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CASE REPORT

Current Microbiological, Clinical and Therapeutic Aspects of Impetigo

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Abstract

Impetigo is a highly contagious infection of the epidermis, seen especially among children, and transmitted through direct contact. Two bacteria are associated with impetigo: *S. aureus* and *GAS*. Over 140 million people are suffering from impetigo at each time point, over 100 million are children. Two forms of impetigo exist, namely impetigo contagiosa, known as the non-bullous form and the second one being bullous impetigo which presents with large and fragile bullae. Treatment options for impetigo include systemic antibiotics, topical antibiotics as well as topical disinfectants.

List of Abbreviations

EDIN: Epidermal Cell Differentiation Inhibitor; ETA: Exfoliative Toxin A; ETB: Exfoliative Toxin B; GAS: Group A Streptococcus (*Streptococcus pyogenes*); MRSA: Methicillin Resistant *Staphylococcus aureus*; MSSA: Methicillin Sensitive *Staphylococcus aureus*; MSCRAMM: Microbial Surface Component Recognizing Adhesive Matrix Molecules; OR: Odds Ratio; PMN: Polymorphonuclear Cells; PSGN: Poststreptococcal Glomerulonephritis; RBC: Red Blood Cell; SSSS: Staphylococcal Scalded Skin Syndrome

Introduction

Impetigo is a common acute superficial bacterial skin infection (pyoderma) which is highly contagious. It is characterized by pustules and honey-colored crusted erosions ("school sores"). Impetigo involves the epidermis and is seen mostly in preschool children. It is caused by two microorganisms: *S. aureus* and *GAS*.

Other bacterial infections that involve deeper parts of the skin are erysipelas and cellulitis. Erysipelas involves the upper dermis and is most commonly caused by b-hemolytic *streptococci*. Cellulitis involves the deeper dermis and subcutaneous fat and is most commonly implicated by *S. aureus* and *GAS*. It can be divided into nonpurulent and purulent cellulitis, and treatment is based on extent of infection and risk factors. Abscesses involve the dermis and deeper skin tissues as a result of pus formation.

Impetigo is observed most frequently among children 2-5 years of age and is transmitted through direct contact [1]. Risk factors for impetigo include poor hygiene, low economic status, crowding and underlying scabies [2,3]. Important consideration is carriage of GAS and *S. aureus* which predisposes to subsequent impetigo [4]. Over 140 million people are suffering from impetigo at each time point, over 100 million are children [5,6]. In the past impetigo was caused by either *S. aureus* or group A β-hemolytic *streptococci*. Currently, however, the most frequently isolated pathogen in cases of impetigo is *S. aureus* [7].

The first type of impetigo is impetigo contagiosa, known as non-bullous impetigo and this it is one of the most common skin infection in children [8].

Differential diagnoses for this type are atopic dermatitis, candidiasis, contact dermatitis and other [9].

The second type of impetigo, bullous impetigo, is caused exclusively by *S. aureus.* Differential diagnosis for this type is bullous erythema multiforme, bullous lupus erythematosus, bullous pemphigoid etc [9-11].

Treatment options for impetigo can be divided into topical and systemic. Among topical, mupirocin and fusidic acid are most commonly used. Systemic antibiotic is usually reserved for more severe cases, in which topical therapy is impractical, such as cases of bullous impetigo or widespread lesions [12].

The aim of this review is to present the current mi-

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crobiological knowledge of the two organisms mentioned with the relevant virulence factors that enable to initiate skin diseases and how they contribute to the clinical presentation, as well as to show the clinical presentation itself. Lastly, this review will discuss the various treatment options and emerging resistance.

Epidemiology

Over 140 million people are suffering from impetigo at any time point; 100 million are children [5,6].

In the United Kingdom, the annual incidence of impetigo was 2.8 percent in 2003 among children up to the age of four and 1.6 percent among children aged five to fifteen years [1].

Although incidence estimations do exist, they are all based on a limited literature review of impetigo in the context of larger studies and no update has recently been done [8,9].

Furthermore, the most available data arrives from records of hospital departments, which may under represent the true population prevalence of skin diseases [13-18].

Another cross sectional study which took place (n = 265, relative prevalence 5.3%, among 50,237 outpatients) showed a pattern of male predominance in childhood, adulthood and overall (OR 2.0) [19].

Impetigo is a highly contagious infection, direct contact being the main mode of transmission. Patients with impetigo can easily inoculate themselves and spread the infection to people in close contact after excoriating an infected area. This fact may lead to a rapid dissemination of infection, mostly in grade schools, kindergartens, nurseries and day care centers. It is known today that children usually become infected through contact with other children; however, fomites are another important source of infection. Adults may develop impetigo from contact with children or by fomites as seen when sharing grooming devices, in barber shops, in beauty parlors etc [20].

The incidence of impetigo is greatest during the summer time due to the close contact among children [21].

Interestingly, in tropical regions *GAS* causes impetigo, while in temperate areas it leads to pharyngitis [22].

Microorganisms Associated with Impetigo

GAS

GAS, a gram positive bacterium, whose reservoirs are the human mucosal membranes and skin surface, causes an array of infections involving the respiratory tract and soft tissues, ranging in severity from mild to severe. Moreover, it initiates two nonsuppurative sequels: Acute rheumatic fever and PSGN [23].

