**GABARITO-ESPELHO**

**PROVA 2**

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Leia o texto abaixo e responda as questões.

**The Role of the Cutaneous Mycobiome in Atopic Dermatitis**

by

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1. Atopic dermatitis (AD) is a chronic, relapsing, inflammatory dermatosis characterized by eczema, itch, and a frequent association with other atopic disorders. AD is diagnosed worldwide with a prevalence of up to 20.1% in children and 4.9% in adults. It is associated with a significant deterioration in the quality of life, constituting a considerable burden for patients and a challenge for healthcare systems.
2. The pathogenesis of AD is multifactorial and not entirely elucidated. It has been suggested that genetic predisposition, skin barrier malfunction, and disordered innate and acquired immune responses have the greatest impact on the development of AD. These processes trigger dysbiosis of the cutaneous microbiome, which further aggravates skin barrier damage and immune imbalances and increases the risk of secondary infections, complicating the course of AD.
3. Since Leyden et al. first reported the prominent colonization of AD lesions by *Staphylococcus aureus*, most studies have focused on the analysis of the bacterial microbiome. It was shown that *S. aureus* causes displacement of other bacterial species, which disrupts the cutaneous homeostasis dependent on host-microbiome signaling. Numerous virulence factors of *S. aureus*, such as enterotoxins, phenol-soluble modulins, hemolysins, and exogenous proteases, have been reported to induce Th2-type inflammation and damage the epidermal barrier, thereby aggravating the course of AD.
4. The relative paucity of data regarding the role of the fungal microbiome (also called the mycobiome) in AD was partly associated with methodological challenges. However, recent advances in high-throughput sequencing have provided new insights into the cutaneous fungal communities in AD by complementing the data from culture-based studies. The aim of this review is to summarize the current knowledge of the role of the cutaneous mycobiome in AD, as well as discuss the clinical implications and new opportunities for research in this field.
5. Microbial communities can be studied using culture-based or molecular approaches. Although the culture-based identification of fungi remains the gold standard in clinical practice, it is also associated with high time consumption, limited ability to investigate a wide range of microbes in selected conditions, and uncertainty in discriminating between different species due to the mainly phenotypic analyses of the obtained colonies. The sensitivity of culture-based methods is generally lower than that of molecular studies, which may be associated with the difficulty in obtaining positive cultures, particularly in species with high growth requirements.
6. Despite the apparent superiority of the sequencing approach, fungal communities may be even more fully appreciated by using a combination of culture and sequencing. This methodology is relatively common and was used, among others, by Hamm et al. to help in discriminating the seasonal variation and microhabitat preference of keratinophilic fungi. Although the sequencing approach enables the identification of a wider spectrum of non-culturable fungi, cultures highlight the relative potential of different fungal species to proliferate in favorable conditions. Furthermore, the testing of susceptibility to antifungal agents and the pathogenicity of fungi also require culture-based methods. In this regard, future studies of mycobiome in AD could provide more insights if a combination of those two techniques is used.
7. Skin microbiota plays an important role in immune homeostasis, maturation of the epidermis, and protection against pathogens. Commensal microorganisms occupy niches with a microenvironment supporting their growth. Therefore, certain locations (e.g., moist, dry, and sebaceous) tend to harbor microbial communities that are comparable between different individuals. Nevertheless, the composition of the ‘physiological’ microbiota can be influenced by several factors such as age, ethnicity, hygienic habits, temperature, and moisture. Therefore, an adequate interpretation of mycobiome studies in patients with AD requires the knowledge of its composition and the variables that affect healthy individuals.
8. Baseline therapy for AD can have a beneficial effect on the cutaneous mycobiome. Interventions, such as emollient therapy and irritant removal, improve the epidermal barrier status and reduce the risk of sensitization to environmental factors including the members of the cutaneous mycobiome. Emollient use was shown to have a beneficial effect on the cutaneous fungal communities and aid the host-microbe balance on AD skin. In one interventional study, a 12-week emollient application resulted in a significantly decreased richness and increased Shannon diversity on the lesional and nonlesional skin, respectively. Analysis of pre- and post-treatment AD samples revealed distinct microbial clusters at those time points. However, certain components such as olive oil were shown to support *Malassezia* spp. growth and should therefore be avoided.
9. Fungicidal plant extracts and essential oils were found to show promising in vitro properties against the common cutaneous fungal taxa playing a role in AD. For example, bacillomycin D and dipeptide antibiotic bacilysin extracted from seaweed-associated *Bacillus amyloliquefaciens* were active against several *Malassezia* strains. Furthermore, *Lactiplantibacillus plantarum* derived from green tea was observed to inhibit *C. albicans*, *M. globosa*, and *M. restricta*. The elaboration of emollients containing these preparations could help to control the overgrowth of pathogenic fungal species on the skin of patients with AD.
10. Current European guidelines for the treatment of AD encourage the use of topical or systemic antifungal therapy primarily in patients suffering from the head and neck variant of AD or with demonstrated IgE sensitization to *Malassezia* spp. As large randomized clinical trials of antifungal use in AD are lacking, proposed treatment regimens can be derived only from small interventional studies, case series, and case reports. One double-blinded placebo-controlled trial of 53 patients randomized to three groups receiving either itraconazole 200 mg/day, itraconazole 400 mg/day, or a placebo for 7 days revealed a significant improvement in the itraconazole-treated individuals. After 14 days, the most significant difference was reported in the group receiving itraconazole 200 mg/day. A retrospective case series showed that treatment with itraconazole 200 mg/day for a mean time of 8.4 months resulted in an improvement of patch-test-negative head and neck dermatitis in 71% of patients. Another report considered adults and adolescents treated with itraconazole 100 mg/day for 1 month and then 100 mg/week for another month as maintenance therapy. Concomitant use of topical steroids and calcineurin inhibitors was allowed. The described treatment regimen resulted in the clearance of head and neck dermatitis in 15/17 (88%) adolescent and 8/14 (57%) adult patients
11. Dysbiosis of the cutaneous mycobiome is a characteristic feature of atopic dermatitis. An impaired barrier function facilitates the penetration of fungal antigens, triggering a wide range of immune responses, sensitization to fungal antigens, and subsequent aggravation of skin lesions. The pathogenic role of fungi in atopic dermatitis has been attributed primarily to the genera *Malassezia* and *Candida*. The head and neck variant of atopic dermatitis seems to be the most closely associated with mycobiome dysbiosis due to high rates of detected IgE-specific *Malassezia* antibodies and favorable results following antifungal treatment. Novel treatment options are being developed and could be a successful additive to the routine treatment of atopic dermatitis in the future.

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As questões de 1 a 5 são de múltipla escolha. Para cada questão será aceita apenas uma resposta. (Cada questão vale 6, totalizando 30 pontos de 100)

1. De acordo com o parágrafo I, indique a afirmação correta:
2. A dermatite atópica é diagnosticada em quase todos os países.
3. A dermatite atópica prevalece em adultos em todo o mundo.
4. A dermatite atópica atinge a maioria das crianças no mundo.
5. **A dermatite atópica é considerada um fardo para os pacientes.**
6. A dermatite atópica é a doença prevalente nos sistemas de saúde no mundo.
7. Marque a opção verdadeira de acordo com o parágrafo II.
8. A patogênese da dermatite atópica é multifatorial e está completamente elucidada.
9. A predisposição genética é, comprovadamente, o maior fator de impacto no desenvolvimento da dermatite atópica.
10. **A disbiose do microbioma cutâneo agrava ainda mais os danos à barreira cutânea.**
11. A dermatite atópica aumenta os riscos de infecções secundárias.
12. O curso da dermatite atópica complica os desequilíbrios imunológicos.
13. Com relação ao *Staphylococcus aureus* (parágrafo III), marque a opção correta.
14. Os primeiros relatos já apontavam lesões causadas por *Staphylococcus aureus.*
15. **O *Staphylococcus aureus* causa deslocamento de outras espécies bacterianas.**
16. A maioria dos estudos relatam homeostase cutânea dependente da sinalização hospedeira do microbioma.
17. Numerosos relatórios indicam virulências causadas por indutores de inflamação do tipo Th2.
18. A barreira epidérmica pode agravar o curso da dermatite atópica.
19. Segundo o parágrafo IV, qual é a única opção verdadeira?
20. **A relativa escassez de dados sobre o papel do microbioma fúngico na dermatite atópica foi parcialmente associada a desafios metodológicos.**
21. O alto número de dados sobre o papel do microbioma fúngico na dermatite atópica foi totalmente associada a desafios metodológicos.
22. A preocupante ausência de dados sobre o papel do microbioma fúngico na dermatite atópica foi, em parte, associada a desafios metodológicos.
23. A conclusão relacionada a dados sobre o papel do microbioma fúngico na dermatite atópica foi praticamente associada a desafios metodológicos.
24. A necessidade de dados sobre o papel do microbioma fúngico na dermatite atópica foi parcialmente associada a desafios metodológicos.
25. De acordo com o parágrafo V, indique a única opção correta.
26. As comunidades microbianas devem ser abordadas de acordo com a cultura molecular.
27. A identificação baseada em cultura de fungos é o tipo mais rápido de abordagem em vigor.
28. O padrão-ouro de identificação na prática clínica promove uma investigação de uma vasta gama de micróbios.
29. **Os estudos moleculares apresentam maior sensibilidade do que os métodos baseados em cultura.**
30. A dificuldade de obtenção de cultura positiva é alta em espécies de rápido crescimento.

Responda as questões a seguir em língua portuguesa. (Cada questão vale 8, totalizando 40 pontos de 100)

1. De acordo com o parágrafo VI, quais são os benefícios de uma combinação de cultura e sequenciamento?

***Although the sequencing approach enables the identification of a wider spectrum of non-culturable fungi, cultures highlight the relative potential of different fungal species to proliferate in favorable conditions. Furthermore, the testing of susceptibility to antifungal agents and the pathogenicity of fungi also require culture-based methods.***

***(Embora a abordagem de sequenciamento permita a identificação de um espectro mais amplo de fungos não cultiváveis, as culturas destacam o potencial relativo de diferentes espécies de fungos para proliferar em condições favoráveis. Além disso, o teste de suscetibilidade a agentes antifúngicos e a patogenicidade de fungos também requerem métodos baseados em cultura).***

1. O que pode influenciar na composição da microbiota (parágrafo VII)?

***The composition of the ‘physiological’ microbiota can be influenced by several factors such as age, ethnicity, hygienic habits, temperature, and moisture.***

***(A composição da microbiota “fisiológica” pode ser influenciada por vários fatores, como idade, etnia, hábitos higiênicos, temperatura e umidade).***

1. Qual foi o resultado obtido após uma aplicação de emoliente de 12 semanas (parágrafo VIII)?

***A 12-week emollient application resulted in a significantly decreased richness and increased Shannon diversity on the lesional and nonlesional skin, respectively.***

***(Resultou numa diminuição significativa da riqueza e aumento da diversidade de Shannon na pele na pele lesionada e não lesionada, respectivamente).***

1. O que poderia auxiliar no controle do supercrescimento de espécies fúngicas patogênicas na pele de pacientes com dermatite atópica (parágrafo IX)?

***Fungicidal plant extracts and essential oils were found to show promising in vitro properties against the common cutaneous fungal taxa playing a role in AD.***

***(Extratos de plantas fungicidas e óleos essenciais mostraram propriedades in vitro promissoras contra os táxons fúngicos cutâneos comuns que desempenham um papel na dermatite atópica).***

1. Segundo as diretrizes europeias atuais, de que forma deve ser tratada a dermatite atópica (parágrafo X)?

***The use of topical or systemic antifungal therapy primarily in patients suffering from the head and neck variant of AD or with demonstrated IgE sensitization to Malassezia spp.***

***(As diretrizes européias atuais para o tratamento da DA encorajam o uso de terapia antifúngica tópica ou sistêmica principalmente em pacientes que sofrem da variante de cabeça e pescoço da DA ou com sensibilização IgE demonstrada para Malassezia spp).***

Tradução –

Converta para o português a passagem a seguir extraída do texto em questão (total de 30 pontos de 100):

Dysbiosis of the cutaneous mycobiome is a characteristic feature of atopic dermatitis. An impaired barrier function facilitates the penetration of fungal antigens, triggering a wide range of immune responses, sensitization to fungal antigens, and subsequent aggravation of skin lesions. The pathogenic role of fungi in atopic dermatitis has been attributed primarily to the genera *Malassezia* and *Candida*. The head and neck variant of atopic dermatitis seems to be the most closely associated with mycobiome dysbiosis due to high rates of detected IgE-specific *Malassezia* antibodies and favorable results following antifungal treatment. Novel treatment options are being developed and could be a successful additive to the routine treatment of atopic dermatitis in the future.

***(A disbiose do micobioma cutâneo é uma característica da dermatite atópica. Uma função de barreira prejudicada facilita a penetração de antígenos fúngicos, desencadeando uma ampla gama de respostas imunes, sensibilização a antígenos fúngicos e subsequente agravamento de lesões cutâneas. O papel patogênico dos fungos na dermatite atópica tem sido atribuído principalmente aos gêneros Malassezia e Candida. A variante de cabeça e pescoço da dermatite atópica parece ser a mais intimamente associada à disbiose do micobioma devido às altas taxas de anticorpos Malassezia específicos de IgE detectados e aos resultados favoráveis ​​após o tratamento antifúngico. Novas opções de tratamento estão sendo desenvolvidas e podem ser um aditivo bem-sucedido para o tratamento de rotina da dermatite atópica no futuro.)***