Staphylococcus aureus (S. aureus) is one of the main infectious agents encountered in the field of dermatology, and is an aggravating factor in numerous chronic dermatoses. A large number of toxins, virulence factors and resistance mechanisms make S. aureus a potentially life-threatening bacteria, thus confronting the treating dermatologist with therapeutic difficulties. The classification of dermatological diseases caused, or partially caused, by S. aureus according to the prevailing toxin patterns of the strain, should help to develop a more efficient therapy and control of these diseases.

Introduction

Staphylococcus aureus (S. aureus) is a ubiquitous Gram-positive bacteria, typically found in grape-like clusters. Temperatures of 37°C provide ideal conditions for the spread of the bacteria as well as food sources rich in sugar. Although the bacteria does not nutritional spores, so-called “small colony variants” can be induced under restrictive growth conditions, which can survive intracellularly for longer time spans. S. aureus is potentially equipped with a large number of toxins and virulence factors, which can be transmitted via plasmid transfer or by phage transduction. Epidemically there is a prevalence of particular “basic strains” with a relatively constant reservoir of pathogenic factors, which however, under selection pressure can quickly develop changed survival characteristics (for example, altered protease production). The prevalent virulence factors include not only many different proteases, lipases, nucleases and haemolysins but also adherence factors such as protein A, as well as various matrix-binding proteins, of which the most clearly characterised are the fibronectin-, laminin- and collagen-binding proteins.

Interestingly, various regulator genes are found in the genome of S. aureus, lead by finely tuned “sensing molecules” which induce the switch of a bacteria from a primary “adherence-guided” to a secondary “toxin-guided” phenotype. Due to its manifold resistance mechanisms, S. aureus is regarded as one of the problem bacteria and is responsible for a great number of morbidities and mortalities, especially among nosocomial infections.

Summary

Staphylococcus aureus (S. aureus) is one of the main infectious agents encountered in the field of dermatology, and is an aggravating factor in numerous chronic dermatoses. A large number of toxins, virulence factors and resistance mechanisms make S. aureus a potentially life-threatening bacteria, thus confronting the treating dermatologist with therapeutic difficulties. The classification of dermatological diseases caused, or partially caused, by S. aureus according to the prevailing toxin patterns of the strain, should help to develop a more efficient therapy and control of these diseases.
The three entities described above are caused by particular subgroups of *S. aureus*, which produce well-characterized combinations of virulence factors.

Although there is overlapping in the individual diseases and the virulence factors of their associated bacteria, the classification is surprisingly homogeneous. Genetic studies on isolates suggest that it is more likely the proliferation of endemic strains than the uptake of virulence factors by “apathogenic” strains as such.

**Blister-building skin diseases caused by *S. aureus***

These clinical patterns include impetigo contagiosa or its maximum form “staphylococcal scalded skin syndrome” (SSSS, Morbus Ritter von Rittershain, dermatitis exfoliativa neonatorum), as well as bulla repens. The underlying cause of all these diseases is infection with *S. aureus* strains producing the exfoliative toxins ET-A and ET-B. These exfoliative toxins, in the form of serine protease, split the epidermal desmoglein 1 at a defined rupture point and cause a histopathological pattern similar to pemphigus foliaceus (Amagai et al. 2000) (Fig. 2).
The first clinical sign of staphylogenic impetigo is a slack blister, which soon ruptures and heals, leaving a crust containing pus. This honey-coloured crust is characteristic of impetigo, which has a predilection for the face, often affecting the corners of the mouth (angulus infectious), the folds of the skin and the extremities. Impetigo mostly occurs during the warm spring and summer months and is, as its name infers, highly contagious. Its pattern ranges from single to multiple lesions or areas of erosion and crusts. The patient's overall condition is normally only slightly affected, or not at all. General symptoms such as fever, chills and changes in the blood picture indicate that the infection has reached the blood, an indication for immediate systemic antibacterial treatment.

Figure 2: Impetigo contagiosa (a) caused by *S. aureus*, with a clinically similar appearance to pemphigus foliaceus (b). In both cases desmoglein is split in the upper epidermis.