The capsule, made from hyaluronic acid, functions as an accessory virulence factor. It prevents phagocytosis by PMN and macrophages of the host. A great variation exists with regard to the level of encapsulation.

The capsule possessed by *GAS* is similar chemically to the one found in the connective tissue of humans. Hence, it is a poor immunogen, and no antibodies production has been demonstrated in humans against this structure [24,25].

The major somatic virulence factor of *GAS* is protein M. This protein is known to confer resistance to phagocytosis by PMNs. It also gives *GAS* the ability to multiply quickly in fresh human blood and to initiate diseases [26].

Recent reports have demonstrated that pili are involved in the formation of biofilms and in the adherence of *GAS* to human tonsils, keratinocytes, lung and throat epithelial cells, which distinguishes it as a major adhesin of the organism [27].

GAS possesses numerous extracellular products during its growth both *in vivo* and *in vitro* (such as hemolysin), however, only a limited number have been well characterized. Two types of hemolysin have been described in the literature. The first hemolysin is streptolysin O. This molecule can be inhibited in a reversible manner by oxygen and irreversibly by cholesterol. Apart from being toxic to RBC, it is toxic to other cells and some cell fractions, such as PMNs and platelets. The production of streptolysin O occurs in almost all strains of *GAS*, as well as in many organisms classified in groups C and G and it is antigenic in origin. The measurement of antibodies targeted to streptolysin O in the human sera can indicate recent streptococcal infection. The second hemolysin to be described is streptolysin S, obtained by strains that grow in the presence of serum [23]. Biopsies taken from pyodermal lesions often reveal *GAS*. To a much smaller extent, there is involvement of serogroups C and G. *GAS* associated with impetigo is different from those which are connected to pharyngitis and tonsillitis. Skin strains belong to different M serotypes than the classic throat strains. Various tests, seeking streptococcal antibodies play no part in the diagnosis of impetigo; however, they can support the evidence of recent streptococcal infection in patients with suspicious PSGN. The response of anti-streptolysin O to *GAS* in patients with impetigo is relatively weak, probably due to inhibition of streptolysin O by skin lipids, such as cholesterol [28-31].

Staphylococcus aureus

Members belonging to *staphylococcus* genus are gram positive cocci, with a diameter ranging between 0.5 to 1.5 µm, and occur singly and in pairs, tetrads, short chains and irregular grapelike clusters. *Staphylococci* are not motile, are not spore-forming and are usually positive to catalase [32].

S. aureus is a highly successful opportunistic patho-

gen. It frequently colonizes the mucosal surfaces and the skin. It is found in 30% of the healthy human population within the anterior nares [33]. *S. aureus* causes a wide variety of diseases. Apart from infections where it is physically present, *S. aureus* can cause "distant" diseases, through the secretion of various toxins. Those toxins may either be produced in a direct way by the bacteria on the surface which it colonizes or in an indirect manner through the colonization of food or beverages. The ability of the bacterium to cause many different diseases is related to its capacity to adapt and survive in a great variety of environments [34].

Skin infections, together with respiratory tract ones, are the most common infections caused by this pathogen. Infections of the respiratory tract are mostly nosocomial, whereas those of the skin are usually community acquired. Pneumonia caused by *S. aureus* usually develops in hospitalized patients with an underlying condition, such as immune deficiencies or infections caused by different viruses. This bacterium may also cause a variety of other, sometimes severe as well as life-threatening diseases; among them are infective endocarditis, osteomyelitis, SSSS and toxic shock syndrome [35].

Initiation of various skin infections is done through ETA and ETB which are active serine proteases produced by some strains of *S. aureus.* While ETA is encoded on a prophage, ETB is encoded on a large penicillinase-type plasmid. ETA and ETB lead to epidermal cleavage, through the effect on desmogelin-1 which is a desmosomal cadherin. This cleavage is directly responsible for the clinical manifestation of the blistering skin disease: Pemphigus neonatorum and/or generalized staphylococcal scalded skin syndrome (SSSS) in neonates, and bullous impetigo in young children and adults [36].

Although similar dermatologic effects exist, strains producing ETB are assumed to be more virulent. Reports have shown that the activity of ETB can be enhanced by EDIN, which facilitates the formation of disseminated foci and serves a risk factor for deep-seated staphylococcal tissue infections following bacteremia [36].

In order to make a diagnosis based on phenotypic characteristics, and to reveal new, yet unknown mechanisms which confer antibiotic resistance, it is crucial to obtain a culture. Colonies grown should be Gram stained and subcultured and further tested for their genus, species, as well as antibiotic susceptibility [35].

Out of the clinical isolates of *S. aureus*, over 90% have elaborated a capsule made of polysaccharides. The capsule was found to exist among 11 serotypes. 75% of clinical infections are attributed to capsule type 5 and type 8. These two are composed of different sugars, among them are fucose and mannose. Both these capsules have antiphagocytic properties and lead to an increase in virulence in several animal models. Animal models of sepsis have shown that antibodies against these capsular types are protective. Although the vaccine showed some promise in an initial Phase 3 trial in ESRD patients on hemodialysis, it was found to be ineffective in a second Phase 3 trial, leading to its development being halted [37].

