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Review Article

Ideal Features of Topical Antibiotic Therapy for the Treatment of Impetigo: An Italian Expert Consensus Report

Iria Neri, MD[1], Michele Miraglia del Giudice, MD[2], Andrea Novelli, MD[3], Giuseppe Ruggiero, MD[4], Giovanni Pappagallo, MD, MPH[5], Luisa Galli, MD[6,7,*]

[1] *Dermatology Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[2] *Department of Woman and Child and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy*
[3] *Department of Health Sciences, Clinical Pharmacology and Oncology Section, University of Florence, Italy*
[4] *Dermatology Study Group of the Italian Federation Italian of Pediatricians, Rome, Italy*
[5] *School of Clinical Research Methodology, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella VR, Italy*
[6] *Department of Health Sciences, University of Florence, Florence, Italy*
[7] *Paediatric Infectious Diseases Unit, Meyer Children's Hospital, Florence, Italy*

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ABSTRACT

Background: A group of Italian experts in impetigo medical care sought to define 10 statements to describe the ideal characteristics of the best local antibiotic treatments, and to provide relevant information re- garding their appropriate use and prescription that should be considered in clinical practice for impetigo management.
Objective: A group of Italian experts in impetigo medical care sought to define 10 statements to describe the ideal characteristics of the best local antibiotic treatments, and to provide relevant information regarding their appropriate use and prescription that should be considered in clinical practice for impetigo management.
Methods: A consensus on ideal features of antibiotic therapy for the treatment of impetigo was appraised by an online Delphi-based method, based on a panel of 61 infectious disease specialists, pediatricians, and dermatologists coordinated by a scientific committee of 5 experts specializing in impetigo management.
Results: Full or very high consensus was reached on the 10 statements identified to describe the characteristics of the best hypothetic antibiotic therapy for impetigo together with indications for appropriate antibiotics use.
Conclusions: Several criteria have to be considered when selecting topical antibacterial therapy for impetigo. Beyond efficacy and safety, antimicrobial susceptibility and pharmacological characteristics of the agent are essential points. Formulation of the antimicrobial product is fundamental, as well as patient and caregiver preference, to facilitate therapeutic adherence, to achieve the infection control, and to obtain the best benefit from treatment (*Curr Ther Res Clin Exp.* 2023; 84:XXXXXX).

Introduction

Impetigo is a common bacterial skin infection that mainly occurs in children from ages 2 to 5 years; however, individuals of any age can be affected by this bacterial condition.[1] Recent data indicate 111 million children and up to 140 million people are affected at a given time in developed countries.[2]

Impetigo is typically due to infection by *Staphylococcus aureus*, group A beta-hemolytic *Streptococcus pyogenes*, or less commonly by anaerobic bacteria. These bacteria habitually reside on healthy skin and some of them, such as *Strep pyogenes* and *Staph aureus*, may colonize the nasal, axillary, pharyngeal, or perineal areas. Susceptible skin can develop infections due to these bacteria.[1] Two types of impetigo have been described: nonbullous (ie, *impetigo contagiosa*) and bullous. Around 70% of cases are nonbullous impetigo (due to *Staph aureus* and group A beta-haemolytic *Streptococcus*), which is generally managed in pediatric primary care settings. Nonbullous impetigo is primarily characterized by maculo-papular lesions and subsequently by thin-

* Address correspondence to: Luisa Galli, Paediatric Infectious Diseases Unit, University Hospital Meyer, Azienda Ospedaliero Universitaria Meyer, Viale Pieraccini 24, Florence IT-50131, Italy
E-mail address: luisa.galli@unifi.it (L. Galli).

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walled vesicles that break, resulting in erosions on the skin surface with crusts on both intact and damaged skin.[1] Bullous impetigo is caused by toxin-producing *Staph aureus* and its features include fragile and large vesicles and flaccid bullae evolving into erosions with a varnish-like and thin crust. This kind of impetigo is typically localized in intertriginous areas of the trunk and extremities.[3]

After excoriating an infected area, patients with impetigo can further spread the infection either to themselves or others, especially in crowded places (eg, schools and ambulatory care centers), with higher probability during summer and in low hygiene areas.[3]