Bulla repens is a particular type of infection in which pus-filled blisters repeatedly occur at the ends of the fingers, probably an indication of repeated re-inoculation with persisting strains. Despite the localized pattern of this disease, a systemic antibiotic should be considered due to the inclination to re-infection.

In typical cases of impetigo, where there are only few individual erosions or crusts, it is usually difficult to decide whether topical or systemic antibiotic therapy is appropriate. Experience has shown that in the case of localized disease areas (up to three lesions) topical treatment is the method of choice, and in the case of disseminated lesions (more than three lesions), systemic therapy is the preferred treatment, thus shortening the course of the infection and the reducing the risk of autoinoculation or spreading amongst peer groups. Apart from adequate topical treatment, antiseptics should be used (see Table 1) according to the pattern of the infection (localization, age, etc.). The patient may return to school or kindergarten the day after adequate antibiotic therapy has been initiated.

The maximum form of the disease, dermatitis exfoliativa (also known as staphylogenic Lyell syndrome) mainly affects younger children in infancy, but can also affect patients with weakened immune systems in intensive care units. In this case the pus-filled crusts are lacking, but there are instead fulminant blisters, causing large parts of the epidermis to disintegrate. It is difficult to clinically differentiate from medication-induced Lyell syndrome, but this can be clarified by histological examination of the surface of the blister (a cryosection for fast diagnosis). Whereas the whole of the epidermis is raised due to necrotizing keratinocytes in medication-induced Lyell syndrome, in staphylogenic Lyell syndrome intraepidermal splits form, as in pemphigus foliaceus. The large areas of detached skin constitute a significant risk factor of secondary colonization with (very often multiresistant) nosocomial bacteria. Antibiotic treatment should, as well as following the generally expedient guidelines (see Table 2), also be administered according to the prevailing resistance situation in the patient's surroundings (e.g., intensive care unit).

Patients should also be treated according to the therapy criteria for burn patients with large surface area burns. Apart from adequate intravenous fluid replacement and the avoidance of hypothermia, sufficient pain medication and antiseptic covering of the erosions are indicated.

Abscesses-forming skin diseases caused by *S. aureus*

*S. aureus* is the main pathogenic organism in abscess-building skin diseases due to its ability to produce many degrading enzymes. Clinically, these diseases range from folliculitis, furuncles, carbuncles to abscesses, but also to the rare perifolliculitis.

A high average incidence of a particular virulence factor, Panton-Valentine leucocidine (PVL), was found in studies performed during the past years on *S. aureus* isolates from abscess pus. Besides skin abscess formation, this toxin plays a particular role in necrotizing pneumonia caused by *S. aureus*, and has been associated with the so-called “community acquired” MRSA strains (CA-MRSA) in epidemiological studies. These strains typically possess the gene for chromosomal meticillin resistance (MecA), which encodes for carboxypeptidase, but they lack the frequent multiresistance found in “hospital-acquired” MRSA strains. Irrespectively, these CA-MRSA strains are associated with high morbidity and mortality in infections of the respiratory tract (Issartel et al. 2005). It is unclear whether PVL plays a causal role in the formation of abscesses or whether it is a marker of particular virulence characteristics of dominant strains, as apart from the toxic effect on
neutrophiles (leucocidine) no further descriptive characteristics have as yet been established.

The clinical spectrum ranges from pustular abscesses in the hair follicles (foliculitis), which progress to larger accumulations of pus surrounding the hair follicle (furuncles) and then to a pus-filled confluence of several furuncles, culminating in a chambered abscess. Independent of the hair follicle openings, actual abscesses can form due to infection in preformed cavities (epidermoid cysts, infected haematoma).

In all of these diseases the main priority is the primary opening of the cavity and pus drainage. Furuncles of the face above the connecting line from the corners of the mouth to the earlobes are an exception to this rule; if these drain into the blood, they will drain into the sinus cavernosus, which can lead to thrombosis. In such cases systemic antibiotics is indicated, preferably intravenously.

