Review

Common Community-acquired Bacterial Skin and Soft-tissue Infections in Children: an Intersociety Consensus on Impetigo, Abscess, and Cellulitis Treatment

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ABSTRACT

Purpose: The main objective of this article was to offer practical suggestions, given the existing evidence, for identifying and managing bacterial impetigo, abscess, and cellulitis in ambulatory and hospital settings.

Methods: Five Italian pediatric societies appointed a core working group. In selected conditions, specially trained personnel evaluated quality assessment of treatment strategies according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Only randomized controlled trials (RCTs) and observational studies were included for quality assessment according to the GRADE methodology. MEDLINE, Ovid MEDLINE, EMBASE, and Cochrane Library databases were searched with a strategy combining MeSH and free text terms.

Findings: The literature review included 364 articles focusing on impetigo, skin abscess, and cellulitis/orbital cellulitis. The articles included for quality assessment according to the GRADE methodology for impetigo comprised 5 RCTs and 1 observational study; for skin abscess, 10 RCTs and 3 observational studies were included; for cellulitis and erysipelas, 5 RCTs and 5 observational studies were included; and for orbital cellulitis, 8 observational studies were included. Recommendations were formulated according to 4 grades of strength for each specific topic (impetigo, skin abscesses, cellulitis, and orbital cellulitis). Where controversies arose and expert opinion was considered fundamental due to lack of evidence, agreement according to Delphi consensus recommendations was included.

Implications: Based on a literature review and on local epidemiology, this article offers practical suggestions for use in both ambulatory and hospital settings for managing the most common bacterial SSTIs. (*Clin Ther*. 2019;41:532–551) © 2019 Published by Elsevier Inc.

Key Words: abscess, cellulitis, children, impetigo, treatment.

INTRODUCTION

Children are frequently affected by bacterial skin and soft-tissue infections (SSTIs) with a variable spectrum, ranging from an exclusive skin involvement (ie, impetigo) to a deeper subcutaneous tissue infection (ie, cellulitis, erysipelas, abscess).[1–3] Recently, the worldwide spread of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), a common pathogen of pediatric SSTIs, has highlighted the need for updated knowledge of and strategies for managing this issue, based on local prevalence of MRSA, patients' age, and risk factors.[4,5]

Because pediatricians, pediatric infectivologists, and dermatologists are more frequently involved in SSTI management, the Italian Pediatric Infectious Diseases Society, the Italian Pediatric Dermatology Society, the Italian Society of Pediatrics, the Italian Society of Preventive and Social Pediatrics, and the Italian Federation of Pediatricians joined together to create a working group. The group's goal was to produce an intersociety consensus document on practical issues of impetigo, abscess, and cellulitis in childhood.

The main objective of the present article was to offer practical suggestions, given the existing evidence, for identifying and managing bacterial impetigo, abscess, and cellulitis in ambulatory and hospital settings.

MATERIALS AND METHODS

The Italian Pediatric Infectious Diseases Society, jointly with the Italian Pediatric Dermatology Society, the Italian Society of Pediatrics, the Italian Society of Preventive and Social Pediatrics, and the Italian Federation of Pediatricians, appointed a core working group of pediatric infectivologists, pediatric dermatologists, and general pediatricians. Experts from other scientific societies (clinical microbiologists, pharmacologists, surgeons, and pediatric radiologists) joined the core working group to formulate recommendations. The core working group identified aims and key words for search strategies, as well as evaluated existing literature by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.[6] The search covered the time period January 1, 2010, to December 31, 2017. Search strategies and key words are reported in Supplemental Appendix 1 (in the online version at doi:10.1016/j.clinthera.2019.01.010). Only randomized controlled trials (RCTs) and observational studies were included for quality assessment according to the GRADE methodology. The MEDLINE, Ovid MEDLINE, EMBASE, and Cochrane Library databases were searched with a strategy combining MeSH and free text terms. Search terms were combined by using Boolean operators; English-language restriction was applied. Gray literature was not included in this study.

The primary search was conducted by reviewing titles and abstracts of the studies; the full texts of eligible studies were then screened for inclusion. Moreover, the bibliographies of the included studies were also evaluated, and a limited number of references considered of particular relevance have been included.

In selected conditions, specially trained personnel evaluated quality assessment of treatment strategies according to the GRADE methodology. Evidence was then graded according to the following 6 criteria: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; (5) publication bias; and (6) other criteria. Quality of the studies was upgraded or downgraded due to magnitude factors, limitations in any of the aforementioned categories, or other factors. Finally, 4 levels of quality of evidence were indicated (high, moderate, low, and very low) (see Supplemental Appendix 2 in the online version at doi:10.1016/j.clinthera.2019.01.010).

Recommendations were formulated according to 4 grades of strength (positive-strong; positive-weak; negative-strong; and negative-weak). A strong recommendation is worded as "we recommend" or "it should…" and a weak recommendation as "we suggest" or "it could…"; where controversies arose and expert opinion was considered fundamental due to lack of evidence, agreement according to Delphi consensus recommendations was included. Survey development consisted of questions formulation by external reviewers (as shown in the Acknowledgments) with expertise in pediatric infectious diseases, dermatology, and epidemiology. Survey questions were formulated for each topic; experts were then asked to consider (according to specific expertise) various aspects of treatment suggestions, including tolerability, pediatric formulation drug availability, cost/benefits, and antimicrobial resistance patterns, to formulate specific recommendations.

The group consisted of 19 experts, who voted anonymously according to 4 scores (strongly agree, agree, disagree, or strongly disagree). The level of agreement was indicated as a percentage. A strong recommendation was considered if the agreement level was $\geq$75% (see Supplemental Appendix 2 in the online version at doi:10.1016/j.clinthera.2019.01.010).[7,8]

RESULTS

The literature review included 364 articles: 73 for impetigo, 111 for skin abscess, and 180 for cellulitis/orbital cellulitis. The articles included for quality assessment according to the GRADE methodology for impetigo comprised 5 RCTs and 1 observational study.[9–13] For skin abscess, 10 RCTs and 3 observational studies were included.[14–25] For cellulitis and erysipelas, 5 RCTs and 5 observational studies were included.[16,22–24,26–31] For orbital cellulitis, 8 observational studies were included.[29–36]

IMPETIGO

Background

Impetigo is one of the most common skin infections in children, especially those between 2 and 5 years of age.[37] The median global prevalence of impetigo has been estimated to be 12.3% in childhood, with a peak in tropical, low-income settings.[1] There are 2 distinct forms: bullous and nonbullous impetigo. Blistering (bullous) dactylitis is a localized form of bullous impetigo, usually affecting children between 2 and 16 years of age, although cases have also been reported in children aged <9 months.[38,39]

Nonbullous impetigo is usually caused by *S aureus* (70% of cases) and *Streptococcus pyogenes*.[37,40] The pathogen responsible for the bullous form is *S aureus*. In this case, blistering formation depends on production of local toxins.[41] Risk factors for impetigo are atopic dermatitis, skin trauma, insect bites, high humidity, and poor hygiene. The disruption of the skin barrier leads to the secondary forms of impetigo.[42] The most common is nonbullous impetigo, which usually involves the face and the extremities, and is characterized by erythematous papules or vesicles progressing to pustules and subsequently to yellow crusts. The bullous form presents with bullae and erosions involving the axillae, neck, and diaper area.[37,40] Occasionally, patients will present with systemic symptoms such as fever and lymphadenopathy. The characteristic lesion of blistering dactylitis is a nonitchy, purulent, fluid-filled blister, usually between 10 and 30 mm in diameter, that can evolve into erosions.[43] The most frequently involved site is the volar fat pad of the distal portion of a hand finger, or more rarely of a toe.[38,43] In uncomplicated infections, impetigo may spontaneously resolve within several weeks without scarring; if not treated, however, lesions can also spread by autoinoculation.[42]

Rare complications, due to local or systemic spread of the infection, include cellulitis, osteomyelitis, septic

arthritis, pneumonia, and sepsis. Noninfectious complications may also occur, such as scarlet fever, guttate psoriasis, and poststreptococcal glomerulonephritis (in ~5% of patients with nonbullous impetigo).[37,40,42] Recurrent toxin-mediated perineal erythema is another reported complication.[44]

The diagnosis is mainly clinical. The identification of causative pathogens relies on culture or polymerase chain reaction (PCR) of skin lesions. The growth of bacteria from culture also allows clinicians to obtain antimicrobial susceptibilities and drives antibiotic treatment[40]; this approach is important especially when the causative agent is *S aureus*, which can be resistant to various antibiotics.

Differential diagnosis includes herpes simplex, atopic dermatitis, scabies, and eczema.[42] If herpes etiology is suspected, the diagnosis could be confirmed by PCR of skin swabs. The bullous form should be distinguished from burns, Stevens-Johnson syndrome, and from other bullous diseases (ie, bullous pemphigoid). Differential diagnosis of blistering dactylitis includes herpetic lesions, epidermolysis bullosa, friction blisters, insect bites, and irritant dermatitis.[45,46]

Treatment

Topical Treatment

Currently, topical disinfectants do not represent a valid treatment for impetigo treatment, although they could be used for prevention of recurrence.[42,47] The topical antibiotic treatment presents the advantage of applying a high dose of drug in the target area with limited systemic absorption. A recent meta-analysis suggests that the most effective topical antibiotics for impetigo treatment are mupirocin, fusidic acid, and retapamulin (Table I).[40,42,48] Other topical antibiotics such as bacitracin, erythromycin, neomycin, and rifamycin are not currently recommended because the available studies are dated and conducted on limited populations.[42]

Retapamulin was developed in 2007 in response to emerging resistance to mupirocin and fusidic acid. The rate of resistance to those drugs is currently reported to be <1%.[4,49–52] However, a higher mupirocin resistance was recently reported in 7.5% of 3173 MRSA isolates in the REDUCE-MRSA (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin-Resistant *Staphylococcus aureus*) trial.[49] This finding is probably due to the wide use of mupirocin for MRSA decolonization. Retapamulin is not currently approved by the US Food and Drug Administration or the European Medicines Agency for treatment of MRSA skin infection because its efficacy seems to be limited in this population.[9,37,53,54]

The length of the topical treatment depends on the product chosen, but in clinical trials, a 7-day course was more effective than placebo for resolution of impetigo.[42] Potential risks of the local treatment are sensitization (developing contact dermatitis) and antibiotic resistance. For this reason, the antibiotics used for topical treatment should differ from those used for oral administration,[40] and new topical drugs

Table I. Topical antibiotics licensed for the treatment of impetigo.[12].