Treatment with antibiotics should be initiated as soon as possible due to the high contagiousness of the disease, the associated discomfort, and bad cosmetic appearance.[4] Therapy depends on different parameters, including the extent and site of lesions and the presence of systemic symptoms. Currently, topical and/or systemic antibiotics and topical disinfectants are the main options for the treatment of impetigo.[3] Topical antibiotics offer several advantages compared with systemic administration, among them the delivery of high concentrations of the antimicrobial agent to the site of infection and the limited toxicity.[5] Unfortunately, the extensive use of several topical antibiotics caused an increase of bacterial resistance in some settings, with a possible reduction of the efficacy of these agents.[5] Results from a Cochrane review (analyzing 68 randomized controlled trials) on impetigo treatments showed that topical antibiotics are more effective than placebo and preferable to oral antibiotics for impetigo of limited extension.[6] Systemic antibiotics are often used for those patients with more generalized or severe infections, in which topical therapy is not appropriate.

When prescribing antibiotics, it is essential to know the antibiotic resistance trends at the local level. The development of new antibiotics represents a current need, considering the increase in multidrug-resistant pathogens, such as methicillin-resistant *Staph aureus* (MRSA) and mupirocin-resistant or quinolone-resistant *Staph aureus*.[7–11] Moreover, fusidic acid monotherapy, specifically topical formulations, has been strongly linked to the emergence of fusidic acid resistance among either MRSA or methicillin-susceptible *Staph aureus* (MSSA).[12]

Besides antibiotic resistance, other disadvantages of topical treatments can be local allergic reactions; skin sensitization; difficulties in application to areas like eyelids, mouth, and back; and, in some cases, longer therapy duration.[1]

Although a wide pool of treatment options for impetigo is available, systematic evidence-based research to identify the most effective treatment of impetigo is lacking. However, some indications for impetigo treatment are available from scientific literature,[13] a comparative review of current topical antibiotics for impetigo was performed by Galindo et al,[14] and Schachner et al[4] recently defined an evidence-based treatment algorithm to address impetigo treatment, both in adult and pediatric populations, considering different antibiotic options.

On the basis of the current scenario, a consensus project on the hypothetical best features for an antibiotic therapy was structured. A group of Italian experts in impetigo medical care was enrolled to describe the ideal characteristic of the best local antibiotic treatments as well as to provide relevant information regarding their appropriate use and prescription during clinical practice.

Methods

To assess the consensus on the ideal features of a topical antibiotic treatment for impetigo, we used an online Delphi-based method (Estimate-Talk-Estimate). Estimate-Talk-Estimate is a method for reaching consensus within a selected group of experts. It combines a nominal group activity restricting verbal interaction with face-to-face interaction processes. Firstly, 5 experts (the steering committee) selected among specialists involved in medical care of patients with impetigo in Italian institutions, individually identified some points of interest (hereafter: items) which, in their opinion, deserved to be explored and discussed using the Delphi method.[15,16] A senior clinical epidemiologist (G. P.) who is an expert in gaining consensus among stakeholders (hereafter: facilitator) harmonized these items, which were then presented to the expert group. During the first meeting, harmonized items were discussed face-to-face to reach an agreement between the facilitator's work and the experts' opinions. Afterward, finalized items were used by clinicians to draft 1 statement for each item, individually. This process resulted in a certain number of statements that were then harmonized by the facilitator. In the second and last face-to-face meeting, the experts and the facilitator reviewed and further discussed the harmonized statements, reaching a final version. The 10 statements generated in this way expressed consensus among the experts involved.

The 10 statements developed by the steering committee were delivered through an invitation sent by e-mail to a group of specialists in allergology, dermatology, infectious diseases, and pediatrics who have an advanced training in the treatment of impetigo and are members of the Edra Medikey database (Certifiquality certified). Among them, 61 professionals, including 3 allergologists (4.9%), 15 dermatologists (24.6%), 5 infectivologists (8.2%), and 38 pediatricians (62.3%), accepted to participate, were included in the panel, and rated agreement or disagreement for each of the10 statements, independently and blindly. Participants expressed their level of agreement on each statement using the RAND 9-point scale (ranging from 1 = completely disagree to 9 = completely agree) and consensus was reached that a statement had to be considered appropriate if the median score was $\geq$7 without disagreement, according to the RAND/UCLA Appropriateness Method User's Manual.[17] The survey was performed online on a secured survey website, using an online dedicated platform. The scientific steering committee collected and analyzed the results before the final consensus meeting. The final phase of the project was based on the Consensus Development Conference method. After the individual and anonymous online survey, the 5 members of the steering committee attended a web meeting and expressed opinions on each statement, with final consensus defined at $\geq$80% agreement.[18]