The abscess cavity should be completely emptied by making an adequate opening with a sterile scalpel or by punch biopsy. The cavity containing pus should then be antisepically rinsed (with polyvidone solution or hydrogen peroxide, for example) and kept open using a clip (a polyvidone gauze strip is suitable) to allow for drainage. Systemic antibiotics is not necessary in most cases, and should be restricted to patients with general symptoms (fever, shivering, and signs of inflammation of the blood). In skin infections which do not fluctuate, ointments containing ichthyl, which lead to “maturation”, e.g. degradation of the skin nodes can be applied. However, exact conceptions of how these ointments work and the proof of their effectiveness in controlled studies are lacking.

Staphylococcus aureus and atopic eczema

The role of S. aureus in sustentation and exacerbation of atopic eczema (AE) is complex and takes place on various levels.

Colonization

The skin of patients with AE varies significantly from healthy skin with regard to colonization by S. aureus. While healthy skin, with the exception of chronic carriers of S. aureus in endemic areas, is rarely (2-25 %) colonized with S. aureus, the bacterium is found in 76-100 % of patients with AE, varying according to the study. Interestingly, this chronically increased rate of colonization is found not only on lesional, eczematous skin, but also on non-lesional areas of skin; this fact is a specific characteristic of patients with AE (Leyden et al. 1974).

S. aureus strains that are isolated from the skin of patients with AE appear to persist there in a specific manner; often the same strains appear again after weeks and months of extensive antibacterial treatment. The nasal entrance (including the nares), the inguinal region and the axillae act as S. aureus reservoirs that are responsible for the persistence of the pathogen, despite adequate treatment (Hoeger et al. 1992). As well as the persistence of staphylococci in these niches, the bacteria are transferred back and forth between the patient and their main persons of contact (ping pong effect). This is presumably the main reason for the low eradication rate in children. Apart from the increased numbers of bacteria in S. aureus colonies, there is a notable shift in the cutaneous bacterial flora in patients with atopical eczema. The predominant corynebacteria and coagulase-negative staphylococci strains found in patients with healthy skin are significantly reduced in patients with atopic eczema. This finding suggests that S. aureus has a local growth advantage over possible antagonistic apathogenic bacterial strains on AE skin.

S. aureus is usually found at a concentration of about $10^5$ colony-building units (CFU/cm²) on lesional skin. However, the concentration can increase to $10^7$ CFU/cm² and is thereby 1000 times higher than on non-lesional skin. An exponential increase in S. aureus on lesional skin (impetiginous eczema) is a common complication in atopic eczema requiring systemic antibiotic treatment and occasionally even hospitalization of the patient.

The mechanisms that allow S. aureus to permanently colonize the skin have been partly clarified in the past years. The bacteria produce different adhesins, including Protein A, “clumping factor”, coagulase and matrix-binding proteins, of which the central role is played by the fibronectin-binding proteins (Mempel et al. 1998). This virulence factor is encoded by two different gene loci. Experiments with knock-out mutants were able to show that S. aureus binds to the matrix protein fibronectin with the aid of this virulence factor (Cho et al. 2001). This mechanism appears to be pivotal for the adherence of S. aureus to cultivated keratinocytes and the colonization of inflamed skin. Interestingly, this adhesion process is supported by pH values of between 7 and 8, an environment typical of atopic skin with a dysfunctional barrier function (Cheung and Projan 1994). What is more, the expression of fibronectin is regulated by IL-4, the central TH2 cytokine, which is found in higher concentrations in patients with atopic eczema.
**Virulence factors**

Within the large group of virulence factors, the staphylococcal superantigens definitely deserve special attention. These proteins contain certain promitotic and pro-inflammatory protein sequences, which activate human as well as murine T cells. As they bind outside the conventional MHC binding groove, they are able to link certain MHC II molecules with a series of defined β-chains of the T cell receptor (TCR Vβ) and thereby bring about a clonally non restricted activation of T cells, thereby amplifying T cell activation in atopic eczema. These staphylogenetic toxins are therefore termed “superantigens”. The superantigens include the enterotoxin SEA to SEO (however, the list is still probably incomplete) as well as “toxic shock syndrome toxin 1” (TSST 1) (Jarraud et al. 2001).

