Staphylococcus aureus and Antibiotics in Cutaneous T-Cell Lymphoma

Lise M. Lindahl^a Lars Iversen^a Niels Ødum^b Mogens Kilian^c

^aDepartment of Dermatology, Aarhus University Hospital, Aarhus, Denmark; ^bLEO Foundation Skin Immunology Research Center, Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark;

^cDepartment of Biomedicine, Aarhus University, Aarhus, Denmark

Dear Editor,

Staphylococcus aureus (SA) is a common pathogen that may cause exacerbations in patients with dermatological diseases such as chronic skin ulcers, atopic dermatitis, and cutaneous T-cell lymphoma (CTCL). As highlighted in a recent study by Blicharz et al. in *Dermatology* [1], colonization of skin lesions and the anterior nares by biofilm-producing SA strains is associated with increased disease severity in atopic dermatitis, supporting the hypothesis that SA may fuel disease activity and the progression of inflammatory skin conditions such as atopic dermatitis.

For decades, enterotoxin-producing SA has also been suspected to play a key role in the pathogenesis of CTCL [2, 3]. This view was supported by the discovery that a majority of patients with severe disease displayed skin colonization by enterotoxin-producing SA [4–6] and the observation that treatment with antibiotics had a beneficial clinical effect in erythrodermic CTCL patients [2, 7]. In a recent study, we found that treatment for 10 days with intravenous antibiotics (cephalosporin and metronidazole) and subsequent oral treatment of 14 days with combined amoxicillin and clavulanate not only inhibited clinical disease activity but also decreased the fraction of malignant T cells in skin lesions colonized by enterotox-

in-producing SA in patients with advanced CTCL [8]. Moreover, SA toxins triggered (i) expression of oncogenic miR-155 and regulatory proteins (PD1, FoxP3, and IL-10), (ii) STAT3 and STAT5 activation, (iii) inhibition of anti-tumor cytotoxicity, and (iv) proliferation of primary malignant T cells ex vivo [8–13], suggesting a mechanistic link between SA and cancer progression in CTCL patients [14].

Taken together, these findings indicate that SA can directly and indirectly fuel disease activity in both benign and malignant inflammatory skin conditions, probably through SA-induced changes in the inflammatory environment.

As two recent studies of CTCL showed that the skin microbiome consists of complex communities of different bacterial species in addition to SA [15, 16], we reexamined the bacterial flora on lesional skin before, during, and after aggressive antibiotic treatment of the patients with advanced disease as described above [8]. Table 1 shows the dominant bacterial colonization disclosed by cultivation in six patients before (Table 1, left), during (Table 1, middle), and 3 months after termination of antibiotic treatment (Table 1, right). As reported [8], 10 days of antibiotics completely eradicated SA from lesional skin in all patients (Table 1, middle vs. left). In agreement with recent

Table 1. Dominant cultivable bacterial microbiota before, during, and after antibiotic therapy on the lesional skin of patients with cutaneous T-cell lymphoma¹