Medication	Posology
Fusidic acid 2% cream or ointment	Apply to affected skin 2–3 times daily for 7 to 12 d (until complete resolution of the lesions) Possible use also as an occlusive dressing
Mupirocin 2% cream* or ointment	Apply to affected skin 3 times daily for 7 to 10 d Possible use also as an occlusive dressing
Retapamulin 1% ointment†	Apply to affected skin twice daily for 5 d Total treatment area should not exceed 2% of total body surface area in children

* Not indicated for children aged <2 months.
† Approved for use in children aged ≥9 months.

Table II. Topical antibiotics for childhood impetigo.

Medication	Formulation	Posology	Study Type	Study Population	Results	Reference
Minocycline	1% or 4% foam	Twice daily for 7 d Two to seven lesions (maximum 0.5 × 0.5 cm)	Phase II randomized, parallel-group, double-blind, comparative clinical trial	32 subjects aged ≥2 y	Clinical cure rate: • 1% foam, 7.1% • 4% foam, 50.0% Microbiologic success rate EOT: • 1% foam, 85% • 4% foam, 74% Response rates for MRSA infections, 100% (11/11)	Chamny et al[48]
Ozenoxacin	1% cream	Twice daily for 5 dAged <12 y: maximum 2% of the body surface area	Phase I	46 Adults and children	Clinical cure rate: • 2−12 months, 52.6% • 1−2 y, 57.1% • 2−12 y, 22.2%	Gropper et al[56]
			Phase II multicenter, randomized, placebo- and retapamulin-controlled clinical trial	465 Adults and children (median age, 16.1 y)	Clinical response rate: • 34.8% ozenoxacin • 19.2% placebo Microbiologic success rate: • 79.2% ozenoxacin • 56.6% placebo	Gropper et al[10]

EOT = end of trial; MRSA = methicillin-resistant *Staphylococcus aureus*.

are under development (Table II).[10,11,48,55–57] The use of topical minocycline foam is promising for treatment of impetigo. However, the data available in children are limited to a Phase II trial, and future studies are needed to clarify the real indication of this formulation.[48]

The use of NVC-422 (*N,N*-dichloro-2,2-dimethyltaurine) topical gel was evaluated in a study of 129 children, with promising results.[11] Another Phase II RCT underway is of the use of LTX-109 gel (1% or 2% vs placebo), a new synthetic antimicrobial peptidomimetic, in patients aged >2 years with nonbullous impetigo.[55]

Finally, ozenoxacin (a new nonfluorinated quinolone) 1% cream seemed to be effective and safe in a multicenter, randomized, placebo-controlled Phase III study in adult and children.[10,56]

Systemic Treatment

In cases of extensive disease, oral antibiotics are indicated in addition to the topical treatment. The antibiotic choice should be driven, when available, by antimicrobial susceptibilities.[40] If treatment is empirically given, local resistance patterns should also be considered. Historically, macrolides (especially erythromycin) have been used, but this treatment regimen is now obsolete due to the spread of macrolide resistance.[40,42,58,59]

Amoxicillin/clavulanic acid, flucloxacillin, or oral cephalosporin (eg, cephalexin) could be valid alternatives.[42,60] If a parenteral treatment is needed, oxacillin could be safely used.

However, the increased prevalence of MRSA has changed the empiric approach for impetigo treatment. In cases of high rates of MRSA infections in the community (>10%), the antimicrobial agents available are clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, and tetracyclines (for children aged >8 years). Linezolid should be limited to severe infections. The length of the treatment is usually of 7–10 days depending on the clinical picture,[40] but recently, a short course (3–5 days) of TMP-SMX was shown to be equally effective, increasing patient adherence with lower side effects.[12] However, its use as empiric treatment is inadequate for the limited coverage of *S pyogenes*.[40] Oral treatment is usually well tolerated, and the side effects reported are usually limited to the gastrointestinal tract or to skin rash.[42]

The prolonged use of clindamycin may, in rare cases, cause *Clostridium difficile* colitis, which could be a serious adverse event and impel halting the treatment.[37] Use of fluoroquinolones is limited in young children because of musculoskeletal side effects.

Treatment of Blistering Dactylitis

Treatment of blistering dactylitis is based on incision and drainage (I&D) of the lesion and systemic antibiotic treatment, usually with amoxicillin-clavulanic acid or cephalosporin for 10 days. If MRSA is isolated, clindamycin (if the local

Recommendations:

1. When is topical treatment indicated for impetigo?

Topical treatment is indicated for limited impetigo extension (<2% of total body surface area) for 5 to 7 days (or until complete resolution) [quality of evidence: very low; strength of recommendation: positive-weak].

2. Which topical treatment is indicated for impetigo?

Topical antibiotics suggested for impetigo are: fusidic acid, Mupirocin (>2 months), or Retapamulin (≥9 months) [quality of evidence: very low; strength of recommendation: positive-strong].

Retapamulin is currently not indicated for MRSA [quality of evidence: very low; strength of recommendation: negative-weak].

Ozenoxacin could be a valid option for treating uncomplicated impetigo [quality of evidence: low; strength of recommendation: positive-weak].

3. When should systemic treatment be performed in children with impetigo?

Systemic treatment should be associated with topical therapy in cases of extensive/multiple lesions (>2% of total body surface area), children <1 year of age, suspected/confirmed MRSA etiology, or in cases of poor response to topical treatment or relapses (ie, Panton-Valentine leukocidin [PVL] positivity). [quality

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of evidence: very low; strength of recommendation: positive-strong].

4. What is the recommended systemic treatment for impetigo?

First-line oral treatment with flucloxacillin or a first-generation cephalosporin (cephalexin) for 7 to 10 days could be indicated [quality of evidence: very low; strength of recommendation: positive-weak].

The use of amoxicillin/clavulanic acid should be limited, considering its broad-spectrum activity [quality of evidence: very low; strength of recommendation: positive-weak].

In cases of high rates of MRSA infection in the community (>10%), oral clindamycin (if the local clindamycin resistance rate is <10%) or TMP-SMX (the latter if *S pyogenes* is excluded) for 7 to 10 days (or until complete resolution) is suggested [quality of evidence: very low; strength of recommendation: positive-weak].

resistance rate is <10%), linezolid, or vancomycin should be used.[38,43]

SKIN ABSCESSES

Background

Skin abscesses are a collection of pus involving epidermis, dermis, and deeper skin tissue (Figure 1). A furuncle (or boil) is a small abscess of a deep hair follicle, characterized by a nodule of purulent and necrotic debris. Larger and deeper abscesses formed by coalescence of multiple furuncles are defined as carbuncles.

The most common isolate in skin abscesses is *S aureus* (40%−87%), followed by *Streptococcus* species and coagulase-negative *Staphylococcus*. Gram-negative and anaerobic organisms are involved in <10% of cases.[14−16,61] Methicillin resistance has been reported in 46% to 77% of *S aureus* isolates, clindamycin resistance in 12.4%, and TMP-SMX resistance in 0.5% to 2.6% of strains.[14−16,61,62] In Europe, the reported percentage of MRSA in 2016 was 13.7%, which reached 33.6% in Italy.[63]

PVL production must be suspected in cases of recurrent SSTIs (especially skin abscesses) in children and/or their family members.[64]

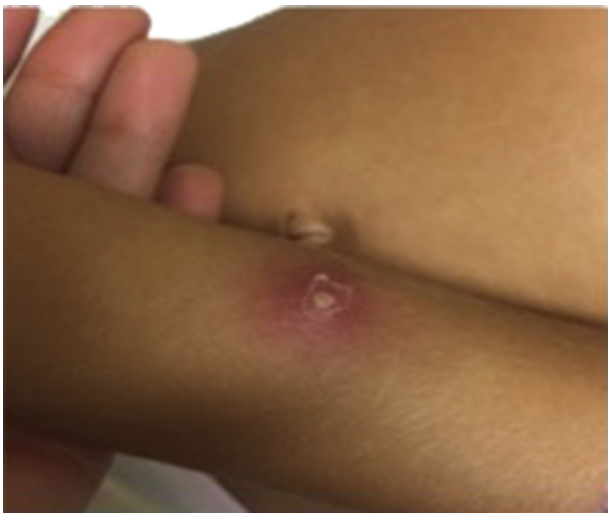

Figure 1. Single and uncomplicated abscess of the arm.

A skin abscess appears as an erythematous, tender, painful induration, often surmounted by a central pustule. Initially, the swelling is fixed; later, the overlying skin becomes thin and appears fluctuant. The abscesses present in different sizes, typically 1 to 3 cm in length, but are sometimes much larger and may occur on any skin surface. Large skin abscesses are surrounded by cellulitis and can be associated with systemic symptoms (eg, fever, malaise, increased inflammatory markers and white blood cells, regional lymphadenitis). Skin abscess often evolves to spontaneous drainage.

Patients with a single abscess of a diameter up to 5 cm (≤3 cm in patients 6−11 months of age and ≤4 cm in patients 1−8 years of age) are considered to be within the simple abscess group.[40] All other patients, including those with an abscess >5 cm in diameter (and proportionally smaller in young children), patients with ≥2 sites of skin infection, and patients with recurrent abscess, are considered within the complicated abscess group.

Risk factors for skin abscesses include a history of atopic dermatitis, skin injuries, insect bites and animal scratches, immunodeficiency (neutrophil defect [ie, chronic granulomatous disease and leukocyte-adhesion molecule deficiency], hyper-immunoglobulin E syndrome, and Wiskott-Aldrich

syndrome), poor hygiene, colonization by MRSA and/or colonization by *S aureus*—producing PVL, and skin abscess in a household contact. Risk factors for MRSA colonization are reported in Table III.