Various surface adhesins are carried by *S. aureus*. These permit the adherence to different host matrix proteins. Those microbial surface components which react with the adherence matrix molecules are reassembled under the acronym MSCRAMM. Most of these molecules are bound to the peptidoglycan component of the cell wall. A conserved mechanism which permits the anchoring of the adhesive molecule exists in gram positive bacteria. This mechanism involves a membrane bound enzyme, called sortase, which has the ability to recognize a conserved amino acid motif (LPXTG) at the carboxyl terminal end of wall attached proteins. Sortase binds the threonine residues of LPXTG in a covalent way to a free acceptor in the peptidoglycan side chain, usually glycine in the case of *S. aureus* [38,39].

Among the MSCRAMM, clinical significance is attributed to clumping factor B, which assists in the colonization of the nasal epithelium, clumping factor A and fibronectin binding proteins A and B which play a role in the development of endocarditis as well as in ventricular assisted device-related infections. It is important to note that *S. aureus* harbors many MSCRAMMs at their surface. Hence, inactivation of only one molecule may not be noticed as its function can be complemented by others [40-42].

In a study conducted on 60 patients with impetigo, only one patient grew *GAS*, six grew *S. aureus* and *GAS* and the rest had *S. aureus.* It is important to note that problems may be encountered when interpreting the results of skin culture and wound, as they are not sterile, and the detection of a common colonizing organism, for example *S. aureus*, may point to a contamination. In another study, cultures containing *GAS* solely were found in two out of 71 patients with impetigo [43].

Clinical Aspects of Impetigo

Impetigo is a highly contagious infection with direct contact being the main mode of transmission [44].

As previously mentioned, children are the main ones to present with impetigo. Further populations that commonly suffer from impetigo are the homeless and patients who received organ transplants. An investigation of renal transplant recipients has found that impetigo was prominent in the first year following the transplant, with a peak being in the third month, and it did not affect a considerable number of recipients after the first year following the transplantation [45].

The most common locations for the lesions are head and neck (65.4%), followed by upper extremity (19.6%) and trunk and lower extremities (7.5% each) [19].

Diagnosis

Impetigo contagiosa typically presents with a single, two to four mm erythematous macule, which quickly becomes vesicular or pustular. Due to their delicacy, the vesicles can easily rupture, leaving an exudate with a characteristic "honey-colored" yellow crust over the superficial erosion. Several individual or coalesced macules and patches erupt due to the direct extension of the primary lesion which quickly follows. The macules and patches may be eroded or crusted [21].

When *GAS* is in high number, pustules with a thick wall and with an erythematous base are an early manifestation [46].

The nares and the perioral region are the surfaces that are subjected to environmental trauma and are involved most often. Very often, a linear distribution may be observed when the patient's fingernails have scratched the skin. Most often the patients only show skin lesions; however, mild lymphadenopathy is a systemic symptom which is frequently encountered [47,48].

An important complication of impetigo contagiosa is acute PSGN, which affects up to 5% of the patients. Few strains of streptococcus are known to commonly affect the kidney, among them are serotypes 1, 4, 12, 25 and 49 [49].

Appropriate treatment with antimicrobials is generally believed to have no effect on the risk of PSGN [47] (Table 1).

Bullous impetigo, the second type of disease presentation, is caused exclusively by *S. aureus* [9-11]. It is characterized by fragile, large, flaccid bullae that can rupture and ooze yellow fluid. It often resolves within a period of two to three weeks without scarring [12].

This form of impetigo most frequently affects the neonates, and *S. aureus* can be isolated from the skin lesions. At first the large and fragile bullae can develop on the trunk and extremities, and it may also affect the anogenital area and buttocks of infants, being one of the most common causes of ulceration in these regions. Most frequently, only remnants of the bullae are seen, and they are observed as oval or annular superficial erosions with typical collaret of scale at the periphery of the bulla [50].

An epidermal separation often occurs due to an exotoxin produced by the pathogen, often made by phage group 2 [51]. *S. aureus* ETA and ETB, which show extreme specificity in causing loss of cell adhesion in the superficial epidermis, brings about the formation of blisters by splitting the granular cell layer of the epidermis [52] (Table 2).

Treatment

Topical antibiotics, systemic antibiotics and topical disinfectants are all considered treatment options for impetigo [10].

A research which demonstrates the most effective treatment is still lacking [1].

For cases of limited impetigo, studies have shown that topical antibiotics are more effective than placebo and are preferable to oral antibiotics [1,53].

It should be noted that systemic antibiotics are usually reserved for severe cases, in which administration of topical therapy is not practical as in situations when large number of lesions appear. In all cases, the ideal treatment should be effective, with limited adverse effects, inexpensive and should not promote bacterial resistance [10,48,54].

Table 1: Differential diagnoses of impetigo contagiosa [9].