Many studies carried out since the discovery of the superantigens have been able to show their pathophysiological role in the immunology of atopic eczema. The following mechanisms have been identified in detail:

1. T lymphocytes of patients with atopic eczema express the decisive “skin homing receptor CLA”, when stimulated with staphylococci superantigens. This process is mediated by interleukin (IL)-12.

2. A proportion of patients with atopic eczema develop IgE antibodies against staphylococci antigens, so that these must not only be seen in their role as effective toxins but also as potent antigens.

3. When superantigens are applied to atopic skin, erythema and infiltration can be provoked, typical physical characteristics of eczema. The skin of mice injected with the superantigen “staphylococcal enterotoxin B” (SEB) also develops a typical eczematous appearance. If SEB is applied to atopic skin using Finn Chambers (similar to an epicutaneous test), T cells infiltrate that carry super antigen-responsive T cells (TCR Vβ3, 12 and 17) around their receptor. Most of these T cell Vβ families are over-expressed in the peripheral blood and lesional skin of patients with atopic eczema.

4. Superantigens induce the steroid receptor GRO-β on infected cells. The increased expression of this receptor is made responsible for the reduced response to steroids, thereby intensifying the chronicity of the disease.

5. Superantigens are able to increase IgE production via their MHC II binding on B cells (which are in parallel good antigen-presenting cells).

**Host-specific factors**

Apart from the analysis of possible virulence factors pertaining to the bacteria, the question arises as to why in patients with atopic eczema, control of colonization and elimination of *S. aureus* are dysfunctional. In normal human keratinocytes, after contact with *S. aureus* or one of its components, a series of defence mechanisms are activated, predominantly those of the innate immune system. The immunological reaction is mainly directed against constituent parts of the bacterial cell wall, such as peptidoglycan (PGN) and lipoteichoic acid (LTA). The activation of the keratinocytes by staphylococcal proteins usually takes place via so-called “pathogen associated molecular pattern recognition molecules”, of which the best-known is the Toll-like receptor family (TLRS). Various defence mechanisms are activated following specific stimulation by bacterial constituents, in particular IL-8 and the inducible NO-synthetase (iNOS) as well as antimicrobial peptides such as the human β-defensin (HBD) 2 and 3 and LL37. The majority of these defence mechanisms is subject to positive regulation by TH1 cytokine IL-1β, interferon(IFN)-γ, and tumour necrosis factor (TNF)-α. TH1 cytokines are found in low concentrations on the skin of patients with atopic eczema. As a result, on atopic skin, in comparison to other inflammatory skin diseases such as psoriasis, fewer anti-staphylogenetic substances such as HBD2, HBD3, LL37, iNOS and IL-8 are produced. This recently published concept might at least partially explain the findings of increased colonization by *S. aureus* in the findings atopic eczema (Ong et al. 2002).

**Treatment**

In *S. aureus* infections the basic question is whether systemic or topical therapy is appropriate. This should be decided after assessment of the dissemination of the infection, the general symptoms, and the possible transmission to third persons. It is unhelpful to set up general guidelines; however, in cases of systemic infection presenting with fever, shivering, increased CRP or even signs of sepsis, systemic treatment should be administered. Systemic antibiosis is also advisable in cases where the infection has spread to other regions of the body, in cases of persistent infection and in the case of recurrence.
Topical treatment

If topical treatment is indicated, it is important to distinguish between an antiseptic (unspecific antimicrobial) and antibiotic (specific antibacterial) treatment. Antiseptic therapies make sense as an accompanying measure, e.g. in the case of systemic antibiosis or as a prophylactic against recurrence, but are often not effective as bactericides. Suitable substances are chlorhexidine (1-2 %), triclosane (1-2 %) and octendine (0.1 %) (Table 1), which can be added to skin protection products or solutions. In addition, isolated super-infections can be treated with antiseptic dyes. If triclosane is used to treat large surface areas in children, the risk of systemic resorption must be taken into consideration. At present, the use of preparations containing silver and their antiseptic effects on *S. aureus* is being studied.

Fusidic acid, retapamulin and mupirocine are the main substances available for use in topical antibiosis, whereby the latter should be restricted to eradication therapy on multi-resistant strains in the intensive care unit. Retapamulin, which is a pleuromutilin antibiotic, is, unlike fusidic acid, not only very effective against *S. aureus*, but is also satisfactorily effective against Group A streptococci. Fusidic acid, in turn, has the advantage that despite the finding of plasmid-encoded resistance in vitro, a high antibiotic concentration in vivo is often still effective. Noncritical application of any topical antibiotic treatment always leads to increased resistance, a phenomenon that can be observed at present in the case of fusidic acid, so that future usage of topical antibiotics is very much dependent on local preferences suited to the resistance situation. Apart from the above-mentioned substances, aminoglycosides and macrolides are specified for topical use. These are, however, unsuitable due to their allergizing potential (aminoglycoside) or the unfavourable resistance situation (macrolide).

As a consequence of the above-listed points, the use of fusidic acid, respectively retapamulin is justified, should topical antibiotic treatment be validly indicated.

In particular, antibacterial textiles provide an interesting alternative in topical supportive treatment of *S. aureus* in atopic eczema. At present these materials are available as silver-coated microfibres and antiseptic-coated silk. Both “intelligent” textiles provide good antistaphylococcal effectiveness and high comfort.

Table 1: Substances suitable for local antiseptic therapy

<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Triclosan 1-2 %</td>
<td>• Bactericidal</td>
<td>• In low concentrations antibiotic activity</td>
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<tr>
<td></td>
<td>• Slight irritative (photo) allergic/toxic potential</td>
<td>• (Enoyl reductase)</td>
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<tr>
<td></td>
<td>• Low toxicity</td>
<td>• Questionable resorption</td>
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<tr>
<td></td>
<td>• Good in hydrophobic creams/ointments</td>
<td></td>
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<tr>
<td>Octenidine 0.1 %</td>
<td>• Bactericidal</td>
<td>• Only available as a solution (compresses)</td>
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<tr>
<td></td>
<td>• Low toxicity</td>
<td>• No data for children under 8 years</td>
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<tr>
<td></td>
<td>• Good for use on mucous membranes</td>
<td></td>
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<tr>
<td>Chlorhexidine (digluconate) 0.5-2 %</td>
<td>• Bactericidal</td>
<td>• Inactivated by blood and pus</td>
</tr>
<tr>
<td></td>
<td>• Slight allergizing potential and toxicity</td>
<td>• Questionable resorption</td>
</tr>
<tr>
<td></td>
<td>• Good in creams</td>
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</table>

Systemic treatment

As systemic treatment must often be commenced without an antibiogram, initial treatment with a β-lactamase-stable penicillin or a first generation cephalosporin for at least 10 days is recommended. If the patient is allergic to penicillin, clindamycin, which is often used for multiresistant strains, is a suitable choice. If a detailed antibiogram is available, the effectiveness of the initial treatment should be evaluated (Fig. 3).
In cases of MRSA skin infection there should be no strict indication for treatment. For instance, MRSA colonization of a crural ulcer in out-patients is not an indication for systemic antibiotic. However, if such treatment is indicated, it should be carried out according to an antibiogram. Glycopeptide antibiotics are an empirical alternative, for example vancomycin or teicoplanine. Linezolid has been available for some years as a reserve antibiotic, but it should only be used in intensive care (Table 2).

