PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

EDUARDO VINICIUS MENDES RONCADA

PREVALÊNCIA DA INFECÇÃO ANOGENITAL PELO PAPILOMAVÍRUS HUMANO (HPV) EM USUÁRIOS DE TERAPIA IMUNOBIOLÓGICA.

Presidente Prudente - SP
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Dissertação apresentada a Pró-Reitoria de Pesquisa e Pós-Graduação, Universidade do Oeste Paulista, como parte dos requisitos para obtenção do título de Mestre em Ciências da Saúde – Área de concentração: Ciências da Saúde.

Orientadora: Prof[a]. Dr[a]. Marilda Aparecida Milanez Morgado de Abreu

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Presidente Prudente, 23 de fevereiro de 2021.

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DEDICATÓRIA

Dedico este trabalho aos meus pais que estiveram comigo ao longo desta jornada, apoiando e incentivando o meu crescimento profissional.

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“Lutando, vencendo e agradecendo a Deus por tudo, é assim que encerro cada dia que Deus me permite viver.” (Cecilia Sfalsin)

RESUMO

Prevalência da infecção anogenital pelo papilomavírus humano (HPV) em usuários de terapia imunobiológica.

Introdução: Pacientes usuários de medicamentos imunobiológicos têm risco aumentado de apresentar ou reativar infecções latentes ou ocultas e neoplasias desapercebidas. O screening prévio ao uso destes medicamentos inclui afastar infecções, incluindo tuberculose, hepatites virais B e C, sífilis, vírus da imunodeficiência humana (HIV) e patógenos oportunistas em imunodeprimidos. Entretanto, o papilomavirus humano (HPV), um agente altamente prevalente no nosso meio e precursor de verrugas benignas ou mesmo cancerígenas, não é rotineiramente rastreado. As informações quanto à infecção pelo HPV nos pacientes usuários de imunobiológicos são escassas ou conflitantes, não havendo estudos que avaliem a prevalência de HPV na região anogenital, entre usuários de classes distintas destas medicações, para o tratamento de diferentes doenças inflamatórias crônicas imunomediadadas, quando comparada com a de não usuários desta medicação. **Objetivo:** Comparar a prevalência da infecção anogenital pelo HPV em usuários de imunobiológicos, para o tratamento de doenças inflamatórias crônicas imunomediadas, com a de não usuários desta medicação. **Materiais e métodos:** Foram avaliados clinicamente e por reação em cadeia da polimerase (PCR), a positividade do HPV em 114 pacientes usuários de imunobiológicos (infliximabe, etanercepte, adalimumabe, secuquinumabe e ustequinumabe) para o tratamento de doenças inflamatórias crônicas imunomediadas (psoríase, artrite psoriásica, hidrosadenite supurativa, artrite reumatoide, espondilite anquilosante e doença de Chron) e 114 indivíduos não usuários desta terapia ou de outros imunossupressores, com dermatoses, exceto psoríase, e não portadores de condições predisponentes à infecção pelo HPV (diabetes mellitus, doenças hematológicas, infecção pelo HIV, hepatite B ou C, neoplasias e transplantes de órgãos). **Resultados:** A prevalência de HPV de baixo risco nos grupos usuários e não usuários de imunobiológicos foi de 16,3% e 10,3%, respectivamente (p= 0,524). Os tipos de baixo risco encontrados foram 6, 11, 40, 42 e 44. A prevalência de HPV de alto risco foi de 20,2% em usuários versus 18,4% em não usuários (p= 0,737), distribuídos segundo os tipos em: 16 (6,8%); 18 (11,4%); não 16/18 (81,8%). Após o pareamento por sexo e idade, a prevalência de HPV de alto risco foi de 21,0% e 12,9% para usuários e não usuários de imunobiológico, respectivamente (p= 0,231). Separando por classe de imunobiológicos, a prevalência de HPV de alto risco entre usuários de anti-TNF-α foi de 20,0% e de anti-IL 21,6%, sem associação significativa (p= 0,482). Assim, não foi constatada associação de ambos os grupos com as prevalências de HPV de baixo risco ou de alto risco. **Conclusão:** A prevalência da infecção anogenital pelo HPV, em pacientes com doenças inflamatórias crônicas imunomediadas, tratados com imunobiológicos, é semelhante à de pacientes não usuários destes medicamentos.

Palavras-chave: Anticorpos Monoclonais; Condiloma Acuminado; Inflamação; Doenças Virais Sexualmente Transmissíveis; Imunossupressores.

ABSTRACT

Prevalence of anogenital infection by human papillomavirus (HPV) in users of immunobiological therapy

Introduction: Patients using immunobiological drugs are at increased risk of presenting or reactivating latent or occult infections and unnoticed neoplasms. Screening prior to the use of these drugs includes warding off infections, including tuberculosis, viral hepatitis B and C, syphilis, human immunodeficiency virus (HIV), and opportunistic pathogens in immunosuppressed patients. However, human papillomavirus (HPV), a highly prevalent agent in our country and precursor of benign or even carcinogenic warts, is not routinely screened. Information on HPV infection in immunobiological users is scarce or conflicting, and there are no studies evaluating the prevalence of HPV in the anogenital region among users of different classes of these medications for the treatment of different immunomediated chronic inflammatory diseases, when compared to that of non-users of this medication. **Objective:** To compare the prevalence of anogenital HPV infection in immunobiological users for the treatment of immunomediated chronic inflammatory diseases with that of non-users of this medication. Materials and methods: HPV positivity in 114 immunobiological users (infliximab, etanercept, adalimumab, secuquinumab and ustequinumab) were evaluated clinically and by polymerase chain reaction (PCR) for the treatment of immunomediated chronic inflammatory diseases (psoriasis, psoriatic arthritis, suputive hydrosadenitis, rheumatoid arthritis, ankylosing spondylitis and Chron's disease) and 114 individuals not using this therapy or other immunosuppressants, with dermatoses, except psoriasis, and not carriers of conditions predisposing to HPV infection (diabetes mellitus, hematological diseases, HIV infection, hepatitis B or C, neoplasms and organ transplants). **Results:** The prevalence of low-risk HPV in the immunobiological users and non-users groups was 16.3% and 10.3%, respectively (p= 0.524). The low-risk types found were 6, 11, 40, 42 and 44. The prevalence of high-risk HPV was 20.2% in users versus 18.4% in non-users (p= 0.737), distributed according to the following types: 16 (6.8%); 18 (11.4%); not 16/18 (81.8%). After pairing by gender and age, the prevalence of high-risk HPV was 21.0% and 12.9% for immunobiological users and non-users, respectively (p= 0.231). Separating by class of immunobiologicals, the prevalence of high-risk HPV among users of anti-TNF-α was 20.0% and anti-IL 21.6%, with no significant association (p= 0.482). Thus, there was no association between both groups and the prevalence of low-risk or high-risk HPV. **Conclusion:** The prevalence of anogenital HPV infection in patients with chronic immune-mediated inflammatory diseases treated with immunobiologicals is similar to that of patients not using these drugs.

Keywords: Monoclonal antibodies; Condyloma Acuminate; Inflammation; Sexually Transmitted Viral Diseases; Immunosuppressants.

LISTA DE SIGLAS

anti-IL	– Anti-interleucina
anti-TNF-α	– Fator de necrose tumoral-alfa
DII	– Doença inflamatória intestinal
DP	– Desvio padrão
HIV	– Vírus da imunodeficiência humana
HPV	– Papilomavírus humano
IST	– Infecções sexualmente transmissíveis
OMS	– Organização Mundial de Saúde
PCR	– Reação em cadeia da polimerase
PSM	– Propensity score matching

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- O que já se sabe sobre este tópico? O que este estudo adiciona?

Pacientes usuários de imunobiológicos têm risco aumentado de apresentar ou reativar infecções latentes ou ocultas. Parte da população adulta possui infecção pelo papilomavirus humano (HPV), cujo rastreio prévio à prescrição destes

medicamentos não é rotineiro. Dados de prevalência da infecção anogenital pelo HPV nestes pacientes são escassos e conflitantes. Este estudo sugere que a prevalência da infecção anogenital por HPV entre usuários vs não usuários de imunobiológicos é similar.

- Qual é a mensagem translacional?

Como a maioria das infecções pelo HPV são subclínicas ou latentes e este vírus predispõe ao aparecimento de verrugas e mesmo a carcinogênese, podemos sugerir que, na presença de fatores de risco identificáveis para o HPV, medidas mais eficazes de rastreio, como a PCR de swab anogenital, podem ser realizadas, antes do uso de imunobiológico, a fim de otimizar a detecção viral.

- Quais são as implicações clínicas deste trabalho?

Embora não tenhamos encontrado associação entre a infecção pelo HPV e o uso de imunobiológicos, um inquérito epidemiológico e um exame físico detalhado da região anogenital deve ser preconizado, previamente ao uso desses medicamentos, visto que esses medicamentos podem agravar infecções.

O trabalho está apresentado sob a forma de artigo, segundo as normas do periódico o qual será submetido: British Journal of Dermatology, Fator de impacto 7, Classificação Qualis A1.

RESUMO

PREVALÊNCIA DA INFECÇÃO ANOGENITAL PELO PAPILOMAVÍRUS HUMANO (HPV) EM USUÁRIOS DE TERAPIA IMUNOBIOLÓGICA.

Introdução: Pacientes usuários de imunobiológicos têm risco aumentado de apresentar ou reativar infecções latentes ou ocultas. Entretanto, as informações quanto à infecção pelo papilomavírus humano (HPV) nestes pacientes são escassas ou conflitantes, e seu rastreio não é rotineiro.

Objetivo: Comparar a prevalência da infecção anogenital pelo HPV em usuários de imunobiológicos para o tratamento de doenças inflamatórias crônicas imunomediadas com a de não usuários.

Métodos: Foram avaliados clinicamente e por reação em cadeia da polimerase (PCR), a presença do HPV anogenital em 114 pacientes usuários de imunobiológicos e 114 não usuários desta terapia ou de outros imunossupressores e que não apresentassem psoríase ou condições predisponentes à infecção pelo HPV.

Resultados: A prevalência do HPV de baixo risco nos grupos usuários e não usuários de imunobiológicos foi de 16,3% e 10,3%, respectivamente (p= 0,524). Os tipos de baixo risco encontrados foram 6, 11, 40, 42 e 44. A prevalência de HPV de alto risco foi de 20,2% em usuários versus 18,4% em não usuários (p= 0,737), distribuídos segundo os tipos em: 16 (6,8%); 18 (11,4%); não 16/18 (81,8%). Após o pareamento por sexo e idade, a prevalência de HPV de alto risco foi de 21,0% e 12,9% para usuários e não usuários de imunobiológico, respectivamente (p= 0,231).

Conclusão: A prevalência da infecção anogenital pelo HPV, em pacientes com doenças inflamatórias crônicas imunomediadas, tratados com imunobiológicos, é semelhante à de não usuários destes medicamentos.

Palavras chaves: Anticorpos Monoclonais; Condiloma Acuminado; Inflamação; Doenças Virais Sexualmente Transmissíveis; Imunossupressores.

ABSTRACT

PREVALENCE OF ANOGENITAL INFECTION BY HUMAN PAPILLOMAVIRUS (HPV) IN USERS OF IMMUNOBIOLOGICAL THERAPY.

Background: Immunobiological users patients are at increased risk of presenting or reactivating latent or occult infections. However, information on human papillomavirus (HPV) infection in these patients is scarce or conflicting, and its screening is not routine.

Objective: To compare the prevalence of anogenital HPV infection in immunobiological users for the treatment of immunomediated chronic inflammatory diseases with that of non-users.

Methods: HPV positivity in 114 immunobiological users and 114 non-users of this therapy or cytotoxic or corticosteroids with non-psoriasis dermatoses and non-HPV predisposing conditions were evaluated clinically and by polymerase chain reaction (PCR).

Results: The prevalence of low-risk HPV in the immunobiological users and non-users' groups were 16.3% and 10.3%, respectively (p= 0.524). The low-risk types found were 6, 11, 40, 42 and 44. The prevalence of high-risk HPV was 20.2% in users versus 18.4% in non-users (p= 0.737), distributed according to the following types: 16 (6.8%); 18 (11,4%); not 16/18 (81.8%). After pairing by gender and age, the prevalence of high-risk HPV was 21.0% and 12.9% for immunobiological users and non-users, respectively (p= 0.231).

Conclusion: The prevalence of anogenital HPV infection in patients with immunomediated chronic inflammatory diseases treated with immunobiologicals is similar to that of non-users of these drugs.