The diagnosis of abscesses is mainly clinical. Gram stain and culture of purulent material are particularly useful in recurrent cases; blood culture can be requested for patients presenting with fever and systemic symptoms or who are immunocompromised. However, blood cultures show a low yield in uncomplicated SSTIs. Ultrasound is a sensitive and easy procedure that allows clinicians to distinguish abscesses from cellulitis, evaluate abscess size, and assign patients to I&D.[65–67]

Differential diagnosis includes inflamed epidermoid cysts, hidradenitis suppurativa, foreign body granuloma, pyoderma gangrenosum, and mycobacterial skin infection.[61,62] About one third of patients with skin abscess experience a recurrence. Recurrences are particularly frequent in cases of MRSA and *S aureus*—producing PVL colonization (up to 70% of cases). Skin abscesses can spread to household contacts.

Treatment

Small abscesses can resolve themselves without treatment, with spontaneous drainage. I&D is routinely performed in cases of skin abscess.[14,15,68] The loop technique has seems to exhibit a significantly lower failure rate than I&D for children.[17] It is still not clear if wound packing after I&D has a significant effect on failure or recurrence rate and healing time.[18] Ultrasound-guided needle aspiration of the abscess is less effective than I&D.[19]

Table III. Risk factors for methicillin-resistant *Staphylococcus aureus* colonization in children.

Age <6 months and 8–13 y
Male sex
Previous hospitalization of a family member
Household members working in health care facility
No. of siblings
Regular visit to health care facility and previous hospitalization
Day care ≥5 d/wk
MRSA-positive mother
Breastfeeding
History of indwelling catheter or other medical devices
Chronic skin diseases
Chronic sinusitis

The need for an adjunctive antibiotic treatment is under discussion. Two meta-analyses have been conducted of the effect of systemic antibiotic treatment after I&D of simple cutaneous abscesses, and they found no evidence to support the routine use of antibiotics.[69,70] However, the majority of studies are based on adult populations. A recent multicenter, prospective, double-blind study on children and adults showed that both clindamycin and TMP-SMX were superior to placebo but not significantly different from one another except in subanalyses.[20] However, one important detail in these subanalyses was that, in children, clindamycin use after I&D was associated with a lower rate of recurrent infection compared with TMP-SMX or placebo.

A 7- to 10-day course of TMP-SMX after I&D is reportedly more effective in preventing treatment failure and recurrence of abscesses in children and adults compared with a placebo or a shorter (3-day) course of treatment. TMP-SMX resulted in lower rates of subsequent surgical drainage procedures, recurrence at new sites, and infections among household contacts.[5,14,15,21] A retrospective cohort study, evaluating children with SSTIs between 2004 and 2007, reported a significantly higher rate of treatment failure and recurrence in patients treated with TMP-SMX and β-lactams than with clindamycin. This difference was greater with children who underwent drainage.[22]

Guidelines have recommended vancomycin or clindamycin (if the local resistance rate is <10%) as the standard of care for complicated SSTIs.[71,72] Miller et al[16] reported similar efficacy and adverse effect profiles in patients with large skin abscesses (>5 cm) treated with clindamycin or TMP-SMX after I&D. Ceftaroline fosamil (in children >12 years of age) seems to have a similar safety and effectiveness profile among children with SSTIs, including major skin abscesses, versus standard comparator therapy (vancomycin or cefazolin).[24] A randomized trial compared once-daily daptomycin versus vancomycin or clindamycin in 389 children aged between 1 and

17 years.[23] Daptomycin was well tolerated, exhibiting safety and efficacy comparable to the standard of care in a setting with a high incidence of MRSA (35% of patients with MRSA infection). Linezolid seems to be more effective and cost-effective than vancomycin in patients treated for SSTIs.[73]

Decolonization strategies based on chlorhexidine body wash or bleach baths and nasal mupirocin ointment, including for all household contacts, have been suggested.[25,47,54,74] The decolonization scheme is based on: hygienic measures; chlorhexidine 4% body wash use once a day for 5 days; chlorhexidine 4% shampoo on days 1, 3 and 5; and mupirocin nasal ointment 3 times a day for 5 days. However, there is currently no clear evidence to support these strategies preventing recurrent infections.[25,74] Moreover, chlorhexidine is not widely available in all settings.

Recommendations:

1. What is the gold standard treatment for abscesses not resolving with spontaneous drainage?

Abscesses not resolving with spontaneous drainage should be treated with I&D [quality of evidence: very low; strength of recommendation: positive-weak].

2. What surgical technique can be considered as an alternative to I&D of skin abscesses?

The loop technique could be an alternative to I&D [quality of evidence: very low; strength of recommendation: positive-weak].

Ultrasonographically guided needle aspiration is not suggested as an alternative therapy for skin abscesses [quality of evidence: very low; strength of recommendation: negative-weak].

3. Is wound packing indicated after I&D of skin abscesses to reduce treatment failure and recurrence rates?

Wound packing is not suggested for reducing treatment failure and recurrence rates after I&D of skin abscesses [quality of evidence: very low; strength of recommendation: negative-weak].

4. Is a systemic antibiotic treatment indicated after I&D in cases of simple cutaneous abscesses for reducing treatment failure?

Treatment with oral TMP-SMX or clindamycin (if the local clindamycin resistance rate is <10%) for 7 to 10 days (or until complete resolution) after I&D of simple cutaneous abscesses is recommended [quality of evidence: high; strength of recommendation: positive-strong].

5. Is a systemic antibiotic treatment indicated after I&D in cases of simple cutaneous abscesses for reducing recurrence rate?

Treatment with oral TMP-SMX or clindamycin (if the local clindamycin resistance rate is <10%) for 7 to 10 days (or until complete resolution) after I&D of simple cutaneous abscesses could reduce recurrences [quality of evidence: high; strength of recommendation: positive-strong].

6. Which systemic antibiotic treatment is indicated after I&D in cases of complicated cutaneous abscesses for reducing treatment failure?

In cases of complicated cutaneous abscesses, empiric treatment with intravenous vancomycin or clindamycin (if the local clindamycin resistance rate is <10%) after I&D is recommended for reducing treatment failure. The treatment should be targeted when susceptibilities become available [quality of evidence: very low; strength of recommendation: positive-weak].

Scale-down to oral treatment with TMP-SMX or clindamycin could be done when systemic symptoms are resolved and at least 3 to 5 days after intravenous treatment. The length of treatment should be 10 to 14 days overall (or until complete resolution) [quality of evidence: very low; strength of recommendation: positive-weak].

(*Continued*)

7. Which systemic antibiotic treatment is indicated as an alternative to the standard of care (vancomycin or clindamycin) after I&D in cases of complicated cutaneous abscesses for reducing treatment failure?

In cases of high rates (>10%) of MRSA infection in the community, intravenous TMP-SMX, daptomycin, and ceftaroline (in children aged >12 years) are equally safe and effective for treatment of complicated cutaneous abscesses compared with the standard of care [TMP-SMX—quality of evidence: high; strength of recommendation: positive-strong; daptomycin and ceftaroline—quality of evidence: moderate; strength of recommendation: positive-weak].

8. Which systemic antibiotic treatment is indicated if *S aureus*–producing PVL is suspected?

If *S aureus*–producing PVL is suspected as a cause of skin abscess, clindamycin (if the clindamycin local resistance rate is <10%) or, as a second option, rifampicin could be added to the standard regimen to counteract the PVL activity [quality of evidence: very low; strength of recommendation: positive-weak]. In severe cases or suspected/proven methicillin-resistant *S aureus*–PVL etiology, linezolid could be an option [quality of evidence: very low; strength of recommendation: positive-weak].

9. Are decolonization strategies indicated in children with recurrent skin abscesses for obtaining *S aureus* eradication?

Decolonization strategies based on chlorhexidine body wash or bleach bath and nasal mupirocin ointment could be indicated to eradicate *S aureus* in cases of recurrent infections [quality of evidence: moderate; strength of recommendation: positive-weak].

10. If decolonization strategies are performed in children, which is the best approach for *S aureus* eradication?

Household decolonization could be more effective than simply performing

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decolonization strategies in the individual child for eradicating and reducing the incidence of subsequent SSTIs [quality of evidence: low; strength of recommendation: positive-weak].

CELLULITIS AND ERYSIPELAS

Background

Cellulitis is an inflammation of the subcutaneous tissue caused by bacterial pathogens. Erysipelas is defined when the bacterial infection involves the dermis and the upper subcutaneous tissue. Recently, most experts have come to consider these conditions as different presentations of the same disease.[75] In European countries, the estimated incidence is 19–24 cases per 10,000 inhabitants. In the United States, there are ~14.5 million cases every year.[76]

The characteristic clinical manifestation of cellulitis is a painful erythematous plaque with ill-defined scales. A warm, edematous, tender, dark red or livid erythema or a pasty swelling surrounding a portal of entry is the most characteristic presentation of cellulitis. The lesion usually has a darker or livid red color and is less shiny and less sharply demarcated than classic erysipelas, probably because it involves deeper tissue layers. In contrast to erysipelas, the lesion is not raised, the demarcation between involved and uninvolved skin is indistinct, and lesions are pink rather than salmon-red in color. Often, however, the clinical differentiation between these entities is not clear-cut. Unusual manifestations of cellulitis are blisters, purpuric or ecchymotic areas, pustules, and abscessed areas. Systemic symptoms can also be associated, especially fever and regional lymphadenopathy.

Erysipelas is characterized by an area with a well-defined edge due to the superficial involvement, typically localized to the face and the lower limbs. It affects the lower legs in 85% of cases, the butterfly area of the face in 2.5% to 19%, the arms in 2% to 9%, or the genital region in 0.5% to 2%. It is usually characterized by a single elevated lesion, averaging 10 to 15 cm, beginning as a localized area of erythema,

brilliant salmon-red in color, which swells and then spreads rapidly with red margins, raised and well demarcated from adjacent normal tissue. There is marked edema, often with bleb formation; in facial erysipelas, the eyes are frequently swollen shut. The lesion may demonstrate central resolution while continuing to extend on the periphery. Systemic symptoms and signs such as fever, malaise, and, less frequently, chills can be present. Differential diagnosis for erysipelas includes acute contact dermatitis, giant urticaria, combustion, burning, or congelation.

It is difficult to establish the real incidence of the causative pathogens because the majority of cellulitis and erysipelas cases are nonculturable.[76–78] In cases in which the etiologic agent is identified, the most common pathogens are β-hemolytic streptococci (groups A, B, C, G, and F) and *S aureus*.

Risk factors for cellulitis are skin lesions, burns, wounds, surgical incisions, insect bites, traumatic injuries, and other conditions with loss of skin integrity. Disruption of the cutaneous barrier (eg, leg ulcers, wounds, dermatophytosis) and anal streptococcal colonization in children are in fact among the most frequent risk factors for the development of cutaneous streptococcal or staphylococcal infection. Possible complications of cellulitis could be local abscess, necrotizing fasciitis, and sepsis. Cellulitis recurrence can also occur.

The diagnosis of cellulitis is mainly clinical. There is no validated or objective score for distinguishing moderate/severe cellulitis from mild cellulitis. The severe form can be defined in presence of any of the following clinical features: rapidly spreading redness (from history), significant swelling/redness/pain, systemic symptoms/signs (fever and lethargy), or failed oral therapy (no improvement despite at least 24 h of oral antibiotics).[79]

Moreover, cellulitis can be distinguished between complicated and uncomplicated types. Complicated cellulitis includes cellulitis associated with abscess requiring surgical drainage, lymphadenitis, underlying soft-tissue malformation, bite or penetrating injury, foreign body, fracture, lymphedema, medical comorbidities, and immunosuppression.[79] Blood cultures have been shown to have a very low diagnostic yield; the infection is usually localized with a low rate of bacteremia.[77,78]

Imaging (ie, ultrasound, magnetic resonance imaging [MRI], computed tomography (CT) scan) can help in detecting the emergence of complications, such as abscess formation, and it is indicated in cases of clinical suspicion. Radiography generally constitutes the initial examination for patients with soft-tissue infections. Changes in radiographs include swelling, effacement of fat planes, presence of gas, or identification of foreign bodies in soft tissues. Radiography can rule out other causes of soft-tissue swelling, such as underlying fractures.

Findings on ultrasound imaging include subcutaneous tissue edema with a characteristic "cobblestone pattern." Moreover, ultrasound can aid in excluding noninflammatory causes of soft-tissue swelling such as deep vein thrombosis and soft-tissue tumors. It also provides localization of superficial non-radiopaque foreign bodies and can be a guide for percutaneous interventions and tissue sampling. CT scanning provides higher sensitivity for detection of soft-tissue gas and foreign bodies, whereas MRI scanning of cellulitis demonstrates diffuse soft-tissue thickening with hyperintensity at T2W imaging and/or short TI inversion recovery MRI and hypointensity at T1W imaging and postcontrast enhancement. Moreover, MRI indicates the presence of periostitis or osteomyelitis and osteoarthritis.

Treatment

Empiric antimicrobial therapy must be started as soon as possible and should be modified on the basis of pathogen recognition. Because erysipelas and cellulitis can be clinically and etiologically overlapping, treatment recommendations should be considered valid for both diseases.[71] Patients with mild cellulitis may be treated empirically with oral β-lactams, either alone or in association with TMP-SMX.[22] The addition of an MRSA-active agent (ie, TMP-SMX, clindamycin, linezolid) could be considered in areas where the MRSA incidence rate in the community is >10% or in cases of clinical suspicion.[16] However, 2 trials involving adults and children showed no advantages from combining a first-generation cephalosporin with TMP-SMX compared with the use of a cephalosporin alone in MRSA-endemic areas.[26,27] It is also possible to administer a short course of intravenous antibiotics (for <24 h), followed by a course of oral antibiotics.[28]

Patients with mild cellulitis typically experience a symptomatic improvement within 24–48 h of

beginning the antimicrobial therapy. Persistence of erythema and/or systemic symptoms after this period of time should promptly lead to consideration of the presence of resistant pathogens or alternative diagnoses. In such cases, microbiologic data should be carefully reviewed; radiographic evaluation is appropriate for deeper infection, and broadening antibiotic therapy to include coverage for gram-negative bacilli pending further diagnostic data is reasonable. In uncomplicated cellulitis, the length of the antibiotic course should be between 5 and 10 days, depending on the disease severity and the clinical response to the treatment. However, treatment durations of 5 or 6 days seem to be as effective as 10 days.[79]

In cases of severe cellulitis with rapid progression of erythema or clinical sepsis, treatment with parenteral antibiotics is indicated. Parenteral therapy should also be considered for children with persistent or progressive infection after 48 to 72 h of an empiric oral therapy. First-line intravenous treatment with oxacillin (or, where available, flucloxacillin) or ampicillin-sulbactam is indicated in settings with a low rate of MRSA infections.[29] If MRSA is suspected, a MRSA-active agent (ie, vancomycin, clindamycin, linezolid) should be used. The combination of oxacillin with ceftriaxone seems to improve children's clinical conditions quickly, but the available data are limited. Moreover, considering that this condition is mainly caused by gram-positive bacteria, the broad-spectrum activity of the third-generation cephalosporin might lead to an avoidable antibiotic exposure.[62]

The use of intravenous ceftriaxone administered at home seems to be a safe option for children with moderate/severe cellulitis, without systemic symptoms, in settings with a low rate of MRSA infection. This protocol has the advantage of reducing hospitalization lengths and seems to have an outcome comparable to that of intravenous flucloxacillin administered to inpatients.[30,79] A randomized trial is ongoing to determine the validity of this approach in children.[31]

Ceftriaxone is also appropriate in cases of erysipelas, because of its activity against β-hemolytic streptococci. In addition, once-daily dosing allows parenteral treatments for outpatients.

Treatment of newborn cellulitis usually requires hospitalization and immediate parenteral therapy with coverage for group B β-hemolytic *Streptococcus* in addition to MRSA. Extension of the duration (up

Recommendations:

1. Which systemic empiric antibiotic treatment is indicated for uncomplicated mild cellulitis and for how long?

Patients with mild cellulitis should be treated empirically with an oral first-generation cephalosporin (ie, cephalexin) for 7 to 10 days (or until complete resolution) in cases of MRSA incidence <10% [quality of evidence: moderate; strength of recommendation: positive-weak].

Oral TMP-SMX or clindamycin (if the local clindamycin resistance rate is <10%) for 7 to 10 days (and until complete resolution) should be prescribed in children with uncomplicated mild cellulitis if MRSA incidence is >10% [quality of evidence: moderate; strength of recommendation: positive-weak].

2. Which systemic empiric antibiotic treatment is indicated for uncomplicated moderate/severe cellulitis and for how long?

In cases of low incidence of MRSA in the community, children with uncomplicated moderate/severe cellulitis could be empirically treated with intravenous anti-staphylococcal penicillin or first-generation cephalosporin (ie, cefazolin, cefalotin) for at least 48 h before switching to oral therapy [quality of evidence: very low; strength of recommendation: positive-weak].

Scale-down to empiric oral treatment with amoxicillin/clavulanic acid or cephalosporin (eg, cephalexin) could be indicated when systemic symptoms are resolved [quality of evidence: very low; strength of recommendation: positive-weak].

The treatment should be targeted when sensitivities become available. The length of treatment should overall be 10 to 14 days (or until complete resolution) [quality of

(*continued on next page*)

(*Continued*)

evidence: very low; strength of recommendation: positive-strong].
In cases of high incidence of MRSA in the community, intravenous TMP-SMX, vancomycin, or clindamycin (if the local clindamycin resistance rate is <10%) should be started in children with uncomplicated moderate/severe cellulitis [quality of evidence: very low; strength of recommendation: positive-weak].
Scale-down to oral treatment with TMP-SMX or clindamycin (if the local clindamycin resistance rate is <10%) could be indicated when systemic symptoms are resolved and after at least 48 h of intravenous antibiotics [quality of evidence: very low; strength of recommendation: positive-weak].
The treatment should be targeted when sensitivities become available.
The length of treatment should be 10 to 14 days (or until complete resolution) overall [quality of evidence: very low; strength of recommendation: positive-weak]

3. Which systemic empiric antibiotic treatment is indicated in patients with complicated cellulitis?

In cases of complicated cellulitis, empiric treatment with intravenous vancomycin or teicoplanin or clindamycin (if the local clindamycin resistance rate is <10%) is recommended for reducing treatment failure [quality of evidence: very low; strength of recommendation: positive-weak].
Adding gram-negative coverage and anaerobes (ie, piperacillin/tazobactam) should be considered in cases of surgical drainage, bite or penetrating injury, foreign body, fracture, medical comorbidities, and immunosuppression [quality of evidence: very low; strength of recommendation: positive-strong].
The treatment should be targeted when sensitivities become available.
Scale-down to oral treatment with TMP-SMX or clindamycin could be done when systemic symptoms are resolved and at least 3 to 5 days after intravenous treatment [quality of evidence: very low; strength of recommendation: positive-weak].
In cases of risk factors for *Pseudomonas aeruginosa* (ie, surgical drainage, bite or penetrating injury, foreign body, fracture, medical comorbidities, immunosuppression), switching to oral ciprofloxacin should be considered [quality of evidence: very low; strength of recommendation: positive-weak].
The length of treatment should be 14 to 21 days (and at least until complete resolution) overall [quality of evidence: very low; strength of recommendation: positive-weak].

4. Which systemic antibiotic treatment is indicated as an alternative to the standard of care (vancomycin or clindamycin) in patients with complicated cellulitis?

In cases of high rates of MRSA infection in the community, daptomycin or ceftaroline (in children >12 years of age) are equally safe and effective for the treatment of complicated cellulitis compared with the standard of care [quality of evidence: moderate; strength of recommendation: positive-weak].

to 14 days) should be warranted in cases of severe infection and/or slow response to therapy.

