receiving biologics or being considered for biologic therapy at enrolment within the rheumatology and dermatology clinics of OHSU in Portland, OR, USA. Patients receiving or being considered for biologic therapy (abatacept, adalimumab, etanercept, infliximab, rituximab, ustekinumab) were asked to participate. At enrolment, participants were assessed for \( S. \) \( aureus \) colonization and surveyed regarding demographics, medication use and presence of \( S. \) \( aureus \) risk factors in the preceding year.

**Colonization assessment**

Using cotton-tipped swabs, we cultured bilateral nares and inguinal folds of all subjects. The Oregon State Public Health Laboratory (Hillsboro, OR, USA) performed standardized laboratory isolation procedures, with positive isolates further screened for MRSA utilizing Spectra MRSA test media (Remel Products, Lenexa, KS, USA) and mannnitol salt agar containing 4\( \mu \)g of oxacillin (MSAO; Remel). Screen-positive organisms isolated from either of these two media were further screened with Mueller–Hinton agar containing 6\( \mu \)g of oxacillin (Remel) and tested for the presence of penicillin binding protein 2’ (PBP2’) encoded by the \( mecA \) gene (PBP2’ Test, DR0900; Oxoid Ltd, Basingstoke, UK). We considered any subjects with MRSA or methicillin-sensitive \( S. \) \( aureus \) (MSSA) isolated from either culture as colonized.

**Follow-up patient assessment**

We asked patients to follow up 6–12 months after enrolment and attempted to repeat assessments during visits within that time period. Follow-up was variable, as some patients did not return in this time frame. We systematically called those lacking follow-up data on three different occasions. If we did not receive a response after three calls, we considered them lost to follow-up.

**Statistical analysis**

We used SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) to compare categorical variables and the relative risk (RR) of association with \( S. \) \( aureus \) colonization in univariate and stratified methods by the \( \chi^2 \) test or Fisher’s exact test. We used the Student’s \( t \)-test and logistic regression to evaluate continuous variables. Due to differences in pathogenesis between IMIDs, we stratified by condition, analysing RA and psoriasis/PsA patients separately. We considered factors with a \( P \)-value <0.2 for inclusion in multivariate logistic regression and performed stepwise backward elimination to determine significance \( (P < 0.05) \) for our final multivariate models.

**Results**

**Demographics**

We enrolled 548 IMID patients. Two hundred and eighty-five (52.0%) patients were taking biologic therapy at the time of the initial assessment; 92.6% of those were on TNF inhibitors. Demographic characteristics are presented in Table 1.

**Baseline \( S. \) \( aureus \) colonization**

At enrolment, 219 (40.0%) patients were colonized with \( S. \) \( aureus \) (nares 21.6%, inguinal 3.3%, both sites 15.0%), of which 27 (12.3%) were colonized with MRSA (Table 1).

**Risk factors for baseline colonization: univariate analysis**

The proportion of patients taking TNF inhibitors was similar between those colonized and not colonized at baseline \( (P = 0.79) \). Colonization did not differ between biologic agents, but was less common in patients receiving prednisone \( (RR = 0.63, P = 0.01) \). We did not observe an association between MTX plus TNF inhibitor exposure and baseline colonization \( (P = 0.26) \). Colonized patients were younger, more likely to report contact with people experiencing skin infections and less likely to undergo surgery in the 12 months preceding enrolment. Antibiotic use in the previous year was highly associated with surgery \( (P < 0.01) \). No other significant associations were identified between \( S. \) \( aureus \) colonization and collected risk factors (Table 2).
TABLE 1 Risk factors, demographics and S. aureus colonization by IMID

<table>
<thead>
<tr>
<th>Demographics</th>
<th>RA</th>
<th>Psoriasis/PSA</th>
<th>AS</th>
<th>Othera</th>
<th>Two or more conditions</th>
<th>Total 548</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>125 (81.2)</td>
<td>146 (51.2)</td>
<td>11 (30.6)</td>
<td>35 (57.4)</td>
<td>11 (91.7)</td>
<td>328 (59.9)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>58 (21–83)</td>
<td>48 (18–79)</td>
<td>43.5 (23–85)</td>
<td>40 (29–76)</td>
<td>57 (30–72)</td>
<td>51 (18–85)</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>126 (81.8)</td>
<td>255 (89.5)</td>
<td>33 (91.7)</td>
<td>55 (90.2)</td>
<td>12 (100.0)</td>
<td>481 (87.8)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Diabetes</td>
<td>17 (11.0)</td>
<td>34 (11.9)</td>
<td>0 (0.0)</td>
<td>6 (9.8)</td>
<td>0 (0.0)</td>
<td>57 (10.4)</td>
</tr>
<tr>
<td>Immunosuppressive medication at enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α inhibitorb</td>
<td>70 (45.5)</td>
<td>120 (42.1)</td>
<td>18 (50.0)</td>
<td>50 (90.0)</td>
<td>6 (50.0)</td>
<td>264 (48.2)</td>
</tr>
<tr>
<td>Median years duration of TNF-α inhibitor use (range)</td>
<td>2.0</td>
<td>1.5</td>
<td>3.3</td>
<td>2.0</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Other biologicalc</td>
<td>19 (12.3)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>21 (3.8)</td>
</tr>
<tr>
<td>Other systemicd</td>
<td>57 (37.0)</td>
<td>59 (20.7)</td>
<td>3 (8.3)</td>
<td>4 (6.6)</td>
<td>4 (33.3)</td>
<td>127 (23.2)</td>
</tr>
<tr>
<td>No systemicd</td>
<td>8 (5.2)</td>
<td>105 (36.8)</td>
<td>15 (41.7)</td>
<td>6 (9.8)</td>
<td>2 (16.7)</td>
<td>136 (24.8)</td>
</tr>
<tr>
<td>Self-reported S. aureus risk factors in 12 months preceding enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of S. aureus infection</td>
<td>13 (8.4)</td>
<td>49 (17.2)</td>
<td>2 (5.6)</td>
<td>5 (8.2)</td>
<td>0 (0.0)</td>
<td>69 (12.8)</td>
</tr>
<tr>
<td>History of boils</td>
<td>11 (7.1)</td>
<td>27 (9.5)</td>
<td>0 (0.0)</td>
<td>6 (9.8)</td>
<td>0 (0.0)</td>
<td>44 (8.0)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>49 (31.8)</td>
<td>71 (24.9)</td>
<td>5 (13.9)</td>
<td>19 (31.2)</td>
<td>4 (33.3)</td>
<td>148 (27.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>46 (29.8)</td>
<td>65 (22.8)</td>
<td>5 (13.9)</td>
<td>19 (31.2)</td>
<td>2 (16.7)</td>
<td>137 (25.0)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>27 (17.5)</td>
<td>53 (18.6)</td>
<td>3 (8.3)</td>
<td>10 (16.4)</td>
<td>0 (0.0)</td>
<td>93 (17.0)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>81 (52.6)</td>
<td>140 (49.1)</td>
<td>18 (50.0)</td>
<td>37 (60.7)</td>
<td>6 (50.0)</td>
<td>282 (51.5)</td>
</tr>
<tr>
<td>Baseline S. aureus colonization</td>
<td>49 (31.8)</td>
<td>124 (43.5)</td>
<td>16 (44.4)</td>
<td>27 (44.3)</td>
<td>3 (25.0)</td>
<td>219 (40.0)</td>
</tr>
<tr>
<td>MRSA only</td>
<td>4 (2.6)</td>
<td>13 (4.6)</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
<td>1 (8.3)</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>MSSA only</td>
<td>44 (28.6)</td>
<td>106 (37.2)</td>
<td>15 (41.7)</td>
<td>25 (41.0)</td>
<td>2 (16.7)</td>
<td>192 (35.0)</td>
</tr>
<tr>
<td>MSSA and MRSA</td>
<td>1 (0.7)</td>
<td>5 (1.8)</td>
<td>1 (2.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Follow-up S. aureus colonization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolment +, follow-up +</td>
<td>24 (23.1)</td>
<td>54 (28.1)</td>
<td>8 (28.6)</td>
<td>14 (29.2)</td>
<td>2 (18.2)</td>
<td>102 (26.6)</td>
</tr>
<tr>
<td>Enrolment +, follow-up –</td>
<td>10 (9.6)</td>
<td>33 (17.2)</td>
<td>5 (17.9)</td>
<td>9 (18.8)</td>
<td>0 (0.0)</td>
<td>57 (14.9)</td>
</tr>
<tr>
<td>Enrolment –, follow-up +</td>
<td>12 (11.5)</td>
<td>23 (12.0)</td>
<td>8 (28.6)</td>
<td>4 (8.3)</td>
<td>2 (18.2)</td>
<td>49 (12.8)</td>
</tr>
<tr>
<td>Enrolment –, follow-up –</td>
<td>58 (55.8)</td>
<td>82 (42.7)</td>
<td>7 (25.0)</td>
<td>21 (43.8)</td>
<td>7 (63.6)</td>
<td>175 (45.7)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values are number (%). aIncludes Crohn’s disease, ulcerative colitis and uveitis. bIncludes MTX plaquenil, prednisone and sulphasalazine. cIncludes topical steroids, no therapy. +: positive adalimumab, etanercept and infliximab. cIncludes abatacept, rituximab and ustekinumab. dIncludes arava, azathioprine, MTX plaquenil, prednisone and sulphasalazine. eIncludes topical steroids, no therapy. +: positive adalimumab, etanercept and infliximab. fIncludes abatacept, rituximab and ustekinumab. gIncludes arava, azathioprine, MTX plaquenil, prednisone and sulphasalazine.

Risk factors for baseline colonization: multivariate analysis

Only prednisone use and contact with people experiencing skin infections were significantly associated with baseline colonization in a multivariate model with TNF inhibitor exposure and psoriasis. No interactions were significant (Table 2).

Stratified analysis of RA and psoriasis/PsA patients

The proportion of patients colonized at baseline differed between RA (31.8%) and psoriasis/PsA (43.5%) patients ($P = 0.02$). After controlling for age, psoriasis had a higher risk of colonization compared with RA patients [odds ratio (OR) = 1.6 (95% CI 1.05, 2.4), $P = 0.03$]. Stratified analyses are presented in Table 2.

Follow-up S. aureus colonization

Follow-up [median 0.63 (range 0.15–3.35) years] data were available for 384 (70.1%) patients. Seventy-two per cent of patients remained on the same immune-modulating therapy type throughout the study, 7.3% of patients started TNF inhibitor therapy and 10.2% of patients stopped TNF inhibitor therapy. One hundred and two (26.6%) patients were persistently colonized with *S. aureus*, 57 (14.8%) were only colonized at baseline, 49 (12.8%) were only colonized at follow-up and 176 (45.8%) had no colonization (Table 2).

Risk factors for *S. aureus* colonization at follow-up: univariate analysis

A higher proportion of patients colonized at baseline were colonized with *S. aureus* at follow-up compared with those who were not colonized at baseline ($RR = 2.95$, $P < 0.01$). Prednisone exposure and older patients were less likely to be colonized at follow-up. Prednisone use was not more common in patients taking TNF inhibitors ($P = 0.58$); however, younger patients were more likely to be exposed to TNF inhibitors ($P < 0.01$) and prednisone ($P < 0.01$). Prednisone use still decreased the risk for colonization when controlling for underlying IMIDs. Antibiotic and TNF inhibitor exposure during the study period were...
not associated with follow-up colonization in univariate analysis (P = 0.09 and P = 0.07, respectively). Patients who were colonized at enrolment were more likely to maintain their colonization at follow-up if they had been exposed to TNF inhibitors during the study (67.7% vs 49.1%, P = 0.02). In patients who were not colonized at baseline, exposure to TNF inhibitors did not increase the risk of colonization at follow-up compared with those unexposed to TNF inhibitors [26 (53.1%) vs 103 (58.5%), RR = 0.84 (95% CI 0.51, 1.38), P = 0.49].

The risk of follow-up colonization was not elevated with any individual agent (infliximab, P = 0.09; etanercept, P = 0.51; adalimumab, P = 0.55) compared with TNF inhibitor unexposed patients. The risk for colonization at follow-up was also no different in those exposed to monoclonal antibodies (infliximab/adalimumab) compared with soluble receptors (etanercept) (P = 0.58).

Risk factors for follow-up S. aureus colonization: multivariate analysis

Colonization at enrolment, age, TNF inhibitor exposure and the interaction between baseline colonization and TNF inhibitor exposure (P = 0.04) remained significantly associated with follow-up colonization. In those colonized at baseline, the OR for follow-up colonization in those with subsequent TNF inhibitor exposure was 2.17 (95% CI 1.11, 4.21) times the risk in those without TNF inhibitor exposure. This estimate was consistent when further stratified by psoriasis (OR = 2.15) and RA patients (OR = 1.9). There was no association between TNF inhibitor exposure and follow-up colonization in those who were not colonized at baseline [OR = 0.80 (95% CI 0.42, 1.51)] Having both baseline colonization and TNF inhibitor exposure was associated with follow-up colonization [OR = 6.16 (95% CI 3.71, 10.24)].

Discussion

We assessed the prevalence of S. aureus colonization among a large cohort of patients with IMIDs. At baseline, regardless of MTX exposure, the use of TNF inhibitors was not associated with colonization. However, among those colonized at baseline, subsequent exposure to TNF inhibitors increased the risk of follow-up colonization.
Patients with psoriasis were more likely to be colonized than RA patients. The previously reported prevalence of S. aureus colonization in those with psoriasis has varied, depending on whether lesional or intact skin was cultured. Most studies have cultured lesional skin, finding 50% colonization with S. aureus [16, 17]. Lower proportions of colonization have been observed when intact skin is cultured [16]. However, these studies were relatively small. We chose to culture nares and the groin, areas with less psoriasis involvement, to gain a better understanding of S. aureus colonization in non-lesional areas. Colonization prevalence in RA was similar to rates in the general population, although the proportion colonized with MRSA (4.9%) differed from reports by Gorwitz (2.0%) [8].

At baseline, colonization did not appear to differ according to immunosuppressive therapy. At follow-up, colonization was more likely in patients with baseline colonization exposed to TNF inhibitors. Follow-up colonization does not appear to be associated with specific TNF inhibitors. Further subset analyses of patients who were unexposed to TNF inhibitors and not colonized with S. aureus at enrolment indicate that TNF inhibitors are likely not a risk factor for new S. aureus colonization, but may play a role in maintaining colonization.

We identified a negative association between prednisone and colonization. This relationship may be driven by reduced prednisone use by patients taking TNF inhibitors during the study. Desrosiers et al. [18] found prednisone use is negatively associated with bacterial recovery in patients with chronic rhinosinusitis. Intranasal corticosteroid use had lower proportions of bacterial recovery (35.4% vs 61.7%, P < 0.01) in their population [18].

This study has limitations. We did not evaluate all potential sites of colonization, limiting samples to the nares and inguinal folds. Previous studies have suggested that the throat, vagina and gastrointestinal tract may be important sites for colonization [8]. Evellard et al. [19] identified 83% of MRSA-colonized patients with cultures of the nares and skin. Likely, our study failed to identify some colonization, however, this misclassification would affect all exposure groups equally and bias our results towards the null.

We are also limited by a lack of long-term follow-up data for these patients with regard to infections. It is unclear if colonized patients are more likely to suffer later infections, or if this risk is modified by immunosuppressive use. This risk of colonization has been demonstrated in other settings with immunosuppressed patients, including HIV populations, the ICU setting and in those receiving haemodialysis [10]. In the ICU, studies have found adjusted hazard ratios of 4.70 and 2.47 for subsequent S. aureus infections in patients colonized with MRSA and MSSA, respectively [10]. In the HIV population, a greater proportion (37% vs 8%) of patients colonized with MRSA developed skin and soft tissue infections [11]. One study found that 20% of ICU S. aureus nasal carriers had a positive S. aureus clinical culture within 90 days of their nasal culture; 79% cultured identical isolates [20]. Our data suggest that the use of TNF inhibitors is associated with S. aureus colonization at follow-up when colonized at baseline. Given the increased risk of serious infections posed by TNF inhibitors and its importance in host defence against S. aureus, it is plausible that persistent S. aureus colonization could represent an important risk factor for serious skin and soft tissue infection in this cohort [3, 6, 7].

In conclusion, we found high rates of S. aureus and MRSA colonization in our IMID population. Colonization prevalence was significantly higher in psoriatics as compared with those with RA. In those with S. aureus colonization at baseline, follow-up colonization was higher in patients using TNF inhibitors. It is unclear if persistence in colonization increases subsequent infection risk of IMIDs as it does in other medical settings. Further studies are warranted to evaluate this question.

### Rheumatology key messages

- Psoriatrics are more likely to be colonized with S. aureus than patients with RA.
- IMID patients with S. aureus are more likely to remain colonized if taking TNF-α inhibitors.

### Acknowledgements

Brian Andrews, Gretchen Barron, Richard Butler, Celine Croft, Melissa Denny, Korana Durham, Stephanie Ryan, Cristina Gaudio, Kelly Griffith-Bauer, Laurel Himes-Ferris, Jennifer Ku, Tim Noland, John Ost, Charles Robertson, Sarah Stanfield, Tamara Timmons and Ngoc Wasson assisted in the collection of data used in this study.

**Disclosure statement:** A.A.D. has received honoraria from Abbvie, UCB, MSD, Novartis and Pfizer for consulting and has also received research grants from Abbvie, Amgen, Pfizer, Novartis and UCB. K.L.W. has received grants from UCB Pharmaceuticals and Pfizer and advisory board fees from Amgen, Abbot, Genentech and Pfizer. All other authors have declared no conflicts of interest.

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