Key words: Monoclonal Antibodies; Condyloma Acuminate; Inflammation; Sexually Transmitted Viral Diseases; Immunosuppressants.

INTRODUÇÃO

A infecção anogenital pelo papilomavírus humano (HPV) é a doença viral sexualmente transmissível mais frequente no mundo[1]. Segundo a Organização Mundial de Saúde, cerca de 630 milhões de homens ou mulheres (1:10 pessoas) estão infectados pelo HPV[2] e, aproximadamente, 70% da população sexualmente ativa será infectada[2]. Estima-se que 10% a 20% da população brasileira adulta tenha infecção pelo HPV[3]. A maior incidência é nos jovens, com pico dos 20 aos 24 anos, chegando a 46% no colo uterino, entre os 20 e 30 anos[4]. As infecções clinicamente aparentes, na forma de verrugas, ocorrem em 1% dos indivíduos infectados, podem ser recidivantes ou persistentes, ocorrendo nas seguintes localizações: vulva, colo uterino, vagina, pênis, sulco balanoprepucial, prepúcio, glande, escroto, uretra e ânus[3]. Já, as infecções subclínicas ou latentes apresentam-se assintomáticas[4]. O diagnóstico pode ser realizado por técnicas moleculares, como a reação em cadeia da polimerase (PCR), identificando o DNA viral e seus tipos[5,6].

A terapia imunobiológica é amplamente empregada em doenças inflamatórias crônicas imunomediadas, melhorando o prognóstico e a qualidade de vida dos pacientes[7]. Dentre os imunobiológicos usados em dermatologia, destacam-se três agentes inibidores do fator de necrose tumoral-alfa (anti-TNF-α): infliximabe, etanercepte e adalimumabe; e dois anticorpos monoclonais anti-interleucina (anti-IL): ustequinumabe (anti-IL 12/23) e secuquinumabe (anti-IL 17A). Entretanto, a imunossupressão decorrente desta terapia aumenta o risco de infecções e neoplasias[7,8]. Por isso, previamente ao início do uso dos imunobiológicos, se preconiza um inquérito epidemiológico e exames laboratoriais e de imagem para a busca destas condições[4-6].

As infecções mais prevalentes associadas aos imunobiológicos são as do trato respiratório superior, seguidas pelas cutâneas e de partes moles e as do trato urinário[9]. A mais temida é a tuberculose[10] e exige especial atenção no Brasil, além de hepatites virais B e C, sífilis e vírus da imunodeficiência humana (HIV) ou patógenos oportunistas em imunossuprimidos. Se alguma delas for detectada, deve ser tratada antes de se iniciar o imunobiológico[7-10].

O HPV pode induzir à carcinogênese[2,11], sendo que 70% dos carcinomas invasivos do colo uterino[3] e até 90% dos anoretais ou da orofaringe[2] são provocados por HPV 16 ou 18[2,3,11]. O rastreio para neoplasia do colo uterino consiste no exame preventivo ginecológico, utilizando a citologia oncótica, a qual possui baixa sensibilidade comparada a PCR[5]. Uma meta-análise encontrou taxa de prevalência de 14,4% de infecção pelo HPV por PCR numa população onde a citologia ou o exame clínico eram negativos[12].

Como os imunobiológicos aumentam a suscetibilidade às infecções ou podem reativar infecções latentes ou subclínicas, este estudo chama a atenção para o HPV, agente infeccioso altamente prevalente no nosso meio, cujo rastreio prévio à sua prescrição não é rotina. Alguns relatos de verrugas anogenitais causadas por HPV, na vigência de imunobiológicos, são descritos na literatura, entretanto os dados são insuficientes e contraditórios[13,14]. O objetivo deste estudo foi comparar a prevalência da infecção anogenital pelo HPV em pacientes com doenças inflamatórias crônicas imunomediadas, tratados com imunobiológicos, com a de pacientes não usuários destes medicamentos.

MATERIAIS E MÉTODOS

Trata-se de um estudo observacional transversal, desenvolvido no Hospital Regional de Presidente Prudente, SP, instituição pública, de atenção terciária, voltada ao atendimento da população do Sistema Único de Saúde (SUS) do Brasil, incluindo 2 grupos:

Grupo usuários: pacientes com psoríase ou outra doença inflamatória crônica imunomediada, usuários de imunobiológicos, em acompanhamento no ambulatório de psoríase, ou cadastrados na farmácia de alto custo do município.

Grupo não usuários: pacientes sem psoríase, não usuários de imunobiológicos, atendidos nos ambulatórios de dermatologia geral.

Os pacientes de ambos os grupos foram investigados concomitante e consecutivamente, à medida que compareciam às consultas. O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade do Oeste Paulista (CAAE:

81833317.4.00005515). Todos os participantes assinaram um termo de consentimento livre e esclarecido.

Critérios de Inclusão:

Grupo usuários: pacientes de ambos os sexos, maiores de 18 anos, em uso de agente imunobiológico anti-TNF-α (infliximabe, etanercepte ou adalimumabe) ou anti-IL (ustequinumabe ou secuquinumabe) para tratamento de doenças inflamatórias crônicas imunomediadas (psoríase, artrite psoriásica, hidrosadenite supurativa, artrite reumatoide, espondilite anquilosante ou doença de Crohn).

Grupo não usuários: pacientes de ambos os sexos, maiores de 18 anos, sem psoríase, não usuários de imunobiológicos ou outros imunossupressores e sem sinais ou sintomas de condições clínicas que levam à imunossupressão (neoplasias, diabetes mellitus, doenças hematológicas, hepatites B e C, soropositividade para o HIV ou transplantes de órgãos).

Critérios de exclusão:

Grupo usuários: pacientes que interromperam o tratamento com imunobiológico, num período maior que cinco meias-vidas do mesmo, ou que apresentavam algum processo infeccioso, exceto verrugas pelo HPV, na região anogenital.

Grupo não usuários: pacientes usando medicamentos imunossupressores ou com qualquer condição imunossupressora, conforme especificado nos critérios de inclusão.

Tamanho da amostra: Pressupondo-se que a prevalência de HPV nos não usuários de imunobiológicos fosse aproximadamente 10%, semelhante às menores taxas da população geral[2-4], e estimando-se que a prevalência nos usuários fosse 25%, considerou-se para o cálculo do tamanho amostral a diferença de 15% entre os grupos (25% vs. 10%), com erro tipo I de 5% e poder estatístico de 80%, encontrando-se o número de 100 pacientes para cada grupo. Foram adicionados mais 14 casos em cada grupo, considerando-se possíveis perdas, totalizando 114 pacientes por grupo.

Dados sociodemográficos e de anamnese: Para todos os pacientes, foram coletadas informações sobre sexo, idade e cor; idade da primeira relação sexual; número de parceiros; vacinação prévia para HPV; e antecedentes de infecções sexualmente transmissíveis, incluindo verruga viral anogenital (ativa ou pregressa). Para o grupo usuários, também os dados relacionados a: imunobiológico (nome, tempo de uso, dose, via de aplicação e indicação), uso anterior de outro imunobiológico; presença de comorbidades; e uso concomitante de outras drogas imunossupressoras.

Dados de exame físico e coleta do material: Foi feita a busca de verrugas anogenitais e, quando presentes, registrados o número e a localização das lesões. A seguir, foi realizado o teste do ácido acético a 5%, para visualizar verrugas diminutas ou subclínicas[1,3]. Independentemente da presença ou ausência de lesões, foi coletado material mucocutâneo da região anogenital por swab, utilizando haste plástica flexível, estéril, com ponta de rayon, chamada escova citológica (Abbott Cervi Collect®, Des Plaines, IL, USA). Esta foi friccionada com movimentos circulares, nos homens, na sequência: óstio uretral, glande, sulco balanoprepucial e região anal; nas mulheres: grandes e pequenos lábios, óstio uretral, introito vaginal e região anal. O material foi colocado em frasco estéril, contendo 2,5 ml de solução preservante, composta por tiocianato de guanidina num tampão tris. Posteriormente, foram encaminhadas ao setor de Biologia Molecular do Laboratório Dasa (Barueri-SP), onde foram mantidas em temperatura ambiente de 15ºC a 30ºC e processadas em até 6 semanas após a coleta.

Exame Molecular: Para as PCRs empregou-se o teste automatizado Abbott Real Time High Risk HPV (Abbott Laboratories, Des Plaines, IL, USA). As amostras foram submetidas, em lotes de 94 amostras e 2 controles (1 positivo e 1 negativo), à extração de DNA. Para a amplificação, utilizou-se primers que amplificam um fragmento do gene L1 dos HPVs de alto risco oncogênico, tipos 16 e 18 em separado, e os tipos 31/33/35/39/45/51/52/56/58/59/66/68 agrupados em uma única sonda, denominada HR HPV. A mistura também continha primers e sonda para o gene endógeno da beta-globina, para verificar o processamento adequado das células humanas das amostras. A positividade do DNA do HPV de alto risco foi testada em todos os participantes e classificada em 4 categorias: HPV 16, HPV 18, ambos HPV 16 e 18 e HPV não 16/18. Algumas amostras que possuíam material

genético suficiente e estavam dentro do prazo de cinco dias da abertura do frasco de coleta, foram aleatoriamente submetidas à triagem de HPV de baixo risco oncogênico. Para isso, empregou-se sequências de primers e sondas para a amplificação do fragmento do gene L1 de HPVs de baixo risco oncogênico do fabricante Integrated DNA Technologies (Coralville, Iowa, USA), permitindo a detecção e a tipagem dos seguintes genótipos: 6/11/40/42/43/44.

Análise estatística: Considerando as características sociodemográficas e clínicas apresentadas pelos participantes do estudo, para as variáveis qualitativas, foram calculadas as frequências absolutas e relativas (%) e para as variáveis quantitativas a média, a mediana, o desvio padrão e valores mínimo e máximo. A associação entre as variáveis qualitativas foi avaliada pelo teste qui-quadrado de Pearson ou teste exato de Fisher, segundo o critério dos valores esperados. O teste Kolmogorov-Smirnov não mostrou normalidade, assim a comparação entre variáveis quantitativas entre grupos foi realizada pelo teste de Mann-Whitney. O método de *propensity score matching* (PSM) foi utilizado para controlar o efeito de variáveis de confusão em relação aos grupos de usuários e não-usuários de imunobiológicos. A medida de odds ratio foi calculada usando a regressão logística com intervalo de confiança de 95% (IC 95%). O nível de significância adotado foi de 5% para todos os testes de hipóteses. As análises foram realizadas no software IBM SPSS for Windows version 25 ©.

RESULTADOS

Resultados relacionados aos dados sociodemográficos, de anamnese e exame físico

A distribuição dos pacientes segundo o sexo foi diferente entre os grupos. Os homens representavam 56,1% da amostra nos usuários de imunobiológicos versus 63,2% de mulheres nos não-usuário (p= 0,003). Dentre os usuários, os pacientes tiveram, em média, 50 anos (desvio padrão [DP]= 13,6 anos), enquanto os não usuários 44,3 anos (DP= 14,3 anos), diferença estatisticamente significativa (p= 0,004); assim como entre a cor da pele, com maior número de pacientes pretos e o uso de imunobiológicos (p= 0,025). Também entre os usuários, 13,2% relataram verrugas pregressas, enquanto esse achado ocorreu em 5,3% dos não usuários (p=

0,039). As outras características estudadas não se associaram estatisticamente com o uso ou não uso do medicamento (Tabela 1).

As características dos pacientes do grupo usuários de imunobiológicos, separadamente, são apresentadas na Tabela 2.

Resultados relacionados ao exame molecular

HPV de baixo risco

Uma sub-amostra de 78 casos da amostra total (usuários e não usuários) foi avaliada para a presença de HPV de baixo risco, encontrando prevalência de 14,1% (11 casos), sendo 10 casos em homens (32,3%) e 1 em mulheres (2,1%), com associação estatisticamente significativa (p< 0,001). Essa prevalência aumentou conforme o número de parceiros sexuais (p= 0,025). Os tipos encontrados foram os 6, 11, 40, 42 e 44, sendo a maioria 42 e 44 associados em 7 casos (63,6%), mas sem relevância estatística.

Ao se comparar a prevalência do HPV de baixo risco nos grupos usuários e não usuários de imunobiológicos, obteve-se 16,3% (8 casos) e 10,3% (3 casos), respectivamente, não havendo associação estatisticamente significativa (p= 0,524) (Figura 1). Dentre os 8 usuários positivos, 3 (17,6%) usavam adalimumabe, 2 (20%) ustequinumabe e 3 (16,7%) secuquinumabe (p= 0,999) e todos eles possuíam doença psoriásica (p= 0,581).