ORBITAL AND PERIORBITAL CELLULITIS

Background

Orbital cellulitis is distinguished as preseptal and postseptal depending on the position with respect to the palpebral ligament (Figure 2). It is also known as periorbital and orbital cellulitis, respectively. The first type is relatively common in children, whereas the second form is rare and more severe.[3,80,81] According to the Chandler classification, orbital cellulitis is divided into 5 groups: group I, inflammatory edema limited to the eyelid (or "preseptal cellulitis"); group II, extension of inflammation to include the orbital contents posterior to the septum (or "orbital cellulitis"); group III, purulent collection between the bony orbital wall and periorbital (a "subperiosteal abscess"); group IV, purulent collection within the

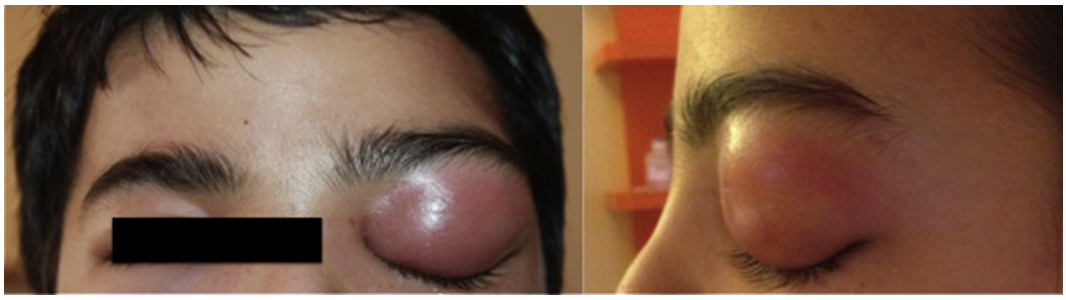

Figure 2. Left orbital cellulitis.

orbit itself (an "orbital abscess"); and group V, retrograde phlebitis extending to the cavernous sinus, presenting with bilateral eye findings (and referred to as "cavernous sinus thrombosis").[82]

The causative pathogens of periorbital/orbital cellulitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *S pyogenes*, and *S aureus*.[83,84] However, other pathogens can also be involved, such as other streptococci and anaerobic bacteria.[84] In children, the incidence of *Haemophilus* species and *S pneumoniae* cellulitis has fallen dramatically since the introduction of vaccination.[85,86] The staphylococcal etiology is therefore becoming more frequent in children with periorbital/orbital cellulitis.[22]

The most common predisposing factor for orbital and periorbital cellulitis is sinusitis, usually spreading directly from the ethmoidal sinus or by hematogenous dissemination. Other risk factors are dacryocystitis, upper respiratory infection, or infection from contiguous areas (ie, after trauma, surgery, insect bites).[32]

Preseptal cellulitis is characterized by edema and hyperemia limited to the eyelid with no restrictions in eye movements or vision alterations. In postseptal cellulitis, the edema involves orbital tissues, causing proptosis, ophthalmoplegia, and deteriorating visual acuity or color vision.

Orbital cellulitis is a potentially blinding and life-threatening condition. Moreover, it can be a cause of subperiosteal abscess formation, meningitis, and cavernous sinus thrombosis.[80,87] In cases of periorbital/orbital cellulitis, an ophthalmology evaluation is crucial to identify patients at risk of intra-orbital abscess. Proptosis, pain, or limitation of extra-ocular movements are red flags for this complication.[88]

Diagnosis is mainly clinical. Routine blood examinations (cell-blood count and C-reactive protein) can be performed. Blood cultures and blood PCR for bacterial pathogens, if available, are indicated in cases of fever, despite the low diagnostic yield. In cases of surgical drainage of the abscesses, cultures and PCR for the following bacteria are recommended: *S pneumoniae*, *H influenzae*, *S pyogenes*, *S aureus*, and PCR 16S.[89]

Radiologic assessment with CT scanning is indicated for patients in whom an abscess is suspected. There are no univocal indications for CT scanning in cases of periorbital/orbital cellulitis, but some authors suggest considering performing a scan in cases of neurologic signs, proptosis, ophthalmoplegia, deteriorating visual acuity or color vision, bilateral edema, lack of improvement or deterioration within 24 h of treatment, or persisting pyrexia.[89,90] MRI is the test of choice when an intracranial extension of the infection is suspected.

Orbital/periorbital cellulitis should be differentiated from dacryocystitis, orbital neoplasms (ie, retinoblastoma), angioedema, allergic conjunctivitis, and orbital injuries.[91]

Treatment

The management of periorbital and orbital cellulitis should involve a multidisciplinary team including a pediatric infectologist, ophthalmologist, and otorhinolaryngologist.[88] Conservative treatment with intravenous broad-spectrum antibiotics is indicated in cases of preseptal cellulitis. The suggested first-line treatment is based on an intravenous third-generation cephalosporin (ie, ceftriaxone) or amoxicillin/clavulanic acid.[33] If MRSA is suspected, or in cases

of no clinical improvement after 48 h of treatment, an MRSA-active agent (ie, vancomycin, teicoplanin, or, in selected cases, daptomycin) should be used.[16,62] If PVL toxin production is suspected, clindamycin (if local resistance rates are <10%) or linezolid (if the patient is aged >12 years) are indicated.

The length of treatment is not well established. However, in preseptal cellulitis, 5 to 10 days of treatment, in accordance with severity and treatment response, seems to be adequate.[33] There is no evidence regarding the efficacy of switching to oral treatment after the first 48 to 72 h of intravenous treatment. In a recent retrospective study of 213 children with preseptal cellulitis, those cases following insect bites turned out to be less severe compared with other causes, with a significantly shorter mean length of stay (3 vs 5 days; $P < 0.05$).[31] Therefore, in selected cases, the authors suggest the possibility of an oral treatment at home with close outpatient follow-up.

Abscess formation, especially in cases of orbital form, is an indication for surgery.[92] However, some authors suggest vigorous medical therapy alone for postseptal involvement in selected cases (normal vision, absence of ophthalmoplegia, intraocular pressure <20 mm Hg, proptosis of ≤5 mm, or abscess width ≤4 mm on CT scan). Those patients should be closely followed up to determine if surgery is needed in cases of worsening of ocular signs or failure to improve after 48 h of parenteral antibiotics.[32,35,93] In cases of orbital abscess, antibiotic treatment should be prolonged for at least 4 weeks (combined with a

Recommendations:

1. Which systemic empiric antibiotic treatment is indicated for periorbital (preseptal) cellulitis?

In settings with low MRSA prevalence, children with periorbital cellulitis could be treated with intravenous ceftriaxone or amoxicillin/clavulanic acid or, as a third option, oxacillin, for at least 48 to 72 h before switching to oral therapy [quality of evidence: low; strength of recommendation: positive-weak].

Scale-down to empiric oral treatment with amoxicillin/clavulanic acid could be indicated when systemic symptoms are resolved [quality of evidence: very low; strength of recommendation: positive-weak].

The treatment should be targeted if sensitivities become available. The length of treatment should be 5 to 10 days (or at least until complete resolution) overall [quality of evidence: very low; strength of recommendation: positive-strong].

If MRSA is suspected or in cases of no clinical improvement after 48 h of treatment, an MRSA-active agent (ie, vancomycin, teicoplanin, or, in selected cases, daptomycin) should be used [quality of evidence: very low; strength of recommendation: positive-strong].

2. Which systemic antibiotic treatment is indicated for orbital (postseptal) cellulitis alone or in combination with surgery?

In absence of immediate indications for surgery, children could be treated with intravenous ceftriaxone plus clindamycin (if the local clindamycin resistance rate is <10%) [quality of evidence: very low; strength of recommendation: positive-weak].

In settings with high clindamycin resistance rates (>10%), ceftriaxone plus vancomycin plus metronidazole should be used [quality of evidence: very low; strength of recommendation: positive-weak].

3. Is treatment with intravenous steroids indicated in children with orbital cellulitis in addition to the antibiotic treatment?

The addition of intravenous steroids to the antibiotic treatment in children with orbital cellulitis is not suggested [quality of evidence: very low; strength of recommendation: negative-weak].

4.Is surgery indicated in cases of postseptal cellulitis?

Orbital abscess formation, worsening of ocular signs, and failure to improve after 48 h' treatment with parenteral antibiotics should be considered indications for surgery [quality of evidence: very low; strength of recommendation: positive-weak].

surgical approach or wherever a surgical approach is not applicable). Intravenous steroids might be helpful in treating orbital cellulitis.[36]

LIMITATIONS

The main limitation of the present consensus statement is the lack of evidence regarding specific topics, especially for the pediatric population. In addition, for some topics, large studies were conducted before 2010 and, therefore, were excluded according to the search strategy. This decision was made considering the epidemiologic changes of resistance patterns. Thereafter, panel experts' opinion were requested when the literature evidence was not exhaustive.

Moreover, a possible limitation of the applicability of this consensus statement could be related to the lack of available epidemiologic data regarding resistance patterns (ie, clindamycin resistance) in each clinical setting.

CONCLUSIONS

Despite limitations, this article offers practical suggestions to clinicians for managing the most common bacterial SSTIs, based on current evidence. When lacking, panel experts' opinions were considered the best substitute to formulate treatment recommendations.

Large pediatric studies are needed to overcome the lack of clear indications regarding treatment regimens. Moreover, periodic updates are pivotal due to changes in epidemiologic and vaccine coverage.

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LG and IN conceived the manuscript. LG, EV, AB, GCG, EC, AD, SE, SG, AG, AK, SL, ALV, PM, CM, GN, AN, GMR, MEH and IN voted as experts. CT and EV joined as experts for methodology, CD as expert in the radiology fields and AV guaranteed the collaboration between the core working group. All authors equally contributed in manuscript writing and/or revision.

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CONFLICT OF INTERESTS

EV, AB, GCG, CD, AD, SG, AG, SL, AL, PM, CM, GN, CT, AV, MEH declare no potential conflict of interests.