Patient number	Day 0	Day 10	3 months after termination of antibiotic therapy ²
1	<i>S. aureus</i> ST1_SEA,SEJ,α (75%) <i>S. aureus</i> no toxin (15%) <i>S. capitis</i> (5%) <i>S. haemolyticus</i> (5%) <i>S. hominis</i> (5%) <i>Stenotrophomonas maltophilia</i> (5%)	<i>Corynebacterium</i> sp. (90%) <i>Stenotrophomonas maltophilia</i> (10%)	<i>S. aureus</i> ST1-SEA,SEJ,α (50%) <i>S. capitis</i> (50%)
2	<i>S. aureus</i> ST188_SEA,SEJ,α (10%) <i>Stenotrophomonas maltophilia</i> (75%) <i>S. epidermidis</i> (5%) <i>S. lugdunensis</i> (5%) <i>S. capitis</i> (<5%) <i>S. caprae</i> (<5%)	<i>Stenotrophomonas maltophilia</i> (99%) <i>S. epidermidis</i> (<1%) <i>S. lugdunensis</i> (<1%) <i>S. capitis</i> (<1%)	<i>S. warneri</i> (60%) <i>S. epidermidis</i> (20%) <i>S. pettenkoferi</i> (10%) <i>S. lugdunensis</i> (10%) <i>S. caprae</i> (<1%)
3	<i>S. aureus</i> ST15_SEA,SEJ,α (80%) <i>S. aureus</i> no toxin (5%) <i>S. pettenkoferi</i> (5%) <i>S. capitis</i> (5%) <i>S. epidermidis</i> (<5%) <i>S. haemolyticus</i> (<5%) <i>S. hominis</i> (<5%)	<i>S. pettenkoferi</i> (85%) <i>Stenotrophomonas maltophilia</i> (10%) <i>S. lugdunensis</i> (5%)	<i>S. aureus</i> ST15_SEA,SEJ,α (20%) <i>Moraxella osloensis</i> (60%) <i>S. pettenkoferi</i> (10%) <i>Acinetobacter johnsonii</i> (10%)
4	<i>S. aureus</i> ST6_SEA,SEJ,α (90%) <i>Haemophilus haemolyticus</i> (5%) <i>Strep. pneumoniae</i> (5%) <i>Dermatobacter hominis</i> (<1%)	Non-identified gram-positive rod (75%) <i>Corynebacterium tuberculostearicum</i> (15%) <i>Paenibacillus</i> sp. (10%)	<i>Micrococcus luteus</i> (85%) <i>S. epidermidis</i> (5%) <i>S. capitis</i> (<5%) <i>Lactobacillus</i> sp. (<5%) <i>Dermabacter hominis</i> (<5%)
5	<i>S. aureus</i> ST30_SEA,SEB,SEC,SEE,SEG,SEI,SEJ,SEK,SEL,α (90%) <i>S. hominis</i> (10%)	<i>Kocuria marina</i> (60%) <i>Moraxella</i> sp. (20%) <i>Paenibacillus amylolyticus</i> (10%) <i>Roseomonas mucosa</i> (10%)	<i>S. aureus</i> ST30_SEA,SEB,SEC,SEE,SEG,SEI,SEJ,SEK,SEL,α (40%) <i>Cutibacterium acnes</i> (55%) <i>S. capitis</i> (<5%) <i>S. epidermidis</i> (<5%)
6	<i>S. aureus</i> ST188_SEA,SEE,SEH,SEI,SEJ,SEK,SEL,α (98%) <i>S. aureus</i> no toxin (2%) <i>Corynebacterium striatum</i> (<1%) <i>S. capitis</i> (<1%) <i>Stenotrophomonas maltophilia</i> (<1%)	<i>S. epidermidis</i> (97%) <i>S. haemolyticus</i> (2%) <i>Stenotrophomonas maltophilia</i> (1%)	<i>S. aureus</i> ST188_SEA,SEE,SEH,SEI,SEJ,SEK,SEL,α (40%) <i>S. aureus</i> no toxin (55%) <i>Corynebacterium striatum</i> (<5%) <i>Strep. agalactiae</i> (<5%)

¹ *S.*, *Staphylococcus*; SEA–L, staphylococcal enterotoxins A–L; α, α-toxin. The figures in brackets represent the relative proportions of the respective species. ² In patient 2, the last samples were collected 45 days after antibiotic therapy.

studies of the skin microbiome in CTCL [15, 16], untreated skin was (in addition to SA) colonized by a series of commensal bacteria (such as several coagulase-negative *Staphylococcus* species) (Table 1, left), which – for a large part – were observed also during and after antibiotic treatment (Table 1, middle and right). Of notice, SA reappeared in 4 of 6 patients after termination of antibiotic therapy (Table 1, right). In all four patients, the reappearing clone was identical to the one initially detected both by multilocus sequence type (ST) and by the toxins produced.

Thus, these findings show that (i) antibiotic treatment was associated with a complete eradication or sup-

pression to below detection level of SA but not of other species, and (ii) re-colonization of skin lesions by SA was observed in most patients shortly after termination of antibiotics. These data suggest that the effect of antibiotics on disease activity was likely associated with eradication of SA (and probably not of other species) and importantly, that lifelong anti-bacterial measures would be needed to prevent re-colonization by SA and SA-mediated disease aggravation in CTCL. Whereas aggressive antibiotic treatment is relevant in case of clinically severe and life-threatening SA infection, life-long aggressive antibiotic treatment to prevent SA skin colo-

nization is neither feasible nor is it recommendable due to the risk of side effects and the development of antibiotic resistance. Indeed, a recent study by Emge et al. [17] found a high frequency of skin colonization by methicillin-resistant SA (MRSA) in CTCL patients, stressing the risks and problems associated with long-term antibiotic treatment in CTCL. Essentially similar findings of increased risk of MRSA have been reported in atopic dermatitis [18]. Accordingly, there is an urgent need for novel non-antibiotic and highly selective anti-SA treatment modalities in order to gain life-long control of SA colonization of susceptible skin lesions in patients with malignant and benign chronic inflammatory skin diseases.

Key Message

Antibiotics may inhibit disease activity but are not recommended for long-term treatment of CTCL.

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Conflict of Interest Statement

Niels Ødum has an advisory consultant honorarium from Microcos Human Health B.V and Almirall. All other authors declare no potential conflicts of interest.

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Author Contributions

M.K., L.M.L., L.I., and N.Ø. conceived the research. L.M.L. collected the samples and M.K. performed the bacteriological analyses. M.K. and L.M.L. analyzed and made the table. M.K., L.M.L., L.I., and N.Ø. designed the research and N.Ø. wrote the paper. All authors read, commented on, and approved the manuscript.