HPV de alto risco

Na amostra total (usuários e não usuários), a prevalência de HPV de alto risco foi de 19,3% (44 casos). Os pacientes positivos para HPV de alto risco tiveram, em média, 41,1 anos, idade menor que aqueles cuja PCR foi negativa (48,6 anos), apresentando diferença significativa (p= 0,002). Destes, 23 eram usuários de imunobiológicos, sendo que 11 (23,4%) usavam adalimumabe, 5 (20,8%) ustequinumabe e 7 (20%) secuquinumabe (p= 0,908); 20 deles (21,7%) tinham psoríase (p= 0,558). Segundo a positividade e a tipagem do HPV, a média da idade dos pacientes com infecção pelo HPV 16 foi de 28,7 anos, menor que a dos não infectados por este tipo, que foi de 47,4 anos (p= 0,030), associação esta não observada nas análises das infecções por HPV 18 ou não 16/18. Nenhuma das

demais características estudadas se associaram à infecção por qualquer tipo de HPV.

Comparando-se os grupos usuários e não usuários de imunobiológicos, a prevalência de HPV de alto risco foi de 20,2% versus 18,4%, respectivamente (p= 0,737) (Figura 2). HPV de alto risco não 16/18 foram os mais prevalentes, encontrados em 18 casos (50%) de cada grupo (p= 0,999). Pacientes mais jovens (18 a 50 anos) apresentaram maior prevalência destes subtipos comparados com aqueles acima de 50 anos (p= 0,033). Dentre os usuários positivos para não 16/18, 8 (17%) usavam adalimumabe, 5 (20,8%) ustequinumabe e 5 (14,3%) secuquinumabe (p= 0,952); e 15(16,3%) possuíam psoríase (p= 0,861). A prevalência e a distribuição dos subtipos de HPV de alto risco, segundo os grupos usuários e não usuários, estão expressas na Figura 3.

Observou-se que a distribuição das variáveis sexo e idade eram diferentes entre os usuários e não usuários de imunobiológicos. Utilizando o método de PSM, foi realizado um pareamento destas variáveis e, assim, pode-se avaliar o efeito do uso de medicamento (usuários vs não usuários) sem o efeito das variáveis de confusão, formando-se 62 pares de dados homogêneos.

Para a amostra geral pareada, a prevalência de HPV de alto risco foi de 16,9%. Comparando-se os grupos usuários e não usuários de imunobiológicos, a prevalência de HPV de alto risco foi de 21,0% e 12,9%, respectivamente, sem associação estatisticamente significativa (p= 0,231) (Tabela 3). Separando-se por classe de imunobiológicos, a prevalência de HPV de alto risco entre usuários de anti-TNF-α foi de 20,0% e de anti-IL 21,6%, sem associação significativa (p= 0,482).

DISCUSSÃO

Este trabalho difere daqueles já publicados em vários aspectos. A maioria pesquisou HPV associado a outras infecções no sítio da coleta, como herpes simples[13], molusco contagioso[14,15] ou clamídia[16], o que aqui foi nosso critério de exclusão. Este estudo avaliou, por PCR, o esfregaço mucocutâneo de toda região anogenital, onde o HPV pode provocar verrugas benignas ou malignas,[1,2,5,6,11] de indivíduos com psoríase, DII ou doenças reumatológicas, em uso de imunobiológicos de classes distintas, diferente da maioria que avaliou somente

usuários de anti-TNF-α[17-21] para a presença de HPV no colo uterino[16-19], em pelos das sobrancelhas[21] e combinados com raspado da pele do pescoço[22].

Em contraste ao aumento da suscetibilidade às infecções com o uso dos imunobiológicos[8], o conhecimento sobre o risco da infecção anogenital pelo HPV é limitado e controverso[13,14]. Como o HPV predispõe a malignidades[12] e pode ser subdiagnosticado[3,4], é fundamental sua detecção previamente à prescrição dos imunobiológicos[17].

Aqui, a positividade para o HPV na amostra total foi maior em homens jovens, à semelhança do que ocorre na população geral[3-5]. No grupo usuários de imunobiológicos, houve antecedentes de verrugas virais pregressas mais frequentemente, o que pode ser atribuído ao predomínio de pacientes com psoríase extensa neste grupo, os quais apresentam disfunção da barreira cutânea, facilitando a penetração do HPV. Como a psoríase é predominante nos brancos, e estes compunham a maioria da nossa amostra, não encontramos justificativa plausível para o achado do maior número de pretos nos usuários de imunobiológicos, podendo tratar-se de mera coincidência.

Há relatos do aparecimento de verrugas anogenitais após o início dos anti-TNF-α[14,15], mas poucos autores associaram a infecção por HPV à terapia imunobiológica isolada[15], uma vez que muitos pacientes com doenças inflamatórias crônicas imunomediadas usam mais de uma droga imunossupressora concomitantemente[16].

Terapias imunossupressoras combinadas, incluindo imunobiológicos, prednisona e metotrexato, por períodos prolongados, contribuem para o aumento da infecção ou reativação do HPV latente[17,18] e até mesmo à carcinogenese[12]. Neste estudo, o metotrexato foi a droga mais associada aos imunobiológicos, entretanto, não foi possível determinar uma associação de causa-efeito. Ainda assim, caso a positividade do HPV fosse induzida pelo imunobiológico, não é possível afirmar se a infecção foi adquirida após o seu uso ou se houve reativação de infecção latente desapercebida[18].

Por outro lado, em um outro estudo avaliando mulheres com artrite reumatoide, foi investigado a presença de HPV de alto risco no colo uterino, antes e

6 meses após o início do tratamento com anti-TNF-α, e não foi observado aumento da prevalência da infecção em comparação a indivíduos saudáveis[16]. Esses achados poderiam ser atribuídos ao curto tempo do estudo[16].

Em concordância, um estudo mais prolongado, que avaliou 222 pacientes com psoríase ou doença inflamatória intestinal (DII) usando anti-TNF-α, não encontrou aumento da prevalência de HPV anogenital em comparação a controles com as mesmas doenças[20]. Entretanto, uma maior positividade do HPV de alto risco foi observada nos pacientes com psoríase[20], à semelhança da nossa coorte. Poder-se-ia justificar esses achados pressupondo-se que, na psoríase, a desregulação de células T e a liberação de citocinas pró-inflamatórias pudessem prejudicar a eliminação do HPV[21].

Porém, um estudo com pacientes psoriásicos, recebendo anti-TNF-α, não encontrou aumento da prevalência de HPV cutaneomucoso quando comparada a de indivíduos com psoríase, recebendo metotrexato ou nenhuma terapia sistêmica[21], o que vem corroborar com os nossos achados, nos quais 80% dos usuários de imunobiológicos possuíam psoríase, o que parece não ter interferido na positividade do HPV.

Adicionalmente, foram pesquisadas, separadamente, neste estudo, as prevalências do HPV entre os usuários de anti-TNF-α e anti-IL e foram encontrados 23 usuários de imunobiológicos positivos para HPV de alto risco, dos quais 11 usavam anti-TNF-α e 12 anti-IL, sem diferença estatisticamente significativa entre a positividade do HPV e as duas classes de imunobiológicos, ou quando comparados com indivíduos não usuários da medicação. Os anti-IL parecem ser mais seguros em relação ao desencadeamento ou reativação de infecções[23,24]. Secuquinumabe, inibidor da IL-17A, associou-se com diminuição das taxas de infecção por HPV[22,25], evoluindo para negatividade da PCR após curto tempo do início do uso, pressupondo-se que exerça papel protetor contra a persistência viral[25]. Também, raríssimos casos de verrugas virais por HPV têm sido descritos associados ao uso do ustequinumabe[26].

Quando os grupos usuários vs. não usuários foram pareados por sexo e idade, a positividade do HPV de alto risco pouco variou comparada a da amostra

total e não sofreu influências quanto ao tipo de imunobiológico usado, o que vem ratificar nossos achados de que a prevalência do HPV não se altera pelo uso de imunobiológico.

Estudo recente mostra que a exposição à inflamação crônica, induzida por TNF-α, contribui para a persistência dos queratinócitos infectados pelo HPV em células imortalizadas com maior potencial mutagênico. Sugere-se que o HPV sozinho não seria suficiente para a conversão oncogênica e que o TNF-α atuaria como cofator crucial desta transformação[27]. Logo, pressupõe-se que o bloqueio do TNF-α pelo imunobiológicos possa exerça papel protetor contra malignidades envolvendo o HPV.

Embora a infecção pelo HPV não seja motivo para contrainidicar o uso dos imunobiológicos, é consenso que um inquérito epidemiológico e um exame físico detalhado da região anogenital sejam preconizados, rotineiramente, antes do início dos imunobiológicos e, mesmo sugerir que, na presença de fatores de risco identificáveis para o HPV, a PCR de swab anogenital seja realizada, pois constitui importante arma para o diagnóstico do HPV incipiente.

As limitações deste estudo constituem-se no cálculo amostral, que considerou dados de prevalência da população geral; o fato dos pacientes de ambos os grupos terem sido examinados simultaneamente, resultando numa amostra total heterogênea antes do pareamento; e que apenas uma subamostra foi triada para o HPV de baixo risco, o que é justificado pela limitação de material genético. Além disso, o número de usuários em cada grupo de doenças e tipos de imunobiológicos avaliados foi pequeno para determinar associações precisas entre a posivitidade do HPV e o uso de imunobiológicos.

Conclui-se que a prevalência da infecção anogenital pelo HPV, em pacientes com doenças inflamatórias crônicas imunomediadas, tratados com imunobiológicos, é semelhante à de pacientes sem condições imunossupressoras e não usuários destes medicamentos.

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TABELAS

Tabela 1. Características sociodemográficas, dados de anamnese e exame físico dos participantes do estudo, segundo o uso ou o não uso de imunobiológicos. Presidente Prudente, SP, 2020.

Característica	Uso de imunobiológicos		Total	Valor de p
	Não n = 114 n (%)	Sim n = 114 n (%)	n = 228 n (%)	
Sexo				0,003[1]
Masculino	42 (36,8)	64 (56,1)	106 (46,5)	
Feminino	72 (63,2)	50 (43,9)	122 (53,5)	
Idade (anos)				0,004[3]
Média (DP)	44,3 (14,3)	50,0 (13,6)	47,2 (14,2)	
Mediana (mín-máx)	44 (18-78)	52 (22-82)	48 (18-82)	
18 a 30 anos	27 (23,7)	13 (11,4)	40 (17,5)	0,026[1]
31 a 50 anos	46 (40,4)	41 (36,0)	87 (38,2)	
51 a 70 anos	38 (33,3)	53 (46,5)	91 (39,9)	
>70 anos	3 (2,6)	7 (6,1)	10 (4,4)	
Cor				
Branco	85 (74,6)	70 (61,9)	155 (68,3)	
Pardo	23 (20,2)	23 (20,4)	46 (20,3)	
Preto	5 (4,4)	14 (12,4)	19 (8,4)	0,025[2]
Amarelo	1 (0,9)	6 (5,3)	7 (3,1)	
Verruga ativa				0,811[1]
Não	104 (91,2)	105 (92,1)	209 (91,7)	
Sim	10 (8,8)	9 (7,9)	19 (8,3)	
Número de verrugas				0,847[2]
Zero lesões	104 (91,2)	105 (92,1)	209 (91,7)	
1-4 lesões	9 (7,9)	7 (6,1)	16 (7,0)	
5-10 lesões	1 (0,9)	2 (1,8)	3 (1,3)	
Local da verruga				0,582[2]
Genital	9 (90,0)	7 (77,8)	16 (84,2)	
Anal	1 (10,0)	0	1 (5,3)	
Outra localização	0	1 (11,1)	1 (5,3)	
Genital+uretral+anal	0	1 (11,1)	1 (5,3)	
Idade da 1ª relação sexual				0,570[3]
Média (DP)	17,0 (3,1)	17,1 (3,2)	17,0 (3,1)	
Mediana (mín-máx)	16 (12-28)	17 (12-28)	17 (12-28)	
Nº de parceiros				0,104[1]
1 parceiro	29 (25,4)	38 (33,3)	67 (29,4)	
2 parceiros	19 (16,7)	15 (13,2)	34 (14,9)	
3 parceiros	20 (17,5)	9 (7,9)	29 (12,7)	
4 parceiros	7 (6,1)	6 (5,3)	13 (5,7)	
5 parceiros	7 (6,1)	3 (2,6)	10 (4,4)	
>5 parceiros	32 (28,1)	43 (37,7)	75 (32,9)	
Vacinado para HPV				NA
Não	114 (100)	114 (100)	228 (100)	

Antecedente pessoal de verruga				0,039[1]
Não	108 (94,7)	99 (86,8)	207 (90,8)	
Sim	6 (5,3)	15 (13,2)	21 (9,2)	
Teste do ácido acético				
Não	114 (100)	103 (90,4)	217 (95,2)	0,001[2]
Sim	0	11 (9,6)	11 (4,8)	

DP: desvio padrão; mín: valor mínimo; máx: valor máximo; NA: não avaliável. [1] Teste qui-quadrado de Pearson; [2] Teste exato de Fisher; [3] Teste de Mann-Whitney.

Tabela 2. Características dos pacientes do grupo usuários de imunobiológicos. Presidente Prudente, SP, 2020.

Característica			**n = 114 n (%)**
Medicamento biológico	Infliximabe		4 (3,5)
	Etanercept		4 (3,5)
	Adalimumabe		47(41,2)
	Ustequinumabe		24(21,1)
	Secuquinumabe		35(30,7)
Tempo de uso do medicamento biológico (meses)	Média (DP)	16,3(21,1)	
	Mediana (mín-máx)	7 (1-120)	
Indicação do medicamento biológico	Psoríase somente		57(50,0)
	AR somente		6 (5,3)
	EA		3 (2,6)
	Crohn somente		3 (2,6)
	Hidradenite Supurativa		9 (7,9)
	Psoríase + A. PSO		35(30,7)
	AR + Crohn		1 (0,9)
Uso anterior de outro medicamento biológico	Não		86 (75,4)
	Sim		28 (24,6)
Uso de outros imunossupressores	Nenhum		81(71,1)
	Prednisona		4 (3,5)
	Metotrexato		19(16,7)
	Ciclosporina		2 (1,8)
	Azatioprina		1 (0,9)
	Outro imunossupressor		4 (3,5)
	Prednisona+metotrexato		3 (2,6)
Presença de comorbidades	Nenhuma		71(62,3)
	IST		12(10,5)
	Hepatite B		1 (0,9)
	DM		5 (4,4)
	Hematológica		2 (1,8)
	Outra doença		15(13,2)
	IST+DM		1 (0,9)
	IST+outra doença		2 (1,8)
	HIV+outra doença		1 (0,9)
	DM+outra doença		4 (3,5)

DP: desvio padrão; mín: valor mínimo; máx: valor máximo. AR: artrite reumatoide; EA: espondilite anquilosante; A. PSO: artrite psoriásica; IST: Infecção sexualmente transmissível; DM: Diabetes mellitus; HIV: vírus da imunodeficiência humana.

Tabela 3. Comparação entre os grupos, usuários ou não usuários de imunobiológicos, e a prevalência de HPV de alto risco após o pareamento, utilizando *Propensity Score Matching*. Presidente Prudente, SP, 2020.

Característica	**HPV de alto risco**		**Total**			
	Negativo	**Positivo**				
	n = 103	**n = 21**	**n = 124**	**Valor de p[1]**	**OR (IC95%)**	**Valor de p[2]**
	n (%)	n (%)	n (%)			
Uso do medicamento biológico				0,231		0,235
Não	54 (87,1)	8 (12,9)	62		1	
Sim	49 (79,0)	13(21,0)	62		1,79 (0,68-4,69)	
Uso do medicamento biológico				0,482		
Não usa	54 (87,1)	8 (12,9)	62		1	
Anti-TNF-α	20 (80,0)	5 (20,0)	25		1,69 (0,49-5,77)	0,404
Anti-IL	29 (78,4)	8 (21,6)	37		1,86 (0,63-5,48)	0,259

OR: odds ratio; IC95%: intervalo de confiança de 95%. [1] Teste qui-quadrado de Pearson; [2] Regressão logística não ajustada. Anti-TNF-α (anti fator de necrose tumoral alfa); Anti-IL (anti-interleucinas).

FIGURAS

Figura 1. Prevalência de HPV de baixo risco, segundo o uso de imunobiológicos. Presidente Prudente, 2020.

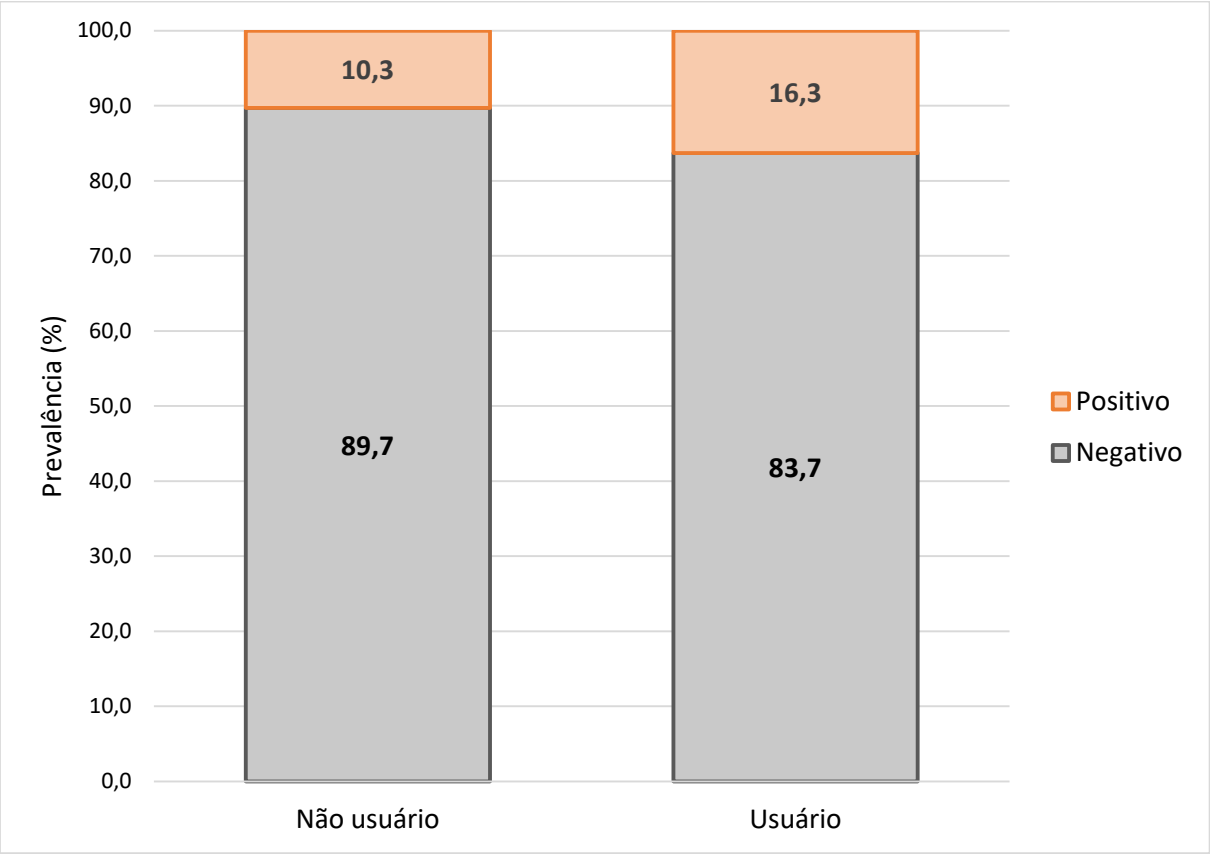


Figura 2. Prevalência de HPV de alto risco, segundo o uso de imunobiológicos. Presidente Prudente, 2020.

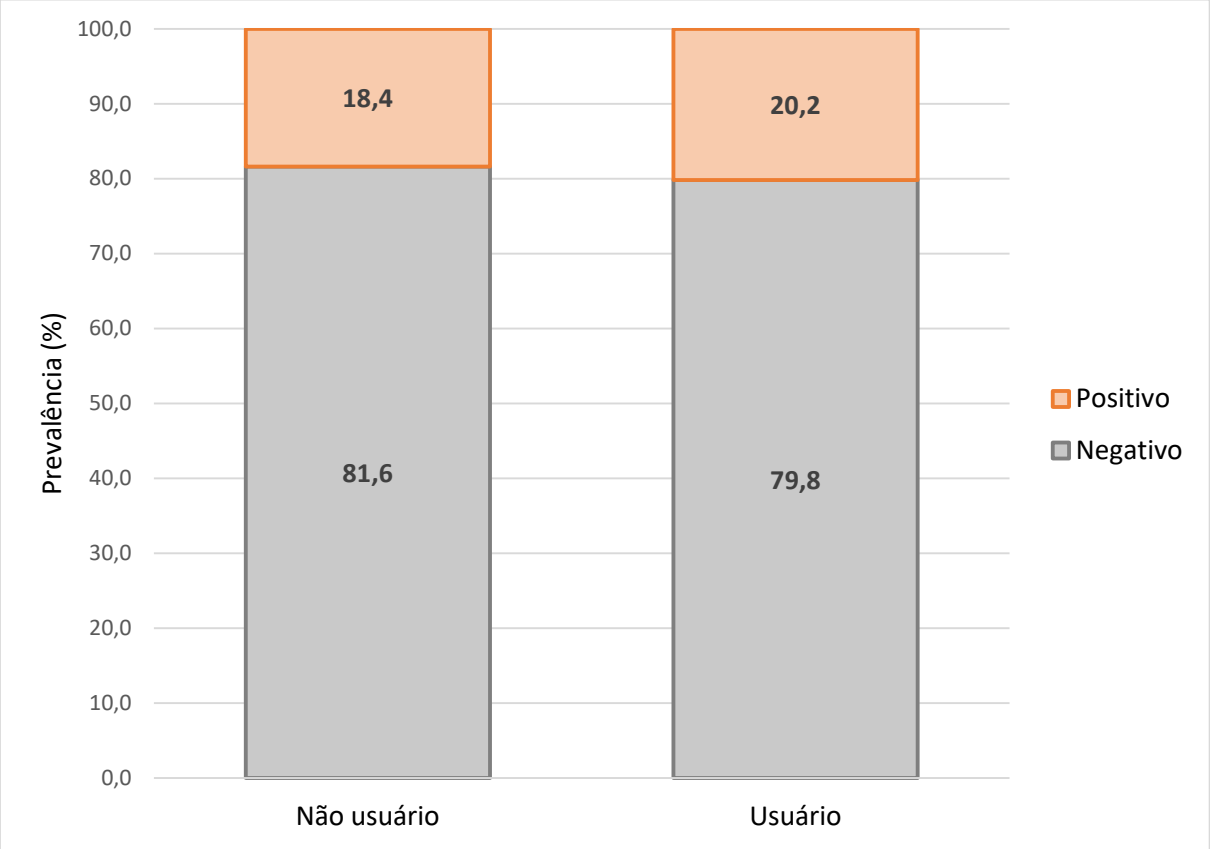
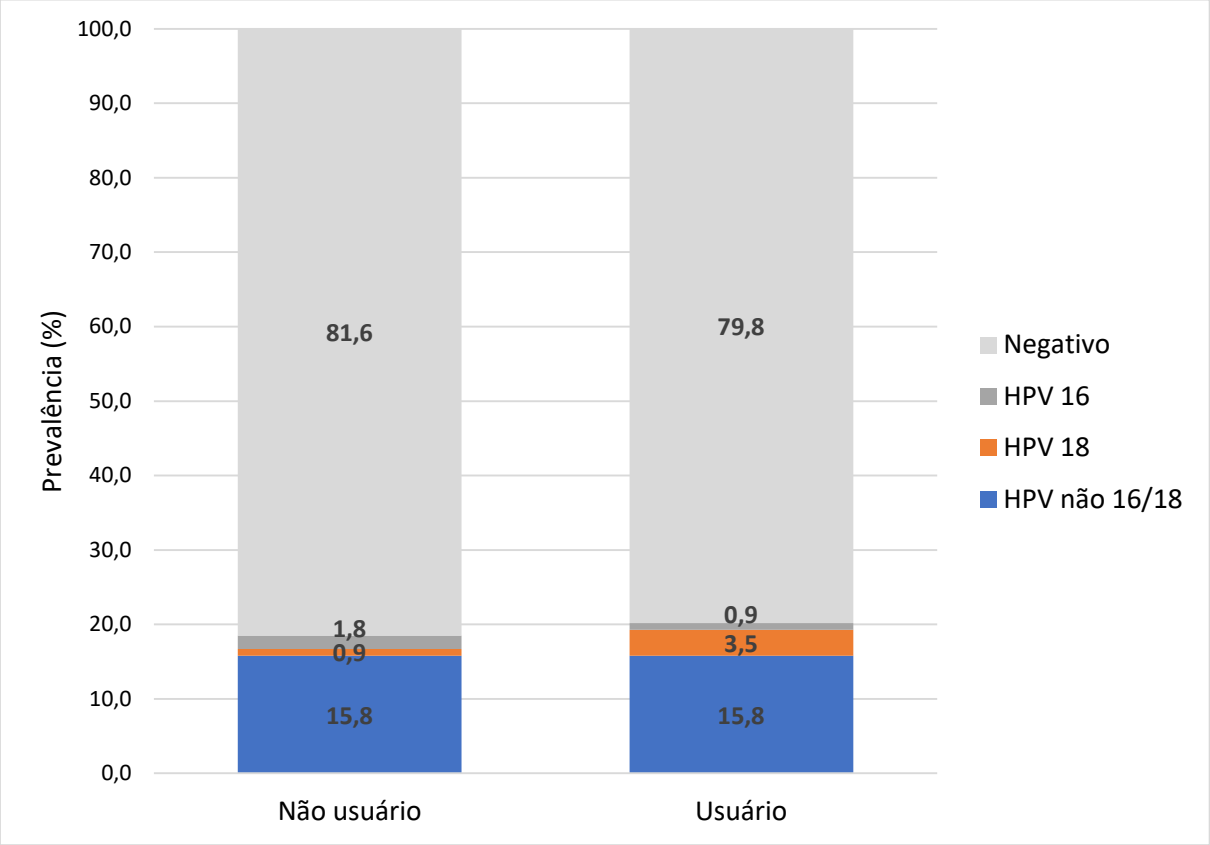