### Table 2: Suitable antibiotic treatment of *S. aureus* infections with possible alternatives

<table>
<thead>
<tr>
<th>Evidence of MRSA</th>
<th>Initial therapy</th>
<th>Penicillin allergy</th>
<th>Available as juice</th>
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<tbody>
<tr>
<td>1998</td>
<td>• Penicillin-stable penicillins (50 mg/kg) (Flucloxacillin Staphylex©, Dicloxacillin Infectostaph®)</td>
<td>• Clindamycin (20-30 mg/kg)</td>
<td>• Staphylex© Juice, Cephalexine TS©, Cefaclor Panoral®, Loracarbef Loraem®, Cefixime Cephoral®, Sobeline Granulate®</td>
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<td>2003</td>
<td>• Cephalosporins (1st Gen.) (30-50 mg/kg) (Cefaclor, Cefalexine, Cefadroxil, Locarbacef)</td>
<td>• Macrolide antibiotics (30-50 mg/kg)</td>
<td></td>
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<tr>
<td></td>
<td>• Clindamycin (50 mg/kg)</td>
<td>• Vancomycin</td>
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<td></td>
<td>• Moxifloxacin</td>
<td>• Linezolid (strict indication)</td>
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<tr>
<td></td>
<td>• Doxycycline</td>
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<td></td>
<td>• Erythromycin</td>
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<td></td>
<td>• Oxacillin/Cephalosporins</td>
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<td></td>
<td>• Pefloxacin</td>
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<tr>
<td></td>
<td>• Clindamycin</td>
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<tr>
<td></td>
<td>• Macrolide antibiotics</td>
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<tr>
<td></td>
<td>• Vancomycin</td>
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<tr>
<td></td>
<td>• Linezolid</td>
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Conflict of interest
The author declares that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

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**Question 1**
Diagnosis of *S. aureus* is performed using smears cultured on to:
- a. Blood agar
- b. Chocolate agar
- c. Löwenstein-Jensen agar
- d. Sabouraud agar
- e. Oil agar

**Question 2**
Which toxin is not produced by *S. aureus*?
- a. Haemolysin
- b. Enterotoxin
- c. Epidermolysin
- d. Leucocidine
- e. All are produced by *S. aureus*.

**Question 3**
Unlike in furunculosis strains, which of the following is typically found in impetigo strains?
- a. An accumulation of toxins with superantigen characteristics.
- b. Antibiotic multiresistance.
- c. Exfoliatotoxin A or B.
- d. The Panton-Valentine leucocidine gene.
- e. Protein A on the surface of the bacteria.

**Question 4**
Which of the following is atypical in patients with atopic eczema?
- a. Colonization with *S. aureus* in the affected areas.
- b. Colonization with *S. aureus* in the unaffected areas.
- c. Persistent colonization with identical strains.
- d. The reactive upregulation of the cutaneous defensins HBD2 and HBD3.
- e. Colonization of the nares.

**Question 5**
Which of the following diseases are not induced/aggravated by *S. aureus*?
- a. Carbuncle
- b. Bulla repens
- c. Morbus Ritter von Rittershain
- d. Impetigo herpetiformis
- e. Abscess-forming pneumonia

**Question 6**
The product of choice for the systemic treatment of skin diseases caused by *S. aureus* is:
- a. Tetracycline
- b. Macrolide
- c. Penicillinase-stable penicillins
- d. Gyrase inhibitors
- e. Aminoglycosides

**Question 7**
Which substance should not be used for topical treatment of chronic *S. aureus* infections?
- a. Triclosane
- b. Chlorhexidine
- c. Netilmicin
- d. Octinidine
- e. Silver

**Question 8**
Which of the following apply to fusidic acid?
- a. Significant changes in resistance are not to be expected with widespread use.
- b. It is an alternative to mupirocin.
- c. It is very effective against staphylococci and streptococci.
- d. It is the substance of choice for systemic treatment of cutaneous staphylococci infections.
- e. It is effective in higher doses in vivo, although there are signs of resistance in vitro.

**Question 9**
Which statement is incorrect?
Superantigens
- a. are exclusively produced by staphylococci,
- b. preferentially interact with certain Vβ-chains of the T cell receptors,
- c. lead to a massive output of cytokines,
- d. are an independent provocation factor in atopic eczema,
- e. in the intestines are responsible for diarrhoea.

**Question 10**
Which statement is incorrect?
Impetigo contagiosa
- a. mainly occurs in the warm months,
- b. is equally frequently caused by *S. aureus* and *S. pyogenes*,
- c. should be treated topically or systemically according to the area affected,
- d. is often found at the corners of the mouth,
- e. does not typically affect the general condition of the patient.