Discussion

Consensus was reached for all the 10 statements and for 3 out of 10 the consensus was 100%. Comments provided by the participants have been collected and considered to guide the discussion for the following final statements regarding the ideal features of a topical antibiotic treatment in patients with impetigo. See **Supplemental Figures 1** through **10**.

Topical antibiotics for impetigo should have the following features

Statement 1. Narrow spectrum of action, including Strep pyogenes *and* Staph aureus, *including MRSA strains*

In the final consensus meeting, there was no unanimous response to this statement (see Supplemental Figure 1). The expert panel reached consensus on the need to select a topical antibiotic treatment considering staphylococci and streptococci susceptibility. Moreover, MRSA infections have emerged globally, are increasingly occurring in patients without exposure to the health care system (ie, community-associated MRSA) and are hard to treat due to resistance to beta-lactam antibiotics.[19] For this last reason beta-lactam antibiotics, both topical or systemic (which could be necessary for extensive or complicated impetigo), should be avoided if

MRSA is suspected. Compared with health care-associated MRSA community-associated MRSA is less resistant to non-beta-lactam antimicrobial agents and primarily cause skin and soft tissue infections (SSTIs).[20]

Topical agents commonly used to treat impetigo-associated SSTIs include fusidic acid and mupirocin, for which resistance is emerging in *Staph aureus*, including MRSA and MSSA strains. A recent study showed a fusidic acid low-level resistance >10% and a fusidic acid high-level resistance <3.5% for both MSSA and MRSA. Mupirocin high-level resistance was at least 10% in MRSA.[19] However, topical mupirocin is active against Gram-positive bacteria, including MRSA and streptococci[4] and intranasal mupirocin is effective in staphylococci elimination, also against MRSA from chronic carriers.[21] A recent nonfluorinated topical quinolone (ozenoxacin) resulted to be active versus SSTI pathogens, including MRSA resistant to fluoroquinolones, macrolides, clindamycin, fusidic acid, and mupirocin.[20]

Moreover, 1 participant underlined that, although Gram stain and cultures on skin swabs are not necessary for the diagnosis or evaluation of the healing process, they could help to identify the pathogen involved when MRSA infection is suspected .

Statement 2. Rapid bactericidal activity

Although in the final consensus meeting, there was no unanimous response to this statement (see Supplemental Figure 2), a high level of agreement was reached on this aspect, reflecting the importance of rapid decrease of the bacterial load in impetigo to hasten symptom resolution and prevent the spread of infection.[22,23] Antibiotics with a rapid bactericidal effect are important for symptoms resolution. This is especially relevant in pediatric settings to limit person-to-person transmission of infection.[24,25]

Mupirocin inhibits the metabolic activity of the bacteria in MRSA biofilms after short exposure times.[26] It has been reported that ozenoxacin has a rapid bactericidal activity and penetrates inside the bacterial cell in the first minute after exposure.[22]

Statement 3. Persistence of high concentrations in the stratum corneum and epidermis during the interval between doses, with minimal systemic absorption

A unanimous response to this statement has been obtained (see Supplemental Figure 3).

Topical and transdermal drug delivery systems have shown significant advantages in clinical practice allowing drug targeting to the action site in the body[27] and maximizing the dose of the drug on site while minimizing dermal and systemic absorption, thus limiting the systemic side effects.[28] This was demonstrated by studies that reported negligible systemic absorption for locally applied mupirocin[29] and retapamulin[30] and minimal dermal absorption, but high concentration in the upper layers of epidermis, for topical ozenoxacin.[31] In addition, compared with oral therapy, delivering a drug directly to infected areas can reduce the risk of bacterial resistances.[1,32]

Statement 4. Low incidence of antibiotic resistance and, possibly, no cross-resistance with other classes of antibiotics

For this statement a full consensus has been reached by all experts with no additional comments (see Supplemental Figure 4).