Figura 3. Prevalência e distribuição dos subtipos de HPV de alto risco, segundo os grupos usuários ou não usuários de imunobiológicos. Presidente Prudente, 2020.



ANEXOS

ANEXO A - Aprovação no CEP- Unoeste.

UNOESTE - UNIVERSIDADE DO OESTE PAULISTA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: " Prevalência da infecção ano-genital pelo papiloma vírus humano (HPV) em usuários de terapia imunobiológica"

Pesquisador: Marilda Aparecida Milanez Morgado de Abreu

Área Temática:

Versão: 2

CAAE: 81833317.4.0000.5515

Instituição Proponente: UNOESTE - Universidade do Oeste Paulista

Patrocinador Principal: UNIVERSIDADE DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 2.539.324

Apresentação do Projeto:

Vide parecer anterior.

Objetivo da Pesquisa:

Vide parecer anterior.

Avaliação dos Riscos e Benefícios:

Vide parecer anterior.

Comentários e Considerações sobre a Pesquisa:

Foi enviado os anexos faltantes. As fichas clínicas que serão utilizadas não trazem nenhum tipo de constrangimento aos participantes da pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Todos ok.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Foram atendidas as solicitações não havendo nenhuma pendência.

Considerações Finais a critério do CEP:

Em reunião realizada no dia 12/03/2018, o Comitê de Ética em Pesquisa da Universidade do Oeste

Endereço: Rodovia Raposo Tavares, Km 572
Bairro: Bairro Limoeiro **CEP:** 19.067-175
UF: SP **Município:** PRESIDENTE PRUDENTE
Telefone: (18)3229-2077 **Fax:** (18)3229-2080 **E-mail:** cep@unoeste.br

UNOESTE - UNIVERSIDADE DO OESTE PAULISTA

Continuação do Parecer: 2.539.324

Paulista (CEP-UNOESTE), concordância com o parecerista, considerou o projeto APROVADO.

Solicitamos que sejam encaminhados ao CEP:

1. Relatórios anuais, sendo o primeiro previsto para 30/11/2020.
2. Comunicar toda e qualquer alteração do Projeto e Termo de Consentimento Livre e Esclarecido. Nestas circunstâncias a inclusão de participantes deve ser temporariamente interrompida até a aprovação do Comitê de Ética em Pesquisa.
3. Comunicar imediatamente ao Comitê qualquer Evento Adverso Grave ocorrido durante o desenvolvimento do estudo.
4. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 (cinco) anos, após conclusão da pesquisa, para possível auditoria dos órgãos competentes.
5. Este projeto está cadastrado na CPDI-UNOESTE sob o número 4346.

Obs.: O PROJETO SÓ PODE SER INICIADO (EXECUTADO) QUANDO RECEBER O PARECER FINAL APROVADO TANTO NO CEP QUANTO NO COMITÊ ASSESSOR INSTITUCIONAL DE PESQUISA (CAPI).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1045199.pdf	21/02/2018 16:25:10		Aceito
Outros	Planilha_anexo_4.xlsx	21/02/2018 16:24:41	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO.doc	21/02/2018 16:22:48	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Outros	Sujeito_da_pesquisa_ok.pdf	20/12/2017 09:51:34	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Outros	Uso_de_prontuario_ok.pdf	20/12/2017 09:51:07	Marilda Aparecida Milanez Morgado de Abreu	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	01/12/2017 10:25:53	Marilda Aparecida Milanez Morgado de Abreu	Aceito

Endereço: Rodovia Raposo Tavares, Km 572
Bairro: Bairro Limoeiro **CEP:** 19.067-175
UF: SP **Município:** PRESIDENTE PRUDENTE
Telefone: (18)3229-2077 **Fax:** (18)3229-2080 **E-mail:** cep@unoeste.br

UNOESTE - UNIVERSIDADE DO OESTE PAULISTA

Continuação do Parecer: 2.539.324

Outros	OficioHR.pdf	01/12/2017 10:21:01	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Outros	Termoderesponsabilidade.pdf	01/12/2017 10:20:08	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Outros	Termodecompromisso.pdf	01/12/2017 10:19:18	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Outros	DeclaracaodeinfraestruturaFMRPUSP.pdf	01/12/2017 10:15:50	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Declaração de Instituição e Infraestrutura	Declaracaoinfraestrutura.pdf	01/12/2017 10:14:19	Marilda Aparecida Milanez Morgado de Abreu	Aceito
Folha de Rosto	Folharosto.pdf	01/12/2017 10:09:35	Marilda Aparecida Milanez Morgado de Abreu	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PRESIDENTE PRUDENTE, 12 de Março de 2018

Assinado por:
Rosa Maria Barilli Nogueira
(Coordenador)

Endereço: Rodovia Raposo Tavares, Km 572
Bairro: Bairro Limoeiro **CEP:** 19.067-175
UF: SP **Município:** PRESIDENTE PRUDENTE
Telefone: (18)3229-2077 **Fax:** (18)3229-2080 **E-mail:** cep@unoeste.br

ANEXO B - NORMAS DE SUBMISSÃO BRITISH JOURNAL OF DERMATOLOGY

O trabalho está apresentado sob a forma de artigo, segundo as normas do periódico o qual será submetido:

British Journal of Dermatology

Fator de impacto 7

Classificação Qualis A1

Normas do Periódico: Disponível em: https://onlinelibrary.wiley.com/pb-assets/assets/13652133/BJD%20Instructions%20to%20authors%20Edited%202020.pdf

1. Submission and Manuscript Guidelines

1.1 Online Submission

All submissions should be made online through the BJD ScholarOne Manuscripts submission system. New users should create an account first. Please avoid creating multiple accounts for the same user. When entering your coauthor details, please check if they already have an account before adding them, as multiple accounts for the same user may result in e-mails going to the wrong address. Once a user is logged onto the site, submissions should be made via the Author Centre. The system will guide you through the process step by step. During submission, you must submit the following information:

• Author Consent. This section of the submission process must be completed to confirm that all authors listed qualify for authorship according to the ICJME guidelines and that all authors agree to its submission to the British Journal of Dermatology.

• Conflicts of interest. This is essential; please see the policies section for complete details.

• Funding statement. State sources of funding for the research, including a short description of involvement of the funder in study design, data collection, data analysis, and manuscript preparation.

• Patient Consent. Patient consent for publication, including for use in social media, is required for all case reports and all clinical images whether or not the patient is identifiable. See our patient consent policy for full details.

• Contributor statement. • Data statement.

• A Plain Language Summary (optional - please see Preparation of Manuscripts for more details).

A complete **submission checklist** is available here.

1.2 Fast-Track Submission

The BJD offers a fast-track process for a select number of high-priority manuscripts, such as phase II or III RCTs, and time-sensitive data. The BJD will provide a first decision within 7 working days. Revisions will also be handled swiftly. Approval for fast track is entirely at the discretion of the Editor. There is no charge for the fasttrack service; however, the following requirements must be met to permit the fast-track process to proceed:

• A presubmission enquiry at least 3 weeks before submission. The enquiry should include the abstract of the article and the reason for requesting fast track. Please send to the Editor of the BJD at bjd@bad.org.uk

• If approved for the fast-track process all correspondence should be copied to bjd@bad.org.uk

• Authors must specify a submission date at least 3 weeks in advance and adhere to this date, allowing the journal to prepare reviewers in advance.

To ensure a rapid time to online publication, authors must commit to responding comprehensively to reviewers' comments within 7 working days.

1.3 Preparation of Manuscripts

General guidance

• Manuscript text must be saved in Word (.doc or .docx) or rich text format (.rtf). We would like authors not to submit text in PDF format (.pdf).

• Figures must be saved as separate figure files. GIF, JPEG, PICT or BMP files are acceptable for submission, but only JPEG, TIFF or EPS files are suitable for printing. After acceptance, you will be contacted to provide print-quality figures if you have not already done so. Please note that if you supply figures in PDF format only, they must be distilled using the 'print optimized' option.

• Abbreviations must be defined when first used in the abstract and in the main text, as well as when first used in table and figure captions.

• All relevant files must be included with each revision of the paper.

• Manuscripts must be as succinct as possible. Repetition of information or data in different sections of the manuscript must be carefully avoided. Text must comply with the word limits defined in Section 1.4, and, where appropriate, include the following.

Title page

The first page of all manuscripts should contain the following information:

• The title of the paper.

• A running head not exceeding 70 characters (not needed for correspondence-type items).

• Manuscript word, table and figure counts.

• Names of authors as initial(s) followed by surnames.

• Names of the institutions at which the research was conducted, clearly linked to the respective authors using superscript Arabic numbers.

• Name and e-mail address of the corresponding author.

• A statement of all funding sources that supported the work.

• Any conflict of interest disclosures.

• Bulleted statements (maximum 70 words per question) in answer to each of the following questions: What's already known about this topic? and What does this study add? (not applicable to correspondence-type items or reviews).

- For translational research papers include a third set: What is the translational message?

- For qualitative research papers include a third set: What are the clinical implications of this work?

Summary

• Authors submitting Original Articles should note that structured Summaries are required. The Summary should adopt the format: Background, Objectives, Methods, Results, Conclusions.

• Case Reports and Review Articles require Summaries, but they should not be structured.

• Summaries should contain no citations to previously published work.

• Correspondence-type items do not require Summaries.

Text

The text should in general be divided into sections with the headings Summary, Introduction, Materials and methods (or Patients and methods), Results, Discussion, Acknowledgments, References, Supporting Information, and Figure Legends for most Original Articles.

Tables

• Authors submitting Original Articles should note that structured Summaries are required. The Summary should adopt the format: Background, Objectives, Methods, Results, Conclusions.

• Case Reports and Review Articles require Summaries, but they should not be structured.

• Summaries should contain no citations to previously published work.

• Correspondence-type items do not require Summaries.

Figures

• Figures must be submitted as a separate file or files.

• Figures should be referred to in text as follows: Figure 1, Figures 2-4

• Where a figure has more than one panel, each panel should be submitted as a separate file with a brief description of each panel given in the figure legend. Please ensure that each file is named appropriately (e.g. Figure 1a, Figure 1b).

• Ideally figures should have a maximum of six panels, but exceptions can be made at the Editor's discretion.

• Please ensure that all text in figures will be easily readable when the figure is printed on an A4 page.

• Colour illustrations are welcomed, and all colour is published free of charge in the BJD.

• Authors should obtain permission to reproduce previously published figures or tables. Please provide any accreditation text required by the copyright holder.

• Digital images should not be manipulated (e.g. contrast, brightness) unless the manipulation is applied to the whole image and does not modify the information in any way. Where images have obviously been cropped the full image should be submitted as a supplementary file for review (for example an entire image of a Western blot with molecular-weight markers).

• A certain degree of image processing is acceptable but the final image must faithfully represent the original data. Image acquisition and processing software must be included in the methods. Authors should be prepared to supply the editors with original images on request.