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APPENDIX

Appendix 1. Search strategy.

Impetigo

impetigo[Title/Abstract] AND children[Title/Abstract] AND (("2010/01/01"[PDAT]: "2017/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Total 73 papers

Papers included (treatment)

Randomized controlled trials 5

Observational studies 1

Forunculosis, abscesses, folliculitis

(furunculosis[Title/Abstract] OR (skin[Title/Abstract] AND (abscess[Title/Abstract] OR abscesses [Title/Abstract])) OR folliculitis[Title/Abstract]) AND children[Title/Abstract] AND (("2010/01/01"[PDAT]: "2017/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Total 111 papers

Papers included (treatment)

Randomized controlled trials 10

Observational studies 3

Cellulitis/Orbital cellulitis

(cellulitis[Title/Abstract]AND children [Title/Abstract]) AND (("2010/01/01"[PDAT]: "2017/12/31"[PDAT) AND "humans" [MeSH Terms] AND English[lang])

Total 180 papers

Papers included (cellulitis treatment)

Randomized controlled trials 5

Observational studies 5

Papers included (orbital cellulitis treatment)

Observational studies 8

APPENDIX 2. RECOMMENDATIONS ACCORDING TO GRADE METHODOLOGY AND PANEL EXPERTS' OPINION

Treatment recommendations for impetigo including quality of studies evaluated with the GRADE methodology and panel experts' opinion

1. When topical treatment is indicated for impetigo?

Topical treatment is indicated for limited impetigo extension (<2% of total body surface area) for 5–7 days (or until complete resolution).

Experts agreement:

Strongly agree: 14/19 (73,7%) Agree: 5/19 (26,3%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak

2. Which topical treatment is indicated for impetigo?

Topical antibiotics suggested for impetigo are: fusidic acid, mupirocin (> 2 months *of age) or retapamulin (*> 9 months *of age).*

Experts agreement:

Strongly agree: 15/19 (79%) Agree: 4/19 (21%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive strong

Retapamulin is currently not indicated for MRSA [quality of evidence: very low; strength of recommendation: negative weak].

N-dichloro-2, 2-dimethyltaurine and ozenoxacin could be valid options for treating uncomplicated impetigo [quality of evidence: low; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Iovino SM, Int J Clin Exp Pathol 2011			
N-dichloro-2, 2-dimethyltaurine 0.1%, 0.5% or 1.5% topical gel is well tolerated with high rates of clinical and microbiological responses. 10% of MRSA.			
Study design	High (randomized trial)		**Low**
Risk of Bias	–1		

(*Continued*)

GRADE criteria	Rating	Footnotes	Quality of the evidence
		Not compared with SOC but only with the same topical gel at different concentrations	
Indirectness	no		
Imprecision	−1	CI non reported	
Other			
Tanus T, Adv Skin Wound Care 2014			
Topical retapamulin 1% was associated with a significantly lower rate of clinical and microbiologic success compared with oral linezolid. High MRSA rate.			
Study design	High (randomized trial)		**Low**
Risk of Bias			
Indirectness	−1	Comparison not highly applicable	
Imprecision	−1	wide confidence intervals	
Other			
Gropper S, Future Microbiol 2014			
Ozenoxacin 1% cream was effective and safe in the treatment of impetigo.			
Study design	High (randomized trial)		**Moderate**
Risk of Bias	−1	sponsored study (by Ferrer Int. SA)	
Indirectness	no		
Imprecision	no		
Other			
Bohaty BR, Int J W Dermatol 2015			
Use of topical retapamulin 1% ointment is indicated in the treatment of cutaneous bacterial infections, particularly those caused by S. aureus, including MRSA. MRSA rate 20%.			
Study design	Prospective (low quality)		Very Low
Risk of Bias	−1	Small sample size	
Indirectness	no		
Imprecision	−1	CI not reported	
Other			

3. When systemic treatment should be performed in children with impetigo?

Systemic treatment should be associated to topical therapy in case of extensive/multiple lesions (>2% of total body surface area), children < 1 year of age, suspected/confirmed MRSA etiology or PVL positivity or in case of poor response to topical treatment or relapse.
Experts agreement:
Strongly agree: 19/19 (100%) Agree: 0 Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive strong

4. Which is the recommended systemic treatment for impetigo?

First-line oral treatment with flucloxacillin or a first-generation cephalosporin (cephalexin) for 7–10 days could be indicated.
Experts agreement:

Strongly agree: 6/19 (31.6%) Agree: 13/19 (68.4%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

The use of amoxicillin/clavulanic acid should be limited, considering its broad-spectrum activity.
Experts agreement:

Strongly agree: 10/19 (52.7%) Agree: 7/19 (36.8%) Disagree: 2/19 (10.5%) Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

In case of high rate of MRSA infection in the community (>10%), oral clindamycin or trimethoprim-sulfamethoxazole (the latter if Streptococcus pyogenes is excluded) for 7–10 days (or until complete resolution) is suggested [quality of evidence: very low; strength of recommendation: positive-weak].

1. Which is the gold standard treatment for abscesses not resolving with spontaneous drainage?

Abscesses not resolving with spontaneous drainage should be treated with incision and drainage.
Experts agreement:

Strongly agree: 13/19 (68,4%) Agree: 6/19 (31,6%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

2. Which surgical technique can be considered as an alternative to incision and drainage of skin abscesses?

LOOP technique could be an alternative to incision and drainage [quality of evidence: very low; strength of recommendation: positive-weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Bowen AC, Lancet 2016			
Twice-daily cotrimoxazole for 3 days or once-daily cotrimoxazole for 5 days is equally effective and safe compared to benzathine benzylpenicillin. Low MRSA rate.			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	–1/no	open-label, outcome-assessment-blinded, non-inferiority, randomised, controlled trial	
Indirectness	no		
Imprecision	no		
Other			
Tong S, J Pediatr Child Health 2010			
Treatment was successful in 7 of 7 children treated with trimethoprim-sulfamethoxazole and 5 of 6 treated with benzathine penicillin. Low MRSA rate			
Study design	RCT (High quality)		**Very Low**
Risk of Bias	–2	Very small sample size	
Indirectness			
Imprecision	–2		
Other			

Treatment recommendations for skin abscesses including quality of studies evaluated with the GRADE methodology and panel experts' opinion

Ultrasonographically-guided needle-aspiration is not suggested as alternative therapy for skin abscesses [quality of evidence: very low; strength of recommendation: negative-weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Gaspari RJ, *Ann Emerg Med* 2011			
Ultrasonographically guided needle-aspiration is an insufficient therapy for skin abscesses			
Study design	RCT (High quality)		**Low**
Risk of Bias	−1	Not blinded	
Indirectness	no		
Imprecision	−1	Wide confidence intervals	
Other			
Ladde JG, *Am J Emerg Med* 2015			
LOOP technique has a lower failure rate compared to incision and drainage			
Study design	Observational retrospective (low quality)		**Very low**
Risk of Bias	−2		
Indirectness			
Imprecision	−1	Wide confidence interval	
Other			

3. Is wound packing indicated after incision and drainage of skin abscesses to reduce treatment failure and recurrence rates?

Wound packing is not suggested to reduce treatment failure and recurrence rates after incision and drainage of skin abscesses [quality of evidence: very low; strength of recommendation: negative-weak].

4. Is a systemic antibiotic treatment indicated after incision and dreinage in case of simple cutanous abscesses for reducing treatment failure?

Treatment with oral TMP-SMX or clindamycin for 7–10 days (or until complete resolution) after incision and drainage of simple cutaneous abscesses is recommended [quality of evidence: high; strength of recommendation: positive strong].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Kessler DO, *Pediatr Emerg Care* 2012			
Wound packing does not appear to reduce treatment failure and recurrence rates			
Study design	RCT (High quality)		**Very low**
Risk of Bias	−2	Single blinded, no intention to treat analysis	
Indirectness	no		
Imprecision	−1	Wide confidence intervals	
Other			

GRADE criteria	Rating	Footnotes	Quality of the evidence
Talan DA, *N Engl J Med* 2016			
In setting where MRSA was prevalent, TMP-SMX resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo			
Study design	RCT (High quality)		**High**
Risk of Bias	no		
Indirectness	no		
Imprecision	no		
Other			
Holmes L, *J Pediatr* 2016			
Patients with MRSA skin abscess are more likely to experience treatment failure if given 3 rather 10 days of TMP-SMX after surgical drainage			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	–1	not blinded	
Indirectness	no		
Imprecision	no		
Other			
Schmitz GR, *Ann Emerg Med* 2010			
After the incision and drainage of uncomplicated abscess in adults, treatment with TMP-SMX does not reduce treatment failure			
Study design	RCT (High quality)		**Very low**
Risk of Bias	–1	no intention to treat analysis	
Indirectness	–1	age >16 years	
Imprecision	–1		
Other			
Duong M, *Ann Emerg Med* 2010			
Antibiotics are not required for pediatric skin abscesses resolution			
Study design	RCT (High quality)		**Very low**
Risk of Bias	–1	selection bias	
Indirectness	no		
Imprecision	–2	(-∞ lower limit of the CI)	
Other			
Daum RS, *N Engl J Med* 2017			
Clindamycin or TMP-SMX after incision and drainage improves short-term outcomes			
Study design	RCT (High quality)		**High**
Risk of Bias	no		
Indirectness	no		
Imprecision	no		
Other			
Williams DJ, *Pediatrics* 2011			
TMP-SMX or beta-lactams are associated with increase treatment failure compared with clindamycin			
Study design	Observational (low quality)		**Very low**
Risk of Bias	–1		
Indirectness	–1		

(*Continued*)

GRADE criteria	Rating	Footnotes	Quality of the evidence
Imprecision	no		
Other			

5. Is a systemic antibiotic treatment indicated after incision and drainage in case of simple cutaneous abscesses for reducing recurrence rate?

Treatment with oral TMP-SMX or clindamycin for 7–10 days (or until complete resolution) after incision and drainage of simple cutaneous abscesses could reduce recurrences [quality of evidence: high; strength of recommendation: positive strong].

6. Which systemic antibiotic treatment is indicated after incision and drainage in case of complicated cutaneous abscesses for reducing treatment failure?

In case of complicated cutaneous abscesses, empiric treatment with intravenous vancomycin or clindamycin (if the local resistance rate is below 10%) after incision and drainage is recommended

GRADE criteria	Rating	Footnotes	Quality of the evidence
Holmes L, *J Pediatr* 2016			
Patients with MRSA skin abscess are more likely to experience recurrence if given 3 rather 10 days of TMP-SMX after surgical drainage			
Study design	RCT (High quality)		**Low**
Risk of Bias	–1	not blinded	
Indirectness	no		
Imprecision	–1		
Other			
Schmitz GR, *Ann Emerg Med* 2010			
After the incision and drainage of uncomplicated abscess in adults, treatment with TMP-SMX may reduce recurrences			
Study design	RCT (High quality)		**Very low**
Risk of Bias	–2	no intention to treat analysis; about 50% lost to follow-up	
Indirectness	–1	age >16 years	
Imprecision	–1		
Other			
Duong M, *Ann Emerg Med* 2010			
Antibiotics may prevent new lesions in the short term			
Study design	RCT (High quality)		**Very low**
Risk of Bias	–2	selection bias; 40% lost to follow-up	
Indirectness	no		
Imprecision	–2	(-∞ lower limit of the CI)	
Other			
Daum RS, *N Engl J Med* 2017			

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(*Continued*)

GRADE criteria	Rating	Footnotes	Quality of the evidence
No differences in recurrent infection rate between clindamycin or TMP-SMX and placebo			
Study design	RCT (High quality)		**High**
Risk of Bias	no		
Indirectness	no		
Imprecision	no		
Other			
Williams DJ, *Pediatrics* 2011			
TMP-SMX or beta-lactams are associated with increase recurrence rate compared with clindamycin			
Study design	Observational (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1		
Imprecision	no		
Other			

for reducing treatment failure. The treatment should be targeted when susceptibilities become available. [quality of evidence: very low; strength of recommendation: positive weak].

Experts agreement:

Strongly agree: 12/19 (63,2%) Agree: 5/19 (26,3%) Disagree: 2/19 (10,5%) Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak

Scale-down to oral treatment with TMP-SMX or clindamycin could be done when systemic symptoms are resolved and, at least, after 3−5 days of intravenous treatment. The length of treatment should be overall 10−14 days (or until complete resolution). [quality of evidence: very low; strength of recommendation: positive weak].

Experts agreement:

Strongly agree: 9/19 (47,4%) Agree: 10/19 (52,6%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak

7. Which systemic antibiotic treatment is indicated as an alternative to the standard of care (vancomycin or clindamycin) after incision and drainage in case of complicated cutaneous abscesses for reducing treatment failure?

In case of high rate (> 10%) of MRSA infection in the community, intravenous TMP-SMX, daptomycin and ceftaroline are equally safe and effective for treatment of complicated cutaneous abscesses compared to the standard of care [TMP-SMX: quality of evidence: high; strength of recommendation: positive strong; daptomycin and ceftaroline: quality of evidence: moderate; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Miller LG, *N Engl J Med* 2015			
No differences in efficacy and safety between clindamycin and TMP-SMX			
Study design	RCT (High quality)		**High**
Risk of Bias	no		
Indirectness	no		

(*Continued*)

GRADE criteria	Rating	Footnotes	Quality of the evidence
Imprecision	no		
Other			
Williams DJ, *Pediatrics* 2011			
TMP-SMX or beta-lactams are associated with increase recurrence rate compared with clindamycin			
Study design	Observational retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1		
Imprecision	no		
Other			
Bradley J, *Pediatrics* 2017			
Once daily daptomycin is well tolerated, safe and effective			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	−1	lack of blinding	
Indirectness	no		
Imprecision	no		
Other			
Korczowski B, *Pediatr Infect Dis J* 2016			
Ceftaroline fosamil is well tolerated and effective			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	−1	Only observer blinded	
Indirectness	no		
Imprecision	no		
Other			

8. Which systemic antibiotic treatment is indicated if PVL-SA is suspected?

If a PVL-SA is suspected as a cause of skin abscess, clindamycin or rifampicin should be added to the standard regimen to counteract the PVL activity.
Experts agreement:
Strongly agree: 13/19 (68,4%) Agree: 6/19 (31,6%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak
In severe cases or suspected/proved MRSA-PVL etiology, linezolid could be an option.
Experts agreement:
Strongly agree: 13/19 (68,4%) Agree: 6/19 (31,6%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

9. Are decolonization strategies indicated in children with recurrent skin abscesses for obtaining *Staphylococcus aureus* eradication?

In case of high rate (> 10%) of MRSA infection in the community, decolonization strategies based on chlorhexidine body wash or bleach bath and nasal mupirocin ointment could be indicated to eradicate Staphylococcus aureus and prevent recurrent infection [quality of evidence: moderate; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Fritz SA, *Clin Infect Dis* 2012			
Individual decolonization is effective in eradicating and reducing the incidence of subsequent SSTI			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	–1	Not blinded	
Indirectness	no		
Imprecision	no		
Other			

10. If decolonization strategies are performed in children, which is the best approach for *Staphylococcus aureus* eradication?

In case of high rate (> 10%) of MRSA infection in the community, household decolonization could be more effective than the individual one in eradicating and reducing the incidence of subsequent SSTI [quality of evidence: low; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Fritz SA, *Clin Infect Dis* 2012			
Household decolonization is more effective than the individual one in eradicating and reducing the incidence of subsequent SSTI			
Study design	RCT (High quality)		**Low**
Risk of Bias	–2	Not blinded, no intention to treat analysis	
Indirectness	no		
Imprecision	no		
Other			

Treatment recommendations for cellulitis and erysipelas including quality of studies evaluated with the GRADE methodology and panel experts' opinion

1. Which systemic empirical antibiotic treatment is indicated for uncomplicated mild cellulitis and for how long?

Patients with mild cellulitis should be treated empirically with an oral first generation cephalosporin (i.e. cephalexin) for 7–10 days (or until complete resolution) in case of MRSA incidence below 10% [quality of evidence: moderate; strength of recommendation: positive weak].
Oral TMP/SMX or clindamycin (if the local resistance rate is <10%) for 7–10 days (and until complete resolution) should be prescribed in children with uncomplicated mild cellulitis if MRSA incidence is above 10% [quality of evidence: moderate; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Williams DJ, *Pediatrics* 2011			
Oral treatment with TMP-SMX or beta-lactams is associated with increase treatment failure compared with clindamycin. Reported treatment duration 9.4 days (+/− 2.6).			
Study design	Observational retrospective study (low quality)		**Very Low**
Risk of Bias	−1		
Indirectness	−1		
Imprecision	no		
Other			
Miller LG, *N Engl J Med* 2015			
No differences in efficacy and safety between oral clindamycin and TMP-SMX. Length of treatment 10 days.			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	no		
Indirectness	no		
Imprecision	−1	wide confidence interval considering cellulitis sub-group	
Other			
Moran GJ, JAMA 2017			
Oral cephalexin plus trimethoprim/sulfamethoxazole compared with cephalexin alone is not associated in higher rates of clinical resolution (per-protocol analysis). Length of treatment 7 days. <10%MRSA colonization.			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	no		
Indirectness	−1	Age>12 years	
Imprecision	no	Considering ITT analysis, −1 for wide CI	
Other			
Pallin DJ, Clin Infect Dis 2013			
The addition of oral trimethoprim-sulfamethoxazole to cephalexin is not associated with higher clinical cure rates. Length of treatment 14 days, <10% MRSA.			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	no		
Indirectness	no		
Imprecision	−1	wide CI	
Other			
Kam AJ, Ann Emerg Med 2008			
Short course of ED IV antibiotics (2 doses) followed by discharge is associated with higher failure rates. MRSA not reported.			
Study design	Observational, retrospective (low quality)		**Very low**
Risk of Bias	−2		
Indirectness	no		

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GRADE criteria	Rating	Footnotes	Quality of the evidence
Imprecision	−1		
Other			

2. Which systemic empirical antibiotic treatment is indicated for uncomplicated moderate/severe cellulitis and for how long?

In case of low incidence of MRSA in the community, children with uncomplicated moderate/severe cellulitis could be empirically treated with intravenous anti-staphylococcal penicillin (ASPs) or first generation cephalosporin (i.e cefazolin, cefalotin) for at least 48 h before switching to oral therapy. Scale-down to empiric oral treatment with amoxicillin/clavulanic acid could be indicated when systemic symptoms are resolved. [quality of evidence: very low; strength of recommendation: positive weak].

The treatment should be targeted when sensitivities become available. The length of treatment should be overall 10−14 days (or until complete resolution) [quality of evidence: very low; strength of recommendation: positive strong].

Experts agreement:

Strongly agree: 15/19 (78,9%) Agree: 4/19 (21,1%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive strong

In case of high incidence of MRSA in the community, intravenous TMP/SMX or clindamycin (if the local resistance rate is <10%) should be started in children with uncomplicated

GRADE criteria	Rating	Footnotes	Quality of the evidence
Ibrahim LF, Pediatr Infect Dis J 2016			
Older children with moderate/severe limb cellulitis without systemic symptoms can be treated at home with intravenous home ceftriaxone			
Study design	Observational prospective study (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	no		
Imprecision	−1	CI not indicated	
Other			
Ibrahim LF, Emerg Med J 2017			
Intravenous ceftriaxone at home does not differ to hospital intravenous flucloxacillin administered for 48h (before switching to oral therapy) in the treatment failure rate in children with uncomplicated moderate/severe cellulitis. MRSA infection rate <6%.			
Study design	Observational prospective study (low quality)		**Low**
Risk of Bias	−1		
Indirectness	no		
Imprecision	no		
Other			

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GRADE criteria	Rating	Footnotes	Quality of the evidence
de Vasconcellos AG, JPN J Infect Dis 2012			
Oxacillin and cephalotin are the most frequent drug used in uncomplicated cellulitis. MRSA infection rate <10%.			
Study design	Observational retrospective study (low quality)		**Very low**
Risk of Bias	−1		
Indirectness			
Imprecision	−1	CI not indicated	
Other			

moderate/severe cellulitis [quality of evidence: very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 6/19 (31,6%) Agree: 12/19 (63,5%) Disagree: 0 Strongly disagree: 1/19 (4,9%)
Quality of evidence: very low; strength of recommendation: positive weak
Scale-down to oral treatment with TMP/SMX or clindamycin (if the local resistance rate is <10%) could be indicated when systemic symptoms are resolved and at least after 48 h of intravenous antibiotics [quality of evidence: very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 6/19 (31,6%) Agree: 12/19 (63,5%) Disagree: 1/19 (4,9%) Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak
The treatment should be targeted when sensitivities become available.
The length of treatment should be overall 10–14 days (or until complete resolution) [quality of evidence: very low; strength of recommendation: positive weak]
Experts agreement:
Strongly agree: 14/19 (73,7%) Agree: 5/19 (26,3%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

3. Which systemic empiric treatment is indicated in patients with complicated cellulitis?

In case of complicated cellulitis, empiric treatment with intravenous vancomycin or teicoplanin or clindamycin (if the local resistance rate is below 10%) is recommended for reducing treatment failure [quality of evidence: very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 13/19 (68,4%) Agree: 5/19 (26,3%) Disagree: 1/19 (5,3%) Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak
Adding Gram-negative coverage and anaerobes (i.e. piperacillin/tazobactam) should be considered in case of surgical drainage, bite or penetrating injury, foreign body, fracture, medical comorbidities and immunosuppression. The treatment should be targeted when sensitivities become available. [quality of evidence: very low; strength of recommendation: positive strong].
Experts agreement:
Strongly agree: 16/19 (84,2%) Agree: 3/19 (15,8%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive strong
Scale-down to oral treatment with TMP-SMX or clindamycin could be done when systemic symptoms are resolved and, at least, after 3–5 days of intravenous treatment [quality of evidence:

very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 9/19 (47,4%) Agree: 9/19 (47,4%) Disagree: 1/19 (5,2%) Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak
In case of risk factors for Pseudomonas aeruginosa (i.e. surgical drainage, bite or penetrating injury, foreign body, fracture, medical comorbidities and immunosuppression), switch to oral ciprofloxacin should be considered [quality of evidence: very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 9/19 (47,3%) Agree: 10/19 (52,7%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak
The length of treatment should be overall 14–21 days (and at least until complete resolution) [quality of evidence: very low; strength of recommendation: positive weak].
Experts agreement:
Strongly agree: 5/19 (26,3%) Agree: 14/19 (73,7%) Disagree: 0 Strongly disagree: 0
Quality of evidence: very low; strength of recommendation: positive weak

4. Which systemic antibiotic treatment is indicated as an alternative to the standard of care (vancomycin or clindamycin) in patients with complicated cellulitis?

In case of high rate of MRSA infection in the community, daptomycin or ceftaroline are equally safe and effective for the treatment of complicated cellulitis compared to the standard of care [quality of evidence: moderate; strength of recommendation: positive-strong].

Bradley J, *Pediatrics* 2017			
Once daily daptomycin is well tolerated, safe and effective			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	–1	lack of blinding	
Indirectness	no		
Imprecision	no		
Other			
Korczowski B, *Pediatr Infect Dis J* 2016			
Ceftaroline fosamil is well tolerated and effective			
Study design	RCT (High quality)		**Moderate**
Risk of Bias	–1	Only observer blinded	
Indirectness	no		
Imprecision	no		
Other			

Treatment reccomendations for orbital and periorbital cellulitis including quality of studies evaluated with the GRADE methodology and panel experts' opinion

1. Which systemic empirical antibiotic treatment is indicated for periorbital (pre-septal) cellulitis?

In setting with low MRSA prevalence, children with periorbital cellulitis could be treated with intravenous ceftriaxone or flucloxacillin for at least 48–72 h before switching to oral therapy [quality of evidence: low; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Goncalves R, *Orbit* 2016			
Intravenous antibiotic treatment with ceftriaxone for 13 ± 2 days is associated with a favourable clinical outcome.			
Study design	Observational, retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	no		
Imprecision	−1	no CI reported	
Other			
Friedel N, *Am J Ther* 2017			
Children with pre-septal cellulitis associated with insect bites can be treated with oral antibiotic therapy			
Study design	Observational, retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	no		
Imprecision	−1	No CI reported	
Other			
De Vasconcellos AG, Jpn J Infect Dis 2012			
Intravenous antibiotic treatment with oxacillin or cefalotin can be considered as the treatment of choice in regions with incidence rates of MRSA < 10%			
Study design	Observational, retrospective (low quality)		**Very low**
Risk of Bias	no		
Indirectness	no		
Imprecision	−1	No CI reported	
Other			
Ibrahim LF, Pediatr Infect Dis J 2016			
Periorbital/facial cellulitis can not be treated with intravenous antibiotics at home (ceftriaxone) Children with periorbital cellulitis are more likely to be hospitalized and treated with intravenous flucloxacillin for about 48h before switching to oral therapy.			
Study design	Observational, prospective (low quality)		**Very low**
Risk of Bias	no		
Indirectness	−1	Low percentage of periorbital cellulitis	
Imprecision	no		
Other			
Ibrahim LF, Emerg Med J 2017			
Periorbital cellulitis is treated with intravenous flucloxacillin for 48−72h before switching to oral therapy			
Study design	Observational, prospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1	Low percentage of periorbital cellulitis	

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GRADE criteria	Rating	Footnotes	Quality of the evidence
Imprecision	no		
Other			
Botting AM, *Int J Pediatr Otor* 2008			
Children with pre-septal cellulitis are mostly treated with intravenous cefuroxime or co-amoxiclav for 48h before switching to oral therapy (with 95% of clinical response)			
Study design	Observational retrospective (low quality)		**Very low**
Risk of Bias	–1		
Indirectness	no		
Imprecision	–1		
Other			

Scale-down to empiric oral treatment with amoxicillin/clavulanic acid could be indicated when systemic symptoms are resolved [quality of evidence: very low; strength of recommendation: positive weak].

Experts agreement:

Strongly agree: 8/19 (42,1%) Agree: 11/19 (57,9%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak

The treatment should be targeted if sensitivities become available. The length of treatment should be overall 5–10 days (or at least until complete resolution) [quality of evidence: very low; strength of recommendation: positive strong].

Experts agreement:

Strongly agree: 16/19 (84,2%) Agree: 3/19 (15,8%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive strong

If MRSA is suspected or in case of no clinical improvement after 48 h of treatment, an MRSA-active agent (i.e. vancomycin, teicoplanin or in selected cases daptomycin) should be used [quality of evidence: very low; strength of recommendation: positive strong].

Experts agreement:

Strongly agree: 18/19 (94,7%) Agree: 1/19 (5,3%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive strong

2. Which systemic antibiotic treatment is indicated for orbital (post-septal) cellulitis alone or in combination with surgery?

In absence of immediate indications for surgery, children could be treated with intravenous ceftriaxone plus clindamycin [quality of evidence: very low; strength of recommendation: positive weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Goncalves R, *Orbit* 2016			
Intravenous antibiotic treatment with ceftriaxone for 17 ± 5 days is associated with a favourable clinical outcome.			
Study design	Observational, retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1	Low percentage of orbital cellulitis	
Imprecision	−1	no CI reported	
Other			
Botting AM, *Int J Pediatr Otor* 2008			
The majority of children (77%) with post-septal cellulitis have a clinical response to intravenous antibiotics			
Study design	Observational retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1		
Imprecision	−1	no information on antibiotics chosen	
Other			
Sciarretta V, *Int J Pediatr Otor* 2017			
Suggested medical treatment is with third generation cephalosporins (cefotaxime or ceftriaxone) or combined penicillin (ampicillin/sulbactam or amoxicillin/clavulanic acid)			
Study design	Observational retrospective (low quality)		**Very low**
Risk of Bias	−1		
Indirectness	−1	More focused on sub-periosteal abscess	
Imprecision	−1		
Other			

In setting with high clindamycin resistance rates (>10%), ceftriaxone plus vancomyicin plus metronidazole should be used [quality of evidence: very low; strength of recommendation: positive weak].

Experts agreement:

Strongly agree: 13/19 (68,4%) Agree: 6/19 (31,6%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak

3. Is a treatment with intravenous steroids indicated in children with orbital cellulitis in addition to the antibiotic treatment?

The addition of intravenous steroids to the antibiotic treatment in children with orbital cellulitis is not suggested [quality of evidence: very low; strength of recommendation: negative weak].

GRADE criteria	Rating	Footnotes	Quality of the evidence
Chen L, *Ophtal Plast Reconstr Surg* 2017			
IV dexamethasone, associated with broad spectrum antibiotic therapy, is associated with faster clinical recovery and lower length of hospital stay			
Study design	Observational prospective (Low quality)		**Very low**
Risk of Bias	no		
Indirectness	no		
Imprecision	−1	No CI reported	
Other			
Sciarretta V, *Int J Pediatr Otor* 2017			
IV Methylprednisolone is not associated with reduction of recurrence rates or complications			
Study design	Observational retrospective (Low quality)		**Very low**
Risk of Bias	−1		
Indirectness	no		
Imprecision	−1	No CI reported	
Other			

4. Is surgery indicated in case of post-septal cellulitis?

Orbital abscess formation, worsening of ocular signs and failure to improve in 48 h of parenteral antibiotics, should be considered indications for surgery [quality of evidence: very low; strength of recommendation: positive weak].

Experts agreement:

Strongly agree: 11/19 (57,9%) Agree: 8/19 (42,1%) Disagree: 0 Strongly disagree: 0

Quality of evidence: very low; strength of recommendation: positive weak