Resistance to widely prescribed antibiotics is a persistent problem with *Staphs aureus* and *Strep pyogenes*, and the number of impetigo cases due to MRSA, although still rare, is increasing.[33] Moreover, the emergence of bacteria showing cross-resistance to topical and systemic antimicrobial agents increases the need for alternative antibiotics.[34]

When prescribing antibiotics, it is essential to know the local antibiotic resistance patterns[4] and to collect information about topical antibiotics previously prescribed to the patient because a repeated or extended use could increase the risk of developing resistance.[33] The evidence-based treatment algorithm for impetigo delineated by Schachner et al[4] includes newer and effective topical antibiotics as a first-line treatment, thus representing an essential step in antimicrobial stewardship.[4] Specifically, mupirocin is considered a valid option to treat SSTIs and to eradicate MRSA nasal carriage; however, the increase in resistance to mupirocin is related to its widespread use for MRSA carrier decolonization. Resistance has been also described for fusidic acid and retapamulin, anyway, for these 2 antibiotics, in vitro activity has been respectively detected against high-level mupirocin-resistant MRSA and against high-level mupirocin and MRSA.[4] Ozenoxacin is characterized by simultaneous affinity for DNA gyrase and topoisomerase IV, appearing to be less prone to the effect of the efflux pumps that confer bacterial resistance to other quinolones, showing low selection of resistant mutants and a mutant prevention concentration below its concentration in skin. These mechanisms could be associated to a less-rapid development of resistance for ozenoxacin.[4]

From a wider point of view, the European Centre for Disease Prevention and Control underlined the importance of antimicrobial resistance (AMR) surveillance in the last report[35] because AMR represents a worldwide challenge and an urgency for the European Union. Last results, relating to the 2016-2020 period, indicated a decrease in the percentage of MRSA isolates for *Staph aureus*. In 2020, 9 (23%) out of 40 countries that shared data on *Staph aureus* had the lowest MRSA percentages (<5%). On the other hand, in 10 (25%) out of 40 countries, MRSA percentage was even more than 25%. It is clear that MRSA still represents a significant pathogen in the European Union and in the European Economic Area, with high levels in several countries and with common combined resistance to other antimicrobial groups. By collecting more national and European data regarding AMR, stronger evidence-based treatment guidelines for skin infections could be generated to limit AMR in Europe.[18,35]

Statement 5. To not be available also for a systemic administration, to limit the onset of antibiotic resistance

There was no unanimous response to this statement (see Supplemental Figure 5), but the majority of experts pointed out that the drug molecules employed for topical formulations are not available also for systemic use.

The extent and the site of lesions and the presence of systemic symptoms are relevant factors for treatment identification. The practical clinical recommendations suggest topical antibiotic therapy for localized lesions and systemic therapy with oral antibiotics in cases of extensive lesion and failure or inability to perform topical therapy.[31] A rotation regimen of topical antibiotics could be performed in case of recurrent infection. Some experts suggest that, in Europe, a rotation of mupirocin, ozenoxacin, and fusidic acid should be used.[4]

Furthermore, as per the UK National Institute for Health and Care Excellence antimicrobial prescribing guidelines, concomitant therapy with topical and oral antibiotics does not improve the efficacy but is associated to increased risk of resistance and adverse effects.[33] However, in addition to a topical treatment, oral antibiotics could be prescribed in those patients with widespread or recurrent impetigo, regardless of its variant (bullous or nonbullous), although the superiority of efficacy of oral antibiotics compared with topical formulations in the treatment of extensive impetigo needs to be further investigated.[6] It is also interesting to notice that, for the more complicated presentation of the disease, combined topical treatment is not required and systemic antibiotic alone is the more indicated option.[36]

Statement 6. Ease of use (in terms of number of administrations and dermocosmetic characteristics) to promote adequate therapeutic adherence

A very high consensus (although not unanimous) was reached by the expert panel on this statement (see Supplemental Figure 6), which is related to a feature beyond efficacy and safety of a product.

Topical treatment is often considered easier to handle compared with oral therapy (in particular for caregivers) and has potential advantages over systemic therapy, including better compliance. However, adherence to topical treatment represents a challenge for some patients who find it easier to take a pill.[37] This depends on several factors, among them patient characteristics and beliefs, route of administration, treatment efficacy and duration, disease chronicity, and its manifestations. When selecting a topical treatment, attention should be paid to cosmetic properties, suitability of the pharmaceutical formulation, and the smell of the preparation as well as the convenience of application[38] because they could influence a patient's adherence to treatment. Indeed, a more pleasing-to-patient formulation allows better therapy adherence and, consequently, better clinical efficacy.[39] The time required for the application of the topical treatment represents another element that strongly influences the therapeutic adherence of patients with infectious skin diseases.[39]

Also, the role of the quality of physician–patient relationship should not be underestimated, because good interactions with the clinician can improve adherence to the prescribed therapy.[40–42] Furthermore, interventions to increase treatment adherence should be applied, ranging from reminders and educational programs to simplifying prescriptions.[40] Among the disadvantages of topical therapy, an important concern is related to the difficulty in monitoring topical antibiotic dose and duration of therapy.[37]

Statement 7. Possibility to be prescribed since the first months of life

A very high consensus (93%) was reached by the expert panel on this statement (see Supplemental Figure 7).

The global prevalence of impetigo has recently been estimated at 12.3% in childhood and, although it occurs more frequently in children ages 2 to 5 years,[43] impetigo could be present even in newborn infants and it can be associated to umbilical scar infection. Children younger than age 2 years account for 90% of cases of bullous impetigo.[44] For newborn infants, the majority of cutaneous bacterial infections are localized to the skin and should be adequately treated, considering pathogen and sensitivity to antibiotic therapy.

In addition, considering that colonization of nasal mucosa and/or skin often precedes invasive infection, decolonization strategies, even with topical antibiotics, were tested to prevent clinical infection, although evidence on such approach in infants are limited.[45,46] Moreover, development of resistant strains, overcrowding, and poor infection control have been linked to nosocomial outbreaks of *Staph aureus*.[46] This is of particular concern in neonatal intensive care units where neonates are more susceptible to infections.[46] Regarding the use of topical antibiotics in newborn infants, a relevant experience came from a Phase II randomized trial where a 5-day course of mupirocin was applied to the intranasal, periumbilical, and perianal areas, resulting in safe and efficacious eradication of *Staph aureus* colonization among infants in a neonatal intensive care unit.[45]

On the basis of these considerations and as per expert opinion, the availability of a topical antibiotic to be used from the first month of life could be a valid support for the management of uncomplicated skin infections, always considering lesion extension and the sites of infection.

Indeed, the majority of currently available local treatment are not indicated in children under age 2 months,[43] whereas for pediatric populations, topical treatment is indicated in case of limited extent of impetigo (<2% of the total body surface) for a duration of 5 to 7 days (and at least until complete resolution).[43]

Statement 8. Good tolerability (with particular reference to contact dermatitis or photosensitization)

A 100% agreement has been reached on this statement (see Supplemental Figure 8), underlying that the efficacy/safety balance is always essential when prescribing a treatment.

Regarding safety in general, a comparative review of current topical antibiotics for impetigo reported that topical treatments (including mupirocin, fusidic acid, retapamulin, and ozenoxacin) showed greater resolution of impetigo in comparison to vehicle, in pivotal clinical trials; moreover, adverse events were negligible (pruritus at the application area was the most common side effect).[13]

On the other hand, several potential risks of local antimicrobial treatment are well known, such as sensitization (eg, development of contact dermatitis) as well as antibiotic resistance. There is a higher risk of sensitization with some molecules such as neomycin and gentamicin; in particular, sensitization with neomycin occurs in 1% to 6% of the general population. Mupirocin may lead to sensitization, with consequent drug withholding in some cases.[36] Although dermatologic reactions related to topical antibiotic ointment are commonly observed, allergic/irritant dermatitis could be improperly diagnosed as an infection by health care professionals.[47]

Photosensitivity reactions also represent an unwanted adverse event linked to commonly administered topical or systemic medications, including antimicrobials (both antibacterial and antifungal) and nonsteroidal anti-inflammatory agents. The main topical agents associated with photosensitivity are nonsteroidal anti-inflammatory drugs,[48] although the main systemic drugs responsible for this side effect are antibiotics, such as tetracyclines, sulfonamides, and fluoroquinolones,[48,49] nonsteroidal anti-inflammatory agents, and drugs for cardiovascular conditions.[48]

Incidence and intensity of drug phototoxicity can vary widely among the different classes of antimicrobial drugs and among the different compounds of a given class.[50] For novel molecules (eg, oxenoxacin) the risk of sensitization is less known; however, a tendency to irritation, sensitization, phototoxicity, or photoallergy have been reported.[36] Therefore, when selecting a topical antibiotic, it should be evaluated whether the benefits of the antimicrobial drug outweight the probability of adverse effects, such as photosensitivity.[50]

Statement 9. Available also in a formulation for nasal use

Because only 80% of experts agreed on this statement (see Supplemental Figure 9), some aspects related to this point need to be deepened.

When prescribing a topical treatment, it is necessary to consider the most appropriate dermatological formulation (eg, cream, ointment, or solution),[39] also in dependance of either the dermatologic characteristic of application area (eg, nasal mucosa) or diffusibility in the mucosa. As a result, experts suggest that ointments are usually more indicated for nasal use compared with creams.

Furthermore, the vestibulum nasi (or anterior nares) is the most frequent carriage site of *Stap aureus*, representing a reservoir for the spread of this pathogen.[51] Up to 62% of patients with impetigo bore staphylococci in the vestibulum nasi.[52]

Moreover, strains of *Staph aureus* producing exfoliative toxins are often isolated from patients with impetigo and are associated with staphylococcal scalded skin syndrome, which usually develops after a localized infection in the conjunctiva, nose, navel, or

perioral region and, more rarely, after pneumonia, endocarditis, and arthritis.[52]

Because the nose is a common reservoir, decolonization strategies for carriers should be applied, including treatment with specific antibiotics in the nostrils[44] and hygiene measures, in particular for domestic contacts.[43]

Statement 10. Appropriate cost

Ninety-eight percent of experts (see Supplemental Figure 10) agreed that an appropriate cost of the treatment should be included in the ideal features for a topical antibiotic for impetigo treatment because this aspect is strictly connected to therapeutic adherence.

Some authors reported inexpensiveness as an ideal feature of a treatment for impetigo, together with efficacy, tolerability, and limited bacterial resistance profile.[1] Indeed, cost-related nonadherence is a relevant aspect that has been investigated and reported in the literature. Several studies on different diseases showed that increased cost-sharing for medications is associated with lower rates of prescription initiation, low adherence among users, and more-frequent treatment discontinuation.[41]

Unemployment, poverty, inadequate medical/prescription coverage, as well as a high out-of-pocket cost of drugs are considered other important factors leading to nonadherence.[53]

Limitations

Overall, the 10 statements underline that several criteria have to be considered when selecting the most appropriate local therapy for impetigo. Efficacy and safety represent the core factors, but they are not sufficient in the treatment choice. Antimicrobial resistance is another essential point, together with pharmacokinetic and pharmacodynamic characteristics of the agent. Formulation of the antimicrobial product is just as relevant, depending on the area of application. Last but not least, patient and caregiver preference and needs should also be taken into account to facilitate therapeutic adherence and to obtain the best benefit from treatment.

In Europe, most antibiotics for human use are prescribed in primary care settings, as well as by dermatologists or other specialists; therefore, the definition of the required topical antimicrobial features and the update of treatment guidelines with additional data on antibiotic resistance could facilitate appropriate prescription, increase treatment effectiveness, and control the development of resistance in impetigo.

Conclusions

The present consensus refers to the ideal features of a topical antibiotic treatment for impetigo. Currently available antimicrobial agents partially cover the 10 desirable characteristics identified by Italian experts; however, more recent topical antibiotic options seem to respond to most of them.

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All authors contributed equally to this article by defining and discussing all statements and by writing the text.

Conflicts of Interest

Luisa Galli has received a grants from Angelini Pharma Italy, Abbott Diagnostics and GSK for consulting activity, presentation or manuscript writing and participation to Advisory Board. Iria Neri received grants as advisor, speaker, investigator and/or consultant for Sanofi, Janssen, Roche-Posay, Giuliani, Leo Pharma. Andrea Novelli received grants from Menarini Italy and Valeas Italy for consulting activity, presentation or manuscript writing, participation to Advisory Board. Giuseppe Ruggiero has received a grant from Angelini Pharma Italy for advisory board. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Supplementary materials

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