• Histopathology slides and graphs should be separate figures and not subpanels of the same figure. Please provide scale bars or the level of magnification used.

• Vector graphics (e.g. line artwork) should be saved in encapsulated postscript format (.eps) at a minimum of 800 dpi.

• Bitmap files (e.g. photographs) should be saved in tagged image file format (.tif) or JPEG at a minimum of 300 dpi.

• We require all clinical images to have patient consent for publication (see Editorial policies on patient privacy). Eye bars or masking of the eyes is not permissible as they do not protect the anonymity of the patients. All case reports must have patient consent for publication before submission.

References

References should be in Vancouver format and appear as consecutive, unbracketed superscript numbers in the text, e.g. in our previous reports 1,2 and those of Smith et al.,3–5 and should be listed numerically in the reference list at the end of the article. Format references as below, using standard (MEDLINE) abbreviations for journal titles. If there are more than four authors, include the first three authors followed by et al. If there are more than six editors of a book, include the first five authors followed by et al.

1 de Berker DAR, Baran R, Dawber RPR. The nail in dermatological diseases. In: Baran and Dawber's Diseases of the Nails and Their Management (Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds), 3rd edn. Oxford: Blackwell Science Ltd, 2001; 172–92.

2 Shuster S. The nature and consequence of Karl Marx's skin disease. Br J Dermatol 2008; 158:1–3.

3 Graham-Brown R, Burns T. Lecture Notes: Dermatology. Oxford: Wiley-Blackwell, 2006.

4 Smith A. Select committee report into social care in the community. Available at: http://www.dhss.gov.uk/reports/report015285.html (last accessed 7 November 2003). If a reference falls into a different category (e.g. conference proceedings, prescribing information), or if in doubt, please provide as much information as possible.

We recommend the use of a tool such as EndNote for reference management and formatting. EndNote reference styles can be found here.

Supporting Information

The BJD encourages the submission of underlying datasets, appendices, video files etc. as online-only Supporting Information. Supporting Information should be uploaded during manuscript submission using the file designation 'Supplementary file for review'. BJD has no restriction around the amount of Supporting Information.

Supporting Information should be important ancillary information that is relevant to the main article and is published online only.

Reference to Supporting Information in the manuscript should be sufficiently specific to allow readers to understand what is being referenced. All tables and figures included in the Supporting Information should be cited in the manuscript.

Please label Supporting Information in the format ‘Table S1’, ‘Figure S1’. Any Supporting Information consisting of just text should be ‘Appendix S1’ etc.

Supporting Information will be published as submitted, and will not be corrected or checked for scientific content, typographical errors or functionality. Supporting Information is not permitted for correspondence, including Research Letters.

Data presentation

• It is recommended that data are displayed in their raw form and not in a way that conceals their distribution. Individual data should be presented as dot plots next to the average for the group with appropriate error bars. The methods should be described in enough detail that the experimental conditions can be repeated in another laboratory. If any equipment or specific reagent used is detailed, provide the name of the manufacturer, city, state (if applicable) and country.

• Any materials generated during the study (e.g. cell lines, animals, plasmids or antibodies) should be made available to other researchers, where this is practicable.

Novel DNA or amino acid sequences should be submitted to a public database such as GenBank or the European Molecular Biology Laboratory (EMBL) and the accession number quoted.

Reporting statistics

Good reporting is important as it ensures a manuscript can be understood by a reader, replicated by a researcher, used to make a clinical decision, and included in a systematic review.

Reporting methods

• Describe the type of study, e.g. randomized clinical trial phase III, pilot, case–control, meta-analysis etc. • Indicate the aim of the statistical analysis (primary objective, secondary objective, exploratory or ancillary analysis).

• Describe the statistical methods in the order in which are used in the results.

• Make it clear which statistical test was used for which variable.

• State if any assumptions were checked and how.

• Describe how missing data were handled (if data are missing).

• Describe any planned sensitivity or subgroup analyses.

• If relevant, include a sample-size calculation, with sufficient detail so it can be verified, and report the minimal clinically important difference (if possible).

• Report the alpha-level (one or two sided) and the statistical package.

• Describe with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. For more details about reporting standards, please see the ICJME recommendations.

Reporting results

• Present in the same order of importance as described in the methods.

• Include effect sizes and their 95% confidence intervals with the appropriate degree of precision, in addition to P-values. Please read this editorial and accompanying paper on how to report confidence intervals.

• Adjusted data for multiple testing.

• Include both absolute and relative measures.

• Provide enough detail that the results can be incorporated into other analyses; for example, in future meta-analytical studies if reporting a continuous outcome, provide mean (standard deviation), while for categorical outcomes when reporting relative summary statistics, please include the frequency of the outcome (numerator) over the total sample observed (denominator). In addition to these recommendations, all applicable general and study-specific SAMPL guidelines should be followed. Further explanation can be found in the editorial 'Guidelines for statistical reporting in the British Journal of Dermatology'

Plain Language Summary (PLS)

We encourage authors to write Plain Language Summaries to accompany their research study. These need to be written with the patient in mind and in plain English, suitable for someone in high school. Explain all scientific terms used.

General guidance

• Plain Language Summaries should be around 250 words in length.

• Start the page with a plain language title, i.e. a simplified title that explains briefly the subject of the study or summary.

• Please include paragraph breaks.

• End the plain language summary with the full title of the study and the author list; the author affiliations are not required.

Please include in the summary:

• The disease, what it is, and how common (e.g. xx is a common skin disease that causes xxx. It affects about xx people in the UK/worldwide) to give some context to the condition or disease.

• Country or countries in which the researchers are based (and where the study took place if different).

• What the study aimed to find out (e.g. This study, from the UK, aimed to find out if xxx).

• How the study was done.

• What the study found.

• Any conclusion, including what this might mean for patients (either now or in the future), and any recommendations (e.g. for future research).

• Write in the first person, e.g. 'We found that…'

• Include the Plain Language Summary in your manuscript submission process.

About the summaries:

• BJD publishes Plain Language Summaries as online-only pages as part of a regular issue, in their own specific section.

• The Plain Language Summary pages are referred to in the printed, hard-copy journal's Table of Contents section (as e1, e2, e3 etc.) but the summaries appear online only.

• The Plain Language Summary pages are freely available to all and are not behind the subscription paywall. The articles that they refer to may be behind a paywall, although Wiley offers a patient access system for those lay readers who may wish to access the full article without a charge to them.

• The summaries are also translated into Mandarin.

1.4 Manuscript Categories

At a Glance

The BJD invites the following types of submission. For a brief overview of the requirements for each article type, please see here.

Please read our editorial about BJD's editorial approach.

Review Articles

BJD aims to publish concise, state-of-the-art review articles of recent advances in laboratory or clinical research.

Review articles may be solicited by the Editor, as part of a set of scholarly reviews, or may be submitted by authors for publication subject to peer review.

Requirements for submission

Review articles should include

• an unstructured abstract (maximum 250 words),

• no more than 3000 words of body text,

• illustrations and figures.

Please see the Evidence-Based Dermatology section for guidance on submission of systematic reviews.

Evidence-Based Dermatology

BJD's Evidence-Based Dermatology section includes systematic reviews, management guidelines, critically appraised topics (CATs) and critically appraised research papers (CARPs). Before commencing a CAT or CARP, please contact the editorial office **(bjd@bad.org.uk)** to discuss your proposal.

Article types

Systematic Review

Our aim is to publish concise, high-quality systematic review articles. Systematic reviews are considered Original Articles by the BJD and must follow the Original Article format.

We are very interested to receive network meta-analyses. In addition, the BJD accepts living systematic reviews, and authors are encouraged to contact the editorial team (bjd@bad.org.uk) to discuss their plans for a living systematic review before submission.

Requirements for submission

Systematic reviews should include

• A structured abstract (maximum 250 words).

• Up to 3000 words of body text.

• Bulleted statements (maximum 70 words per question) in answer to the following questions:' What's already known about this topic?' and 'What does this study add?'

Reporting guidelines

Reporting guidelines should be provided at the time of submission as 'Supplementary file for review'.

• For **systematic reviews and meta-analyses**, follow the PRISMA statement.

For systematic reviews that include a network meta-analysis, follow the extended PRISMA guidance.

• For **meta-analyses and systematic reviews on observational studies**, follow the MOOSE consensus statement.

• For **reviews of qualitative studies**, reference the ENTREQ statement.

• Prospective registration of the **systematic review** on PROSPERO or a similar database is compulsory.

• For a **systematic review protocol**, use a suitable tool that facilitates the development and reporting of systematic review protocols (e.g. PRISMA-P).

• All systematic reviews must include an assessment of the methodological quality of the included studies. We recommend authors follow the methods suggested by Cochrane.

• We encourage effect measures and confidence intervals, and/or meta-analyses and GRADE evaluations of high methodological quality, presented appropriately for our clinical readership.

Critically appraised topics (CATs)

CATs should focus on a specific and usually controversial relevant clinical question. In contrast to a full systematic review, a CAT may include data from different sources, trying to argue the case from different angles.

It may include results of randomized controlled trials or it can summarize registry data and also draw in pathophysiological considerations. A systematic approach on how data were generated must be pursued.

Submission of a PRISMA checklist is not necessary for CATs, although authors are strongly encouraged to familiarize themselves with the PRISMA reporting guidelines before beginning their work on a CAT.

As a result of a CAT, a solution to the specific clinical questions raised should be presented to help doctors with everyday decision making. For suitable topics, at least some evidence should be expected that would allow meaningful conclusions.

CATs are formatted as Original Articles, unless limited evidence permits the Research Letter format.

Requirements for submission

• Structured abstract including Clinical question/scenario and Recommendation for Clinical case.

• Clinical case generating a management question.

• Background.

• The results or identified evidence should provide information on effect sizes with confidence intervals.

• A meta-analysis can be conducted for the primary outcome pertaining to the research question.

• The discussion should critically summarize the identified evidence and discuss applicability to the clinical case.

• The clinical message or recommendation should provide clear clinical guidance and a management strategy; consider how to optimize shared decision making incorporating the patient perspective.

Reporting guidelines

• Describe the methods used for systematic evidence gathering such as the inclusion and exclusion criteria and the methods for study quality assessment (adherence to the PRISMA guidance and use of the Cochrane risk of bias tool or AMSTAR tool are recommended.)

For further guidance, read our article on **how to write a CAT**.

Critically appraised research papers (CARPs)

CARPs aim to alert readers to important papers from the general medical literature that are relevant to clinical practice or research in dermatology, and to offer a critical appraisal of the methodology, findings and conclusions.

Requirements for submission

CARPs should

• not exceed 750 words or 8 references,

• have one small figure only with no more than 4 small panels OR one small table (the equivalent of one Word landscape page),

• have no abstract or bulleted statements,

• have no subheadings or supplementary material.

CARPs should include the following considerations:

• What is already known about this topic?

• Strengths of the research (including a description of how the research advances the field).

• Assessment of validity (please comment on internal and external validity of the methods).

• Overall assessment (please comment on whether the study's conclusions are justified and on the application of the research to clinical practice).

Authors are encouraged to consult guidance for critical appraisal of the medical literature, including the **Centre for Evidence-Based Medicine's Critical Appraisal tools** and **JAMA's Users' Guides to the Medical Literature**

Clinical practice guidelines

BJD welcomes submission of clinical guidelines from any geographical location covering any area of dermatology. These can be pure treatment guidelines, but they can also cover diagnosis and screening. Guidelines are usually based on a systematic review of the literature (see above guidance), as well as structured expert consensus.

All guideline submissions will undergo independent peer review. Guideline developers are encouraged to contact the BJD editorial office (**bjd@bad.org.uk**) at the time of stakeholder review (e.g. society approval) to coordinate with the BJD external peer review process.

• Reporting guidelines. Authors and guideline developers should consult the AGREE II instrument for which items should be reported, as well as the BJD editorial that highlights particular quality aspects of guideline development.

• The BJD gives particular emphasis to the quality of the methods used to construct the guideline, including assessment of evidence quality and a recognized method for converting to strength of recommendation (e.g. GRADE).

• Living guidelines are encouraged, and authors are encouraged to discuss their plans for a living guideline with the BJD Editorial Team prior to submission.

Requirements for submission

• Details of any consensus methodology need to be fully reported, as well as conflicts of interest and funding sources.

• Potential author conflicts of interest should be minimized or mitigated, for example by excluding authors from sections relevant to their conflict of interest.

• Guidelines do not have a fixed maximum word count but should be as succinct as possible and ideally have no more than 3000 words.

• Emphasis is on the methodology and transparency for rigour of guideline development.

• Details of the systematic review(s) that inform the guidelines can be provided in supplementary files, or as a separate BJD paper.

Original Articles

General guidance

All Original Articles should include:

• A structured abstract with background, objectives, methods, results and conclusions (maximum 250 words).

• Up to 3000 words of body text (4000 words for qualitative studies).

• Bulleted statements (maximum 70 words per question) in answer to the following questions: ‘What’s already known about this topic?’ and ‘What does this study add?’. Translational research papers should additionally include bulleted statements answering the question ‘What is the translational message?’. Qualitative research papers should additionally include bulleted statements answering the question ‘What are the clinical implications of this work?’.

• An ethical approval statement with the name of the approving institutional review board(s) in the Materials and methods section.

• Contributor statement.

• A statement regarding patient involvement in the research (optional).

• A Plain Language Summary (optional but encouraged).

BJD has different subcategories of Original Articles; please see the next section for specific submission requirements.

Article types and specific requirements

Clinical trials

The BJD publishes industry-sponsored and investigator-initiated clinical trials covering pharmacological, nonpharmacological and complex interventions. Clinical trial protocols are unlikely to be considered for publication in the BJD. However, publishing a trial protocol in the public domain is good practice and the BJD encourages authors to do so in other suitable journals.

Requirements for submission

• The manuscript should follow the format of an Original Article, but for small studies (e.g. fewer than 50 participants) or analyses of data subsets from larger clinical trials

(whether planned or post hoc), consider submission as a Research Letter (please see the Correspondence section for details).

• The trial must be **prospectively registered on a suitable trial registry**, before any participants have been recruited into the trial. Include the trial registration number (e.g. NCT012345678) at the end of the abstract. **Trials that have not been prospectively registered will be rejected**. For further details about registering your trial, read this editorial.

• Ideally, the trial protocol should be submitted alongside the main manuscript, as a 'Supplementary file for review'. Providing the study protocol enables the editorial team to confirm that all outcomes have been clearly reported as per protocol, and will facilitate the review process, but final acceptance is subject to the final editorial decision.

• Priority will be given to manuscripts reporting the primary outcome(s) for the trial and all registered secondary outcomes for the trial. The BJD discourages the publication of secondary outcomes in separate papers ('salami slicing') and encourages authors to report these outcomes in the same paper as the primary outcome(s) (see this editorial).

• The BJD may consider manuscripts that do not include secondary outcomes relating to very long-term follow-up, whose time points have not yet been reached.

• To avoid publication bias, the BJD encourages the submission of trials even if the outcomes do not reveal a difference between the interventions being compared (so-called 'negative' trials, see this editorial).

Reporting guidelines

The following checklists should be provided at the time of submission as 'Supplementary file for review':

• For randomized controlled trials, please follow the CONSORT statement and submit a completed CONSORT checklist as Supporting Information.

• All requirements of the CONSORT checklist should be addressed in the manuscript, including a power calculation to show how the sample size for the study was determined.

• For randomized controlled trials with specific designs (e.g. pilot/feasibility; noninferiority/equivalence; cluster), data (e.g. harms) or interventions (e.g. nonpharmacological), please refer to the appropriate extensions of the CONSORT statement.

• For nonrandomized trials, refer to the CONSORT statement or another appropriate EQUATOR guideline to ensure that the trial is reported clearly.

Epidemiology

We welcome manuscripts based on findings of epidemiological studies that improve our understanding of skin diseases and have clinical relevance in terms of disease treatment or prevention. Please see this editorial for more information.

Requirements for submission

• Epidemiological studies should stimulate independent thinking and challenge the status quo.

• The robustness of the data collection and methodology used is more important than whether the findings are statistically significant.

• Comprehensive studies investigating multiple (international) data sources to validate will be prioritized.

• Epidemiology manuscripts should follow the Original Article format, but for confirmatory studies or less complicated studies (which can present their findings using one table OR figure), consider submission as a Reseach Letter (please see the Correspondence section for details).

Reporting guidelines

The following checklists should be provided at the time of submission as 'Supplementary file for review' (**Research Letters** are exempt).

• For **observational studies,** follow the STROBE statement. Include the appropriate (cohort, case–control and cross-sectional studies) and completed STROBE checklist.

• For **multivariable prediction models** for diagnostic or prognostic research, follow the TRIPOD guidelines and submit a TRIPOD checklist for model development and/or model validation.

• For **routinely collected health data**, obtained for administrative and clinical purposes without specific a priori research goals, include a completed REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement checklist.

For all epidemiological studies, we assess:

• Use of clinically relevant outcomes. ,

• Presence of clear sample-size calculations based on the primary outcome.

• Clear distinction between association and causality in the interpretation of the results.

• Temporality and dose–response relationship, along with the other Bradford–Hill criteria to gauge the likelihood of causality.

• The extent and dealing with (residual) confounding, in particular for studies using routinely collected data or claims data, or large population-based cohorts that were not created to study the studied association.

• Selective subgroup analyses with sufficient power avoiding data dredging.

• Appropriate statistical testing, please see the Reporting Statistics section for details.

Translational research

The BJD encourages submission of basic research that has the potential to improve clinical practice in the foreseeable future. Authors should clearly communicate the potential clinical relevance of their findings.

The BJD adopts the definition of translational research as described by the National Institutes of Health:

'Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science' (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html).

Requirements for submission

In addition to the usual bulleted statements for Original Articles (What's known and What's new), all manuscripts describing translational studies must also include a third set of bulleted statements (maximum 70 words) in answer to the following question**: 'What is the translational message?'**.

• **Laboratory-based studies** should show direct relevance to the understanding of the clinical features, pathogenesis or treatment of skin diseases in humans.

• Studies performed exclusively with **nonprimary or patient-unrelated cell lines** and **studies using animals** will be considered for peer review only if accompanied by data showing their direct and genuine relevance to human dermatological conditions (read the editorial by Eli Sprecher).

• Manuscripts should be written with a clinical audience in mind. Authors are encouraged to provide one or more summary diagrams to complement their written text to explain complex or novel scientific concepts.

• Provide data from multiple laboratory techniques that support the conclusions (data generated using a single technique are usually insufficient).

• Novel DNA or amino acid sequences should be deposited in a public database such as GenBank or the European Molecular Biology Laboratory (EMBL), including the accession number in the submission.

Please refer to the data presentation section to see how the data should be presented.

Reporting guidelines

Reporting checklists should be provided at the time of submission as a 'Supplementary file for review', but if there are no guidelines, we have provided some reporting guidance.

• **Immunohistochemistry/immunofluorescence.** Provide all antibody sources, preferably with clone names for clear identification and details of secondary antibodies and their conjugated fluorochromes or enzymes. Clearly state negative controls along with the data. Include dilutions, incubation conditions, detection methods and method of data analysis in the methodology. Support expression data by Western blotting and/or reverse-transcriptase polymerase chain reaction (PCR).

• **Quantitative PCR data**. Follow the MIQE guidelines. This should include details on RNA quality, reverse transcription conditions, PCR conditions including PCR primer sequences, how reference genes were chosen and how the data were analysed.

• **Proteomics and genomics**. Full and comprehensive description of all methods used should be provided as Supporting Information along with a detailed list of all software, as well as all details pertaining to the quality of the data obtained (e.g. reading depth).

• **Genetic association studies**. Please include an estimation of the effect size and statistical significance, as well as an estimation of the study power, to allow readers to interpret the findings appropriately. Consider the issues of multiple testing, which are inherent in genome-wide analyses (including transcriptome analysis). Novel genetic associations should be replicated in an independent collection.

• **Biomarker association studies**. Follow the REMARK guidelines.

• **Flow cytometry.** Data plots should be included in the main article or in Supporting Information. The data could be compiled (in addition to plots) into table format for ease of interpretation. Types of plot, labelling of plots, labelling of plot axes, and information required in figure legends are given in Alvarez et al.'s Publishing flow cytometry data.

Mutation reports

While mutation reports are usually not considered for publication unless they represent significant advances in our understanding of a disease's pathogenesis or manifestations, the following may be considered for peer review:

• Reports that describe from **one to a few** previously reported mutations and are associated with a phenotype markedly different from previously reported ones.

• Large (n > 20) series of patients carrying **previously reported or novel** mutations in known genes associated with **typical** phenotypes that provide new insights into genotype–phenotype correlations. Novelty is important (i.e. large series will not be considered if they are already available in the literature).

• Reports of one to a few novel disease-causing mutations in a gene already known to be associated with the same disease will only be considered if the report contains significant and novel functional data (explaining the function of the gene under study and/or the mechanisms of action of the mutations reported).

Mutation pathogenicity should be assessed according to established guidelines such as the recommendations from the **American College of Medical Genetics and Genomics**.

Qualitative and outcomes research

We are interested in publishing studies that provide substantial insight into the perspectives and/or **experiences** of individuals or groups (e.g. patients, carers, clinicians) in relation to the context, process and outcomes of dermatology or dermatological care.

This includes but is not restricted to:

• Qualitative studies exploring psychological wellbeing; social functioning; patient–professional communication; treatment decision making; clinician training; and service content, organization and delivery of care.

• Interventional studies where qualitative components may inform the intervention, or its implementation, or serve to evaluate outcomes and process issues.

• Studies on the development and/or validation of outcomes measures that are useful for clinical trials, observational studies, clinical audits and routine care, particularly patient-reported outcome measure (PROMs) and patient-reported experience measures (PREMs).

• Studies on the development of core outcome sets in dermatology to improve the reporting of clinical trials, particularly papers defining core outcome domains and validation studies for instruments to measure the core domains.

• Outcomes from consensus meetings. These may also be submitted, provided they progress the core outcomes set, and the methodology employed is fully and transparently reported.

• Mixed-methods studies: studies incorporating both qualitative and quantitative elements.

• Studies reporting methodological perspectives in qualitative or mixed-methods research and outcomes research (e.g. item response theory, classical test theory, consensus seeking).

Requirements for submission

• In addition to the usual bulleted statements for Original Articles (What's known and What's new), manuscripts describing qualitative or mixed-method studies must also include a third set of bulleted statements (maximum 70 words) in answer to the following question: '**What are the clinical implications of this work**?'

• Any quotations or images used should not contain unique contextual features that would enable participants to be identified.

• Demonstrate that due consideration has been given to problem formulation, researcher characteristics and reflexivity, sampling strategy, units of study, techniques to enhance trustworthiness and transferability in qualitative research.

• Demonstrate that due consideration has been given to formulation of a clear aim of an instrument or core outcomes set development process, the conceptual framework underlying instrument development, the qualitative research in the development process of an instrument, the clinimetric analyses involved in the validation of an instrument, and aspects of feasibility and interpretability (instrument development or validation research).

• When reporting on the development and/or validation of an instrument, do submit the instrument of interest itself for review. Please ensure that you have valid copyright permission relating to the development or validation of the instrument. As a minimum requirement, our reviewers must be able to judge the face validity of the instrument of interest.

Reporting guidelines

When appropriate, reporting checklists should be provided at the time of submission as a 'Supplementary file for review'.

• Consider, for the content of a core outcome set development study protocol, the COS-STAP statement.

• Consider and address, for qualitative research, the SRQR (Standards for Reporting Qualitative Research) recommendations.

• For mixed-methods studies, consider the SRQR and the appropriate EQUATOR checklist for the methodology of the quantitative element of the mixed methods (for example, the STROBE or CONSORT checklist).

Case Reports

BJD publishes only a few exceptional case reports each year that make a substantial contribution to our understanding of dermatology or raise important new hypotheses. We accept fewer than 2% of the case reports that we receive.

We recommend authors read our **review article** on the type of cases that we publish and about improving them.

BJD regards case reports as original research and manuscripts should follow the Original Article format, with a few differences that are detailed below.

Please also see the Editorial Policies section for details on our patient privacy policy.

Requirements for submission

• It is mandatory to submit BJD's Patient Consent form for publication at the time of submission for all case reports, or ensure you have e-mailed a copy to bjd@bad.org.uk by the time your paper has been accepted.

• Maximum word count of 1200 words.

• No more than 15 references.

• At most four tables or figures.

• Abstract must be unstructured.

• Bulleted statements (maximum 70 words) in answer to the following questions: What's already known about this topic? and What does this study add?

• Include a statement about patient consent in your paper in order to ensure better reporting and transparency.

Reporting guideline

• Follow the CARE guidelines as a guiding framework for your manuscript.

Correspondence

Types of letters

Research Letters

Research Letters are the most prestigious form of BJD correspondence for publishing preliminary research findings that may lead to more substantial research studies. They could also be short summaries of primary research. We would like them to be concise, thought-provoking and of interest to clinicians.

Examples include:

• pilot studies whose aim is to test research methodology,

• preliminary data to inform subsequent study design,

• small observational or experimental studies,

• studies that extend what has recently been published by others,

• studies whose results provide a focused message that can be presented in a concise format,

• studies that use a single research method, where two or three complementary methods would be the norm for an Original Article.

Requirements for submission

BJD research letters should

• not exceed 750 words or 8 references,

• have one small figure only with no more than four small panels OR one small table (the equivalent of one landscape page in Word),

• have no abstract or bulleted statements,

• have no subheadings or supplementary material.

To make it easier, we recommend using this **template for Research Letters.**

Rapid responses

Rapid responses allow readers to participate and debate recently published BJD articles. We encourage rapid responses to be sent when the paper is online in the Accepted Article or Early View section so that the letter can be published in the same issue as the article itself, with a response from the authors if possible.

They should add to the authors' interpretation, enrich the original paper and increase the value for readers.

They should be objective, referenced, respectful to other authors, and concise.

Requirements for submission

Rapid responses shoulda

• not exceed 450 words,

• have a maximum of 4 references,

• have at most one table or figure.

Perspectives articles

These articles provide an opportunity to address any topic relevant to dermatology by articulating a new point of view that is based on evidence or experience from patients and physicians alike, particularly those that may generate philosophical debate.

We especially encourage perspectives from dermatology patients, which could be cowritten with your clinician.

We encourage them to be concise and thought-provoking, and prompt new ways of thinking, but they should be written in a simple and easily accessible format that a wide international audience can understand.

We welcome submissions on all topics relevant to dermatology, and encourage diversity of gender, race/ethnicity, country of origin and background among Perspectives authors.

Our goal is to publish Perspectives relevant to the skin health of all communities, including previously understudied groups and vulnerable populations. This includes the health of the LGBTQ community, people with skin of colour, elderly patients and those with understudied diseases, as described in this editorial.

Requirements for submission

Perspectives should

• not exceed 750 words,

• have at most 5 references,

• have no more than one table or figure,

• be formatted in one continuous section, with no bulleted statements or abstract.

Correspondence: Image Gallery

BJD welcomes submissions of diagrams, scientific figures and photographs for the BJD Image Gallery section. We accept some clinical images provided the case extends our knowledge of dermatology. ‘Textbook’ type submissions that mainly serve a teaching purpose are discouraged.

Requirements for submission

• Composite images with up to three panels are permitted, for example providing histopathology, immunostains or electron microscopy to accompany the clinical image.

• Submit each panel as a separate file as TIFF or JPEG up to 300 DPI, and remove any labels such as A, B, C, but please label the legends carefully.

• Please do not place eye bars on patient photographs as they do not protect their privacy, and instead ensure you have patient consent for publication. Please see the Editorial Policies section for details on our patient privacy policy.

• Include a concise, scholarly caption of up to 100 words and up to two references. Photographs or images should be of high quality and have potential to alter dermatology practice.

A separate figure legend should not be submitted. Images will be selected based on scientific merit, originality, relevance to the journal readership and value added to our understanding of dermatological science.

Additionally, some of the accepted Image Gallery submissions may be adapted to appear in the open-access digital healthcare forum, **Figure1**, or be used in BJD's social media platforms.

The best submissions may be selected for the Cover Image of the journal.

1.5 Revision

If you are planning to submit a revised manuscript, we need the following:

• A version of the manuscript with tracked changes and a clean version to ensure the reviewers and editors can view all of the changes that you have made.

• A point-by-point response to the previous reviewers' comments.

• Upload all the tables and figures even if no changes have been made. The system does not automatically carry over the previous files.

• Please include the word count for the relevant article type, and if you are revising as a Research Letter, please use the provided template.

• Ensure that you have applied for copyright permission for the reuse of material already published in another journal, book or article by the time your paper is accepted. We will be unable to publish any previously published figure or table either adapted or reproduced without appropriate permission. For more details, please see the Permissions page.

You do not need to resubmit Author Consent or Patient Consent forms at revision, if you have already provided these with the original submission. These will however be required if we have not received them previously.

2. Post-Acceptance

2.1 Reaching out to a wider audience

Once your manuscript has been accepted, you will receive a final decision letter along with a request for the following:

• Plain Language Summary, if you haven't already submitted one.

• An author video.

• A set of journal club slides.

All of the above are optional and you can choose to submit them or not. The reason we ask for these additional elements is to add value to your article.

Plain Language Summary

Plain Language Summaries are a great way to ensure that your article has a wider reach beyond the clinician or academic. Please see the Plain Language Summary section in Preparation of Manuscripts for more details.

Author videos

Author videos are great promotional tools and are another way for you to explain your research to a wider audience. Some tips about making a video are explained below.

Tips for recording

• Set the camera or phone on a stable surface or a tripod if you have access to one.

• Record in a well-lit area.

- Professional lighting equipment is not required.

- Ensure that the light source is not behind the subject as this may cause a silhouette effect.

• Ensure that there is minimal background noise.

- If you have access to a microphone then consider using this rather than the built-in microphone in the camera or phone.

Journal club slides

We need your help in preparing a set of PowerPoint slides, using the standard BJD template. The slides include the following:

• Title slide, with authors and institutions; an introductory slide on 'What's already known about this topic?'; and a slide on 'What does this study add?' highlighting the incremental knowledge that your study generates. The 'What's already known' and 'What does this study add?' sections can be populated directly from the corresponding sections of the paper.

• The final slide in the presentation invites readers to contribute a rapid response to the article with a link to the author instructions for the BJD Letters to the Editor section.

• Please aim to include about three bullet points per slide. The methods and results section can be spread over three slides each. None of the text should be smaller than 18 point. Please avoid adding references to the slides because these can be difficult to read.

• If you would like to use particular images from your paper, please add them to your presentation. Please bear in mind that complicated tables containing lots of data may not project well in a presentation and may be best described in a few bulleted statements, rather than including the whole table. It is interesting for your colleagues to see who has done the research, and we have included slides in our template for photographs of the lead researcher at the start of the presentation and the whole team at the end.

Once ready, please submit to the BJD Editorial Office (john@bad.org.uk). You may need to respond to queries from the editorial team.

Once accepted, your BJD journal club PowerPoint slide set will be available from the BJD website, alongside your article. The slide set is free for readers of the journal to use for their local journal club presentations worldwide.

2.2 Accepted Article publication

Once accepted, manuscripts are made available online in the Accepted Articles section within a few days. **Accepted Articles** have been peer reviewed and accepted for formal publication but have not been subject to copy editing or typesetting. This allows articles to be available for earliest possible dissemination following article acceptance.

Accepted articles will appear in PDF format only and are given a Digital Object Identifier (**DOI),** which allows them to be cited and tracked. The DOI is unique to any article in perpetuity and can continue to be used for citation and to access the article even after print publication. Accepted articles will be indexed in PubMed.

Neither the British Association of Dermatologists nor Wiley can be held responsible for errors or consequences arising from the use of information contained in accepted articles, nor do the views and opinions expressed necessarily reflect those of the British Association of Dermatologists or Wiley.

2.3 Proofs

You should expect to receive your page proofs within a few weeks after acceptance. Page proofs will be sent electronically to the corresponding author and should be returned within **2 days** of receipt to the Production Editor. Substantial alterations are

unacceptable at proof stage without the written approval of the Editor and may result in delays.

The corresponding author will receive an e-mail alert containing a link to a secure website. A working e-mail address must therefore be provided for the corresponding author. In the absence of the corresponding author, please arrange for a colleague to access the e-mail to retrieve the proofs.

Please note that you have final responsibility for any content in the proofs of your manuscript. The proofs are also checked thoroughly by the BJD editorial team, and if we do not receive corrections after several reminders to the e-mail address supplied for the corresponding author, we will assume that we have your approval for publication.

2.4 Early View publication

Once proof corrections have been made, the paper will be published in the 'Early View' section of the journal website. Early View articles have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made subsequently to Early View publication. Early View articles can be cited and tracked by their DOI.

2.5 OnlineOpen

If you want to publish your article open access, please refer to the OnlineOpen section the Wiley Online Library.

2.6 Author Services

Author Services enables authors to track their article – once it has been accepted – through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production.

The author will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a current e-mail address is provided when submitting the manuscript.

Visit the **Author Services website** website for more details on online production tracking and for a wealth of resources including frequently asked questions and tips on article preparation and submission and more.

Offprints

Free access to the final PDF offprint of your article will be available via Author Services only. Therefore, please sign up for Author Services if you would like to access your PDF offprint and enjoy the many other benefits that the service offers.

3. Policies

3.1 Editorial policies

Authorship

General Guidance

BJD follows **the ICMJE criteria** for authorship and requires authors to adhere to it based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Corresponding authorship

BJD's policy is to allow only one corresponding author for an article and they should be designated at the time of submission. Changes to authorship are not allowed after acceptance unless there are exceptional circumstances in which case an email will need to be sent to the Editor at **bjd@bad.org.uk** explaining the rationale for such a change. The Journal will then follow **COPE's** process to ensure all authors agree to the changes before making such changes.

Group authorship

For large groups of authors (e.g. more than 100 authors), a smaller group should be designated as the authors acting on behalf of the group. All named authors must fulfil the ICMJE authorship criteria and fill in both the disclosures and author consent forms. If the large multiauthor group would like to be listed as a group name rather an individual, please follow the recommendation provided by **the ICMJE**.

CRediT taxonomy

As of April 2020, we require that all authors use the CRediT Contributor Roles Taxonomy within the Scholarone Submission system at the time of submission. It is a high-level taxonomy, including 14 roles typically played by contributors to scientific scholarly output. The roles describe each contributor's specific contribution to the scholarly output, ensuring a transparent system of attribution and recognition. For more details, see here.

Acknowledging contributors

Please do ensure you have permission in writing from anyone you choose to acknowledge in your paper.

Ethical approval

For studies on people

For studies on people

All clinical investigations reported must be conducted according to the principles expressed in the Declaration of Helsinki.

All studies must conform to appropriate ethical standards and must have been approved by the relevant ethical committees and institutional review board(s). A statement to this effect with the exact name of the approving institutional review board(s) should be included in the Materials and methods section of all papers. This information may be relevant for Research Letters or Letters to the Editor.

Patients' names, initials or hospital numbers should not be used, especially in illustrative material. Moreover, if your study is based in a single centre or in a small-hospital setting and the study is based on a case series with a detailed description of each patient, please ensure that you have informed consent for publication unless the data have been suitably anonymized.

Observational studies using routinely collected anonymous data from regional or national cancer registries, claims data from insurance companies, or data from other national registries do not need ethical approval. If that is the case, please state accordingly in the methods.

For studies on animals

All animal studies should have the relevant approval and follow the **ARRIVE guidelines**. When reporting experiments on animals, indicate whether the institutions or a national research council's guide for, or any national law on, the care and use of laboratory animals was followed.

Patient involvement in research

One of BJD's missions is to ensure that patients are involved in the research process, and hence we encourage authors to provide a short statement in the methods describing how patients were involved in the research.

Patient Privacy

Patients have a right to privacy that should not be infringed without informed consent. Identifying information should not be published in written descriptions, photographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication.

Identifying details should be omitted if they are not essential, but patient data should never be altered or falsified to attain anonymity. Complete anonymity is difficult to achieve and informed consent for publication should be obtained if there is any doubt. Masking the eye region in photographs of patients is not allowed and offers inadequate protection of anonymity.

Authors must take adequate measures to protect participants' privacy in the reporting of any qualitative research submitted to the BJD, for example by anonymizing the names of individuals and locations.

The journal requires that informed patient consent for publication is obtained for all case reports and for all clinical images, whether or not the patient is identifiable. Confirmation of patient consent for publication in accordance with the BAD publications patient consent form is required at the time of submission.

The BAD publications patient consent form can be download here. If the patient is a minor then the parent or guardian's consent must be obtained. For any patient who is deceased, where possible patient consent for publication from the next of kin must be taken.

Data sharing policy

BJD supports the principle that all data should be made available to facilitate research reproducibility, while protecting **patient privacy** and confidentiality.

BJD encourages authors to upload all their data to a repository as recommended by their funder or to a publicly available repository such as **Figshare or Dryad** and to provide the DOI in their paper.

We encourage authors to include a data accessibility statement including a link to the repository that they have used. For more details, see **Wiley's Data Sharing Policies**.

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3.2 Publishing policies

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