Diagnosis	Distinguishing features
Atopic dermatitis	Chronic or relapsing pruritic lesions and abnormally dry skin; there is marked lichenification on the flexural areas which distinguishes it from impetigo
Candidiasis	Erythematous papules or red, moist plaques; unlike impetigo, this disease is usually confined to the mucosal surfaces and intertriginous areas
Contact dermatitis	Pruritic areas with weeping on sensitized skin that comes in contact with haptens (e.g.- poison ivy)
Dermatophytosis	Lesions may be scaly and red with slightly raised "active border" or classic ringworm; or may be vesicular, especially on feet
Discoid lupus erythematosus	Well-defined plaques with adherent scale that penetrate into hair follicles
Ecthyma	Crusted lesions that cover an ulceration, unlike impetigo in which there is an erosion only. The ulceration may persist for weeks and may heal with scarring as the infection extends to the dermis
Herpes simplex virus	Vesicles on an erythematous base that rupture to become erosions covered by crusts, usually on the lips and skin
Insect bites	Papules usually seen at site of bite, which may be painful; there may be an associated urticaria, which is not typical for impetigo
Pemphigus foliaceus	Crusts with occasional vesicles, usually starting on the face in a butterfly distribution or on the scalp, chest and upper back as areas of erythema, scaling, crusting, or occasional bullae
Scabies	Lesions consist of burrows and small, discrete vesicles, often in finger webs; nocturnal pruritus is characteristic
Sweet's syndrome	Abrupt onset of tender or painful plaques or nodules with occasional vesicles and pustules
Varicella	Thin-walled vesicles on an erythematous base that start on trunk and spread to face and extremities; vesicles break and crusts form. Unlike impetigo, in varicella the lesions are in different stages

Table 2: Differential diagnoses of bullous impetigo [9].

Diagnosis	Distinguishing features
Bullous erythema multiforme	Vesicles or bullae arise from a portion of red plaques, 1 to 5 cm in diameter, on the extensor surfaces of extremities, an unusual location for impetigo
Bullous lupus erythematosus	Widespread vesiculobullous eruption that may be pruritic; tends to favor the upper part of the trunk and proximal upper extremities
Bullous pemphigoid	Vesicles and bullae appear rapidly on widespread pruritic, urticarial plaques may appear, unlike in impetigo
Herpes simplex virus	Grouped vesicles on an erythematous base that rupture to become erosions covered by crusts, usually on the lips and skin; may have prodromal symptoms which are not usually observed in impetigo
Insect bites	Bullae seen with pruritic papules grouped in areas in which bites occur
Pemphigus vulgaris	Non-pruritic bullae, varying in size from one to several centimeters, appear gradually and become generalized; erosions last for weeks before healing with hyperpigmentation, but no scarring occurs
Stevens-Johnson syndrome	Vesiculobullous disease of the skin, mouth, eyes, and genitalia; ulcerative stomatitis with hemorrhagic crusting is the most characteristic feature. Ulcerative stomatitis is not seen in impetigo
Thermal burns	History of burn with blistering in second-degree burns
Toxic epidermal necrolysis	Steven-Johnson-like mucous membrane disease followed by diffuse generalized detachment of the epidermis. Much more severe than impetigo
Varicella	Thin-walled vesicles on an erythematous base that start on trunk and spread to face and extremities; vesicles break and crust forms; lesions of different stages are present at the same time in a given body area as new crops develop

Table 3: Dosage and Duration of treatment regimens for Impetigo [10].

Antibiotic	Dosing and duration of treatment
Topical	
Mupirocin ointment 2%	Apply to lesions three times daily for three to five days
Oral	
Amoxicillin/clavulanate	Adults: 250-500 mg twice daily for 10 days Children: 90 mg/kg/day, divided, twice daily for 10 days
Cephalexin	Adults: 250-500 mg four times daily for 10 days Children: 90 mg/kg/day, divided, two to four times daily for 10 days
Dicloxacillin	Adults: 250-500 mg four times daily for 10 days Children: 90 mg/kg/day, divided, two to four times daily for 10 days

Topical therapy

The advantage of topical antibiotics is the fact of it being applied only in areas needed, this way minimizing resistance to antibiotics and avoiding gastrointestinal and other systemic adverse effects [1,48,55-59].

Clinical trials have shown that a seven day course is more effective than placebo for resolution of impetigo [57,58].

Among the disadvantages of topical treatments are local allergic reactions and difficulty with application to areas such as the mouth and eyelids. Three different preparations of topical antibiotics are recommended for impetigo: Mupirocin 2% cream or ointment (Bactroban), Retapamulin 1% ointment (Altabax) and Fusidic acid [60].

Retapamulin is the newest topical antibacterial agent. It's a novel pleuromutilin [21]. This agent acts on three different key aspects of the protein synthesis of the bacteria and hence resistant strains rarely develop. The U.S Food and Drug Administration approved in 2007 Retapamulin 1% ointment for treating impetigo caused by *S. aureus* (only to those strains which are susceptible to methicillin), or to impetigo caused by *GAS* in adult patients and in children bigger than nine months. In this regard, it should be noted that Retapamulin is not approved for intranasal staphylococcal carrier treatment or treatment of MRSA- related skin infections [55,61].

A Canadian review which collected data regarding the treatment between the years 2007-2017 has supported the efficacy of mupirocin and fusidic acid for the treatment of impetigo. Not much information was obtained regarding the clinical efficacy of bacitracin. No evidences were identified regarding either the efficacy or the recommendation towards the use of other antibiotics [62].

A study which took place in Greece in the years 2013-2016 showed an increased rate of community associated MSSA clone, which carries ETA/ETB genes and is resistant to both fusidic acid and mupirocin. Strains that belong to this clone are associated mainly with superficial skin infections like impetigo, and less commonly SSSS. The prevalence of resistance to mupirocin among this stain from 4.2% in 2013 to 37.7% in 2016,

concurrent with increasing rates of resistance to fusidic acid (from 26.8% to 51.9%), whereas the rate of resistance to clindamycin did not change significantly [63].

In 2011, McNeil, et al. showed that resistance to mupirocin was a problem among SSTIs caused by community-associated MSSA and clindamycin-resistant isolates. In the same study, among 136 *S. aureus* isolates from patients who had experienced at least three episodes of SSTI, a gene leading to mupirocin resistance was 14.5% prevalent, compared with 7.5% for the first episode, and 5 of 15 mupirocin resistant strains were also clindamycin resistant [63].

Systemic therapy

Situations in which topical therapy is impractical, or in impetigo with large bullae, oral antibiotic therapy can be used.

Treatment options are: Amoxicillin/clavulanate, cephalexin, clindamycin, dicloxacillin, doxycycline, minocycline, pristinamycin and trimethoprim/sulfamethoxazole. Seven days treatment is usually sufficient, however, this can be extended in case the clinical response is inadequate and upon confirmation of antibacterial susceptibility. It is still in question which oral antibiotic is the preferred one. Studies have shown no significant difference in the cure rates between oral and topical antibiotics [48].

Previously, penicillin and erythromycin were the first line treatment, however, due to emerging drug resistance they are no longer used routinely [64].

Since the rates of resistance vary regionally, health care professionals should check local patterns of resistance to select the proper treatment [48].

Recent studies point to the fact that MRSA related skin and soft tissue infections are declining, in contrast to past studies which have demonstrated an increase [65].

Based on culture results, trimetophrim/sulfamethoxazole, clindamycin or tetracyclin are recommended in case of suspecting a MRSA infection [61].

Trimetophrim/sulfamethoxazole usage in impetigo is limited, due its inadequate coverage of *GAS*. Clindamycin, due to its association with an increased risk of developing pseudomembranous colitis, should be used in patients in whom penicillin allergy exists or in cases where no response has been achieved to other treatment options. It is important to emphasize that tetracycline may be used for MRSA infections, however should not be used in children below the age of eight. Due to their risk of causing tendinopathy and arthropathies, and due to their low staphylococcal activity, oral fluoroquinolones are not preferred [64].

Pristinamycin is an oral streptogramin antibiotic with a similar spectrum of activity to macrolides and lincosamides for Gram-positive bacteria, with a reduced risk of drug resistance. It has a bactericidial effect against *Staphylococci* and *Streptococci*, and somewhat reduced activity against enterococci. Randomized controlled trials which have compared this antibiotic with penicillin and oxacillin for the treatment of skin and soft tissue infections have shown comparable clinical efficacy. High cure rates (86.7%-91.4%) have been reported when pristinamycin was compared with oxacillin, cefuroxime and amoxicillin in controlled trials for the treatment of respiratory tract infections [66]. Interestingly, one study reported pristinamycin to be superior to penicillin (81% versus 67%), although this difference was not statistically significant [66].

Antistaphylococcal beta-lactam is usually the first line therapy. The addition of a beta-lactamase inhibitor and the usage of a third generation cephalosporin as well as the usage of clindamycin are often needed in order to provide broad spectrum coverage for polymicrobial infections. Children who are immunocompromised, patients with nosocomial infections, those with penicillin allergy require specific antibacterial strategies, which in most cases involve a broader coverage with increased activity against Gram negative and aerobic organisms [67] (Table 3).

Other therapies

No recommendation is given today to use disinfectants as they appear to be less effective than topical antibiotics [63].

Several studies in which a comparison was made between hexachlorophene with bacitracin and hydrogen peroxide with topical fusidic acid, found the topical antibiotic to be more effective [48,68,69].

Herbal treatments for impetigo can be neither recommended nor dismissed as there is not sufficient evidence. Natural remedies such as coconut oils, olive, garlic, tea effusions and tea tree oil as well as Manuka honey have led to an improvement. In one of the studies being done, oral cephalexin and tea leaf ointment were found to be effective similarly, with a cure rate of 79% vs. 81% [70].

Treatment in trial

An open label, phase 2 pilot study which took place in Freiburg, Germany, and was posted in 2017, demonstrated the clinical efficacy of Liposomal polyvinyl-pyrrolidone (PVP)-iodine hydrogel, which has a special mode of action, as it combines both the anti-inflammatory and the antiseptic actions of PVP-iodine with drug delivery and moisturizing properties of liposomes. In the study patients with different dermatoses were observed while on treatment for a maximum period of 4 weeks. Overall, the treatment was well tolerated and hence liposomal PVP-iodine hydrogel has potential utility as a treatment for various dermatoses associated with the colonization of bacteria [71].

This pilot study was associated with a number of limitations, including the small number of patients and short duration of study treatment. Absence of a placebo or active comparator group also limits the interpretation of efficacy outcomes. The preliminary findings from this pilot study can be used to inform the design of larger scale studies, including randomized, controlled trials in order to assess the impact of treatment on bacterial load and elucidate how the clinical benefit of liposomal PVP-iodine hydrogel can be maximized for patients with various types of inflammatory, infective dermatoses [71].

Conclusions

Impetigo is a highly contagious bacterial skin infection, caused by *GAS* and *S. aureus*, both which have various factors assisting in skin adhesion. It is seen especially in children at the summer time, due to the close proximity between kids which leads to rapid spreading. The clinical presentation of the bullous form of impetigo, which starts with erythematous macules and progresses to vesicles, is due to ETA and ETB, harbored by *S. aurues*. The areas involved mostly are the nares and perioral regions.

This review emphasized the most important differentials for each form of impetigo (the bullous and the non-bullous one). Atopic dermatitis, candidiasis, contact dermatitis and many other are included. The unique feature for most diseases in the differential was outlined.

The usage of topical treatment for impetigo, mainly with mupirocin and fusidic acid is still prevalent today. It has the advantage of minimizing antibiotic resistancy, although recent study done in Greece demonstrated increased resistancy to these products among certain staphyloccal clone. The percentage of resistance has increased with the repeated use. When systemic therapy is needed, as in cases of the bullous form or widespread lesions, various options exist, with an average treatment of 10 days. Various studies testing new treatments haven't proven adequate efficacy, and larger studies will need to take place.

References

1. George A, Rubin G (2003) A systematic review and meta-analysis of treatments for impetigo. Br J Gen Pract 53: 480-487.
2. Bowen AC, Mahé A, Hay RJ, Andrews RM, Steer AC, et al. (2015) The global epidemiology of impetigo: A systematic review of the population prevalence of impetigo and pyoderma. PLoS One 10: e0136789.
3. Romani L, Steer AC, Whitfeld MJ, Kaldor JM (2015) Prevalence of scabies and impetigo worldwide: A systematic review. The Lancet Infectious Diseases 15: 960-967.
4. Dajani AS, Ferrieri P, Wannamaker LW (1972) Natural history of impetigo: II. Etiologic agents and bacterial interactions. Journal of Clinical Investigation 51: 2863.
5. Carapetis JR, Steer AC, Mulholland EK, Weber M (2005) The global burden of group A streptococcal diseases. The Lancet Infectious Diseases 5: 685-694.
6. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, et al. (2014) The global burden of skin disease in 2010: An analysis of the prevalence and impact of skin conditions. J Invest Dermatol 134: 1527-1534.
7. Pereira LB (2014) Impetigo-review. An Bras Dermatol 89: 293-299.
8. Dagan R (1993) Impetigo in childhood: Changing epidemiology and new treatments. Pediatr Ann 22: 235-240.
9. Brown J, Shriner DL, Schwartz RA, Janniger CK (2003) Impetigo: An update. International Journal of Dermatology 42: 251-255.
10. Cole C, Gazewood J (2007) Diagnosis and treatment of impetigo. American Family Physician 75: 859-864.
11. Amagai M, Nishifuji K, Yamaguchi T, Hanakawa Y, Sugai M, et al. (2002) Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. Journal of Investigative Dermatology 118: 845-850.
12. Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, et al. (2012) Interventions for impetigo. Cochrane Database Syst Rev 1.
13. Hogewoning A, Amoah A, Bavinck JN, Boakye D, Yazdanbakhsh M, et al. (2013) Skin diseases among schoolchildren in Ghana, Gabon, and Rwanda. Int J Dermatol 52: 589-600.
14. Saw SM, Koh D, Adjani MR, Wong ML, Hong CY, et al. (2001) A population-based prevalence survey of skin diseases in adolescents and adults in rural Sumatra, Indonesia, 1999. Trans R Soc Trop Med Hyg 95: 384-388.
15. Lawrence DN, Facklam RR, Sottnek FO, Hancock GA, Neel JV, et al. (1979) Epidemiologic studies among Amerindian populations of Amazônia. I. Pyoderma: Prevalence and associated pathogens. Am J Trop Med Hyg 28: 548-558.
16. Bechelli LM, Haddad N, Pimenta WP, Pagnano PM, Melchior Jr E, et al. (1981) Epidemiological survey of skin diseases in schoolchildren living in the Purus Valley (Acre State, Amazonia, Brazil). Dermatology 163: 78-93.
17. Gibbs S (1996) Skin disease and socioeconomic conditions in rural Africa: Tanzania. Int J Dermatol 35: 633-639.
18. Bissek AC, Tabah EN, Kouotou E, Sini V, Yepnjio FN, et al. (2012) The spectrum of skin diseases in a rural setting in Cameroon (sub-Saharan Africa). BMC Dermatol 12: 7.
19. Kiriakis KP, Tadros A, Dimou A, Karamanou M, Banaka F, et al. (2012) Case detection rates of impetigo by gender and age. Le infezioni in medicina: Rivista periodica di eziologia, epidemiologia, diagnostica, clinica e terapia delle patologie infettive 20: 105-107.
20. Caumes E (2000) Treatment of cutaneous larva migrans. Clinical Infectious Diseases 30: 811-884.
21. Sahl Jr WJ, Mathewson RJ (1993) Common facial skin lesions in children. Quintessence Int 24: 475-481.
22. Bessen DE, Carapetis JR, Beall B, Katz R, Hibble M, et al. (2000) Contrasting molecular epidemiology of group A streptococci causing tropical and nontropical infections of the skin and throat. J Infect Dis 182: 1109-1116.
23. (2015) Streptococcus pyogenes. Amy E Bryant, Dennis L Stevens, Principles and Practice of Infectious Diseases. (8th edn), Saunders, 2286Am.

24. Moses AE, Wessels MR, Zalcman K, Albertí S, Natanson-Yaron S, et al. (1997) Relative contributions of hyaluronic acid capsule and M protein to virulence in a mucoid strain of the group A Streptococcus. Infect Immun 65: 64-71.

25. Dale JB, Washburn RG, Marques MB, Wessels MR (1996) Hyaluronate capsule and surface M protein in resistance to opsonization of group A streptococci. Infect Immun 64: 1495-1501.

26. Lancefield RC (1962) Current knowledge of type-specific M antigens of group A streptococci. J Immunol 89: 307-313.

27. Ryan PA, Juncosa B (2016) Group A streptococcal adherence.

28. Fiorentino TR, Beall B, Mshar P, Bessen DE (1997) A genetic-based evaluation of the principal tissue reservoir for group A streptococci isolated from normally sterile sites. J Infect Dis 176: 177-182.

29. Kaplan EL, Anthony BF, Chapman SS, Ayoub EM, Wannamaker LW (1970) The influence of the site of infection on the immune response to group A streptococci. J Clin Invest 49: 1405-1414.

30. Bisno AL, Nelson KE, Waytz P, Brunt J (1973) Factors influencing serum antibody responses in streptococcal pyoderma. J Lab Clin Med 81: 410-420.

31. Kaplan EL, Wannamaker LW (1976) Suppression of the antistreptolysin O response by cholesterol and by lipid extracts of rabbit skin. J Exp Med 144: 754-767.

32. Götz F, Bannerman T, Schleifer KH (2006) The genera staphylococcus and macrococcus. Prokaryotes, Springer US, 5-75.

33. Gordon RJ, Lowy FD (2008) Pathogenesis of methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis 46: 350-359.

34. Dinges MM, Orwin PM, Schlievert PM (2000) Exotoxins of Staphylococcus aureus. Clinical Microbiol Rev 13: 16-34.

35. Compernolle V, Verschraegen G, Claeys G (2007) Combined use of Pastorex Staph-Plus and either of two new chromogenic agars, MRSA ID and CHROMagar MRSA, for detection of methicillin-resistant Staphylococcus aureus. Journal of Clinical Microbiology 45: 154-158.

36. Botka T, Růžičková V, Svobodová K, Pantůček R, Petráš P, et al. (2017) Two highly divergent lineages of exfoliative toxin B-encoding plasmids revealed in impetigo strains of Staphylococcus aureus. Int J Med Microbiol 307: 291-296.

37. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, et al. (2002) Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. New England Journal of Medicine 346: 491-496.

38. Patti JM, Allen BL, McGavin MJ, Hook M (1994) MSCRAMM-mediated adherence of microorganisms to host tissues. Annu Rev Microbiol 48: 585-617.

39. Roche FM, Massey R, Peacock SJ, Day NP, Visai L, et al. (2003) Characterization of novel LPXTG-containing proteins of Staphylococcus aureus identified from genome sequences. Microbiology 149: 643-654.

40. Que YA, Haefliger JA, Piroth L, François P, Widmer E, et al. (2005) Fibrinogen and fibronectin binding cooperate for valve infection and invasion in Staphylococcus aureus experimental endocarditis. J Exp Med 201: 1627-1635.

41. Piroth L, Que YA, Widmer E, Panchaud A, Piu S, et al. (2008) The fibrinogen-and fibronectin-binding domains of Staphylococcus aureus fibronectin-binding protein A synergistically promote endothelial invasion and experimental endocarditis. Infection and Immunity 76: 3824-3831.

42. Arrecubieta C, Asai T, Bayern M, Loughman A, Fitzgerald JR, et al. (2006) The Role of Staphylococcus aureus Adhesins in the Pathogenesis of Ventricular Assist Device-Related Infections. J Infect Dis 193: 1109-1119.

43. Barton LL, Friedman AD (1987) Impetigo: a reassessment of etiology and therapy. Pediatr Dermatol 4: 185-188.

44. Akiyama H, Kanzaki H, Abe Y, Tada J, Arata J (1994) Staphylococcus aureus infection on experimental croton oil-inflamed skin in mice. Journal of Dermatological Science 8: 1-10.

45. Euvrard S, Kanitakis J, Cochat P, Cambazard F, Claudy A (2001) Skin diseases in children with organ transplants. JAAD 44: 932-939.

46. Akiyama H, Yamasaki O, Kanzaki H, Tada J, Arata J (1999) Streptococci isolated from various skin lesions: the interaction with Staphylococcus aureus strains. J Dermatol Sci 19: 17-22.

47. Scaramuzzino DA, McNiff JM, Bessen DE (2000) Humanized in vivo model for streptococcal impetigo. Infect Immun 68: 2880-2887.

48. Kalia A, Spratt BG, Enright MC, Bessen DE (2002) Influence of recombination and niche separation on the population genetic structure of the pathogen Streptococcus pyogenes. Infect Immun 70: 1971-1983.

49. Wannamaker LW (1970) Differences between streptococcal infections of the throat and of the skin. New England Journal of Medicine 282: 23-31.

50. Halbert AR, Chan JJ (2002) Anogenital and buttock ulceration in infancy. Australasian Journal of Dermatology 43: 1-8.

51. Elias PM, Levy SW (1976) Bullous impetigo: Occurrence of localized scalded skin syndrome in an adult. Arch Dermatol 112: 856-858.

52. Gravet A, Couppie P, Meunier O, Clyti E, Moreau B, et al. (2001) Staphylococcus aureus isolated in cases of impetigo produces both epidermolysin A or B and LukE-LukD in 78% of 131 retrospective and prospective cases. J Clin Microbiol 39: 4349-4356.

53. Lei B, DeLeo FR, Hoe NP, Graham MR, Mackie SM, et al. (2001) Evasion of human innate and acquired immunity by a bacterial homolog of CD11b that inhibits opsonophagocytosis. Nat Med 7: 1298-1305.

54. Feaster T, Singer JI (2010) Topical therapies for impetigo. Pediatric Emergency Care 26: 222-227.

55. Bangert S, Levy M, Hebert AA (2012) Bacterial resistance and impetigo treatment trends: A review. Pediatric Dermatology 29: 243-248.

56. Weinberg JM, Tyring SK (2010) Retapamulin: An antibacterial with a novel mode of action in an age of emerging resistance to Staphylococcus aureus. J Drugs Dermatol 9: 1198-1204.

57. Koning S, van Suijlekom-Smit LW, Nouwen JL, Verduin CM, Bernsen RM, et al. (2002) Fusidic acid cream in the treatment of impetigo in general practice: Double blind randomised placebo controlled trial. BMJ 324: 203-206.

58. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, et al. (2011) Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 52: e18-e55.

59. Cada DJ, Levien T, Baker DE (2007) Retapamulin 1% ointment. Hospital Pharmacy 42: 846-855.

60. Hartman-Adams H, Banvard C, Juckett G (2014) Impetigo: Diagnosis and treatment. American Family Physician 90: 229-235.

61. Yan K, Madden L, Choudhry AE, Voigt CS, Copeland RA, et al. (2006) Biochemical characterization of the interactions of the novel pleuromutilin derivative retapamulin with bacterial ribosomes. Antimicrobial Agents and Chemotherapy 50: 3875-3881.

62. Edge R, Argáez C (2017) Topical antibiotics for impetigo: A review of the clinical effectiveness and guidelines.

63. Doudoulakakis A, Spiliopoulou I, Spyridis N, Giormezis N, Kopsidas J, et al. (2017) Emergence of a Staphylococcus aureus clone resistant to mupirocin and fusidic acid carrying exotoxin genes and causing mainly skin infections. J Clin Microbiol 55: 2529-2537.

64. Silverberg N, Block S (2008) Uncomplicated skin and skin structure infections in children: Diagnosis and current treatment options in the United States. Clinical Pediatrics 47: 211-219.

65. Landrum ML, Neumann C, Cook C, Chukwuma U, Ellis MW, et al. (2012) Epidemiology of Staphylococcus aureus blood and skin and soft tissue infections in the US military health system, 2005-2010. JAMA 308: 50-59.

66. Cooper EC, Curtis N, Cranswick N, Gwee A (2014) Pristinamycin: Old drug, new tricks? J Antimicrob Chemother 69: 2319-2325.

67. Vayalumkal JV, Jadavji T (2006) Children hospitalized with skin and soft tissue infections. Paediatr Drugs 8: 99-111.

68. Ruby RJ, Nelson JD (1973) The influence of hexachlorophene scrubs on the response to placebo or penicillin therapy in impetigo. Pediatrics 52: 854-859.

69. Christensen OB, Anehus S (1994) Hydrogen peroxide cream: An alternative to topical antibiotics in the treatment of impetigo contagiosa. Acta Derm Venereol 74: 460-462.

70. Martin KW, Ernst E (2003) Herbal medicines for treatment of bacterial infections: A review of controlled clinical trials. J Antimicrob Chemother 51: 241-246.

71. Augustin M, Goepel L, Jacobi A, Bosse B, Mueller S, et al. (2017) Efficacy and tolerability of liposomal polyvinylpyrrolidone-iodine hydrogel for the localized treatment of chronic infective, inflammatory, dermatoses: An uncontrolled pilot study. Clin Cosmet Investig Dermatol 10: 373.