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Consensus Guidelines

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Infectious Disease Screening prior to Systemic Immunomodulatory Therapy in Hidradenitis Suppurativa: Consensus Guidelines from the Asia-Pacific Hidradenitis Suppurativa Foundation

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Keywords
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Abstract
Background: Current infectious disease screening recommendations for hidradenitis suppurativa (HS) are adopted from recommendations in chronic plaque psoriasis. No HS-specific guidelines for infectious disease screening prior to immunomodulatory therapy have been developed. ***Objectives:*** The aim of the study was to establish an expert Delphi consensus of recommendations regarding infectious disease screening prior to systemic immunomodulatory therapy in HS. ***Methods:*** Participants were identified via recent publications in the field and were sent a questionnaire regarding infectious diseases encountered in the setting of HS, and opinions regarding infectious disease screening prior to various systemic immunomodulatory therapies. All questions were informed by a systematic literature review regarding infections exacerbated or precipitated by immunomodulatory therapy. Questionnaire responses were followed by round-table discussion with a core group of 8 experts followed by a final round of questionnaires resulting in achievement of consensus. ***Results:*** 44 expert HS physicians from 12 countries on 5 continents participated in the development of the expert consensus recommendations. Consensus recommendations include screening for hepatitis B, hepatitis C and tuberculosis in all individuals with HS prior to therapy. All immunomodulatory therapies (biologic and systemic immunosuppressant therapy) should be preceded by infectious disease screening

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including patient and location-specific considerations for endemic local diseases and high-risk activities and occupations. Clinical assessment has a significant role in determining the need for laboratory screening in the setting of many uncommon or tropical diseases such as leprosy, leishmaniasis and strongyloidiasis. ***Conclusions:*** The presented consensus recommendations are the first specifically developed for pre-treatment infectious disease screening in HS.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder with features of both autoimmunity and autoinflammation [1]. Treatment of HS includes symptomatic management, management of co-existing comorbidities, psychological support, systemic medical management, and surgical management in particular situations [2–5]. There are multiple medical therapies which can be used in the management of HS [4, 5], but, ultimately, the most effective therapy is immunomodulation or immunosuppression with biologic medications [6–9].

Adalimumab[7], a tumor-necrosis alpha inhibitor (TNF-α) is currently the only approved biologic therapy for HS and is associated with an increase in the risk of infections in the dermatological, gastroenterological, and rheumatological literature [10–13]. Chronic inflammatory conditions such as atopic dermatitis, psoriasis vulgaris, and HS may also increase the risk of cutaneous and systemic infections independent of therapy, as illustrated in clinical trial data [14]. Specifically, the use of immunomodulatory medications may increase the risk of exacerbation or reactivation of chronic occult infections.

Regarding infection risk in HS, current infectious disease screening guidelines are taken from experience with psoriasis vulgaris [14]. There are significant differences in the inflammatory milieu and the pathogenic role of chronic bacterial infection and biofilm formation between psoriasis vulgaris and HS [15]. Additionally, treatment modalities, associated comorbidities, and long-term complications differ between conditions [16]. Therefore, it can be hypothesized that current infectious disease screening guidelines for psoriasis are not the most appropriate in the setting of HS. No consensus guidelines have been formally developed for infectious disease screening in the setting of HS.

The concepts of therapy-associated risk and disease-associated risk [14] are appropriate in order to isolate and understand the causative links associated with these infections in the setting of systemic immunomodulatory therapy use in a chronic inflammatory disease. An example of the differences between therapy-associated risk and disease-associated risk is demonstrated with the cessation of biologic therapy during the COVID pandemic [17]. Significant morbidity associated with untreated inflammation was seen in individuals with chronic inflammatory disorders; however, no significant increase in risk of mortality from COVID was seen in the setting of continued immunomodulatory therapy of HS during COVID [17]. This highlights the potential of linking adverse events to a medication when, in fact, they may be disease associated.

The aim of this study was to develop evidence-based global consensus guidelines for infectious disease screening prior to systemic therapy for HS using a modified Delphi consensus method and a panel of international experts in the field. The infectious diseases of interest were those which represent a risk for exacerbation or reactivation in the setting of immunomodulatory therapy rather than acute secondary bacterial infections in the setting of disease.

Materials and Methods

A Delphi consensus technique [17] was used to engage a group of international experts in the field of HS regarding differences in infectious disease screening prior to therapy and to resolve differences and disagreements between practices. The project was initiated by the Asia-Pacific HS Foundation [18] (APHiS) Guideline Development Committee. Experts in HS were identified through recent publications in the field over the last 5 years. An expert was defined as an individual that had published more than 3 peer-reviewed publications in HS in the last 5 years. The study protocol was reviewed and approved by the Human Research Ethics Committee of Sydney South-West Area Health Service and complied with the Declaration of Helsinki (approval code 2021/ETH00387) [19]. Written informed consent was gathered for participation in this study. All participants provided informed consent at the beginning of the study. The development and reporting of the guidelines developed were in line with the appraisal of guidelines research and evaluation (AGREE) checklist [20] (online suppl. material Fig. 1; for all online suppl. material, see https://doi.org/doi/10.1159534575).

Delphi Exercise

The modified Delphi process used for the development of these consensus guidelines consisted of pre-survey preparation, followed by two separate rounds of survey distribution (Fig. 1). Responses to the pre-survey preparation involved a systematic literature review, followed by the development and distribution of survey material. All surveys were distributed, and data collated using the secure web application RedCap [21].

Preparation: Systematic Review of the Literature and Survey Development

The specific infectious diseases to consider were identified through a systematic review of infections reported among patients receiving TNF-α inhibitors, IL-17 inhibitors and apremilast

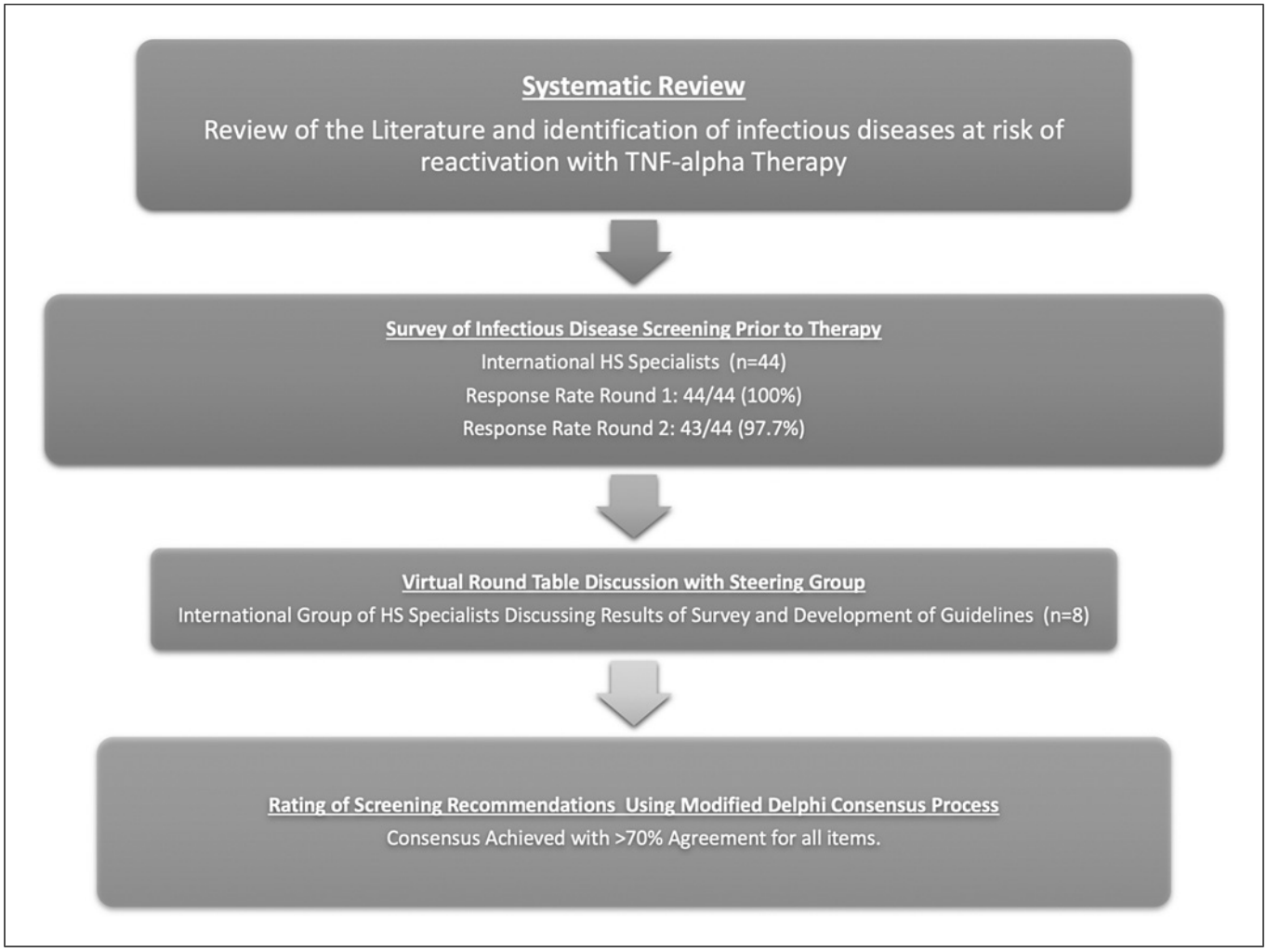

Fig. 1. Flowchart of the guideline development process for infectious disease screening in HS.

(PROSPERO CRD42021238959) [22] and conducted in line with the PRISMA checklist [23]. The search terms "adalimumab," "Infliximab," "etanercept," "secukinumab," "Ixekizumab," "bimekizumab," "apremilast," "hidradenitis suppurativa," "acne inversa," and "infection" were used to identify the relevant literature.

The implemented search strategy and PRISMA diagram [23] are included as online supplementary material. Eligibility criteria included randomized controlled trials, uncontrolled clinical trials, cohort studies, case-control studies, and other observational studies pertaining to infection risk in the setting of immunomodulation with no restrictions on patient age, sex, ethnicity, or language of publication up until March 30, 2021. An update to the literature search was performed on April 30th, 2023. Data collection was independently performed by two authors (E.K.K. and J.W.F.) with any disagreements referred to a third author for mediation. The level of evidence pertaining to infectious disease reactivation in the setting of immunomodulatory therapy was assessed using the strength of recommendation taxonomy (SORT) criteria [24] independently by two authors (E.K.K. and J.W.F.). Any disagreements pertaining to SORT criteria were referred to a third author for mediation. The infectious diseases identified in the systematic review were used as the basis for the distributed surveys, focusing on expert experience with encountering such diseases in the setting of HS therapy and opinions regarding the need for screening for the identified diseases.

First Survey Round

Initial questionnaire distribution (released on the 11 May 2021) included questions regarding infections encountered in the setting of HS (responses of "Yes" and "No") as well as free-text options for opinions regarding which infectious diseases should be screened for in the setting of HS. Responses were binary ("Yes" or "No") with free-text space for comments. This initial round was undertaken to validate the results of the systematic review. Additionally, a list of current HS therapies was listed with options as to which therapies require infectious disease screening prior to commencement. Free-text options were available for additional comments regarding special considerations including specific regional/population-based considerations and emerging therapeutic options.

Round-Table Discussion and Recommendation Development

Round 1 statistics and responses were presented to the core expert group during a round-table discussion on September 14, 2021, in order to discuss the scope of responses and draft initial expert recommendations. The discussion focused on general infectious disease screening as well as specific recommendations for specific population groups/endemic conditions in certain locations as well as the differentiation between clinical and serological screening. The discussion was recorded and transcribed for qualitative analysis.

Second Round

Round 2 surveys were released on November 9, 2021. Respondents were asked whether they agreed or disagreed with the proposed recommendations. If they did not agree, free-text space was provided for further elaboration and feedback.

Third Round Update

An updated survey was performed on May 13, 2023, in order to include the most recent relevant literature.

Data Analysis

Quantitative analysis, focusing on the proportion of respondents that agreed or disagreed with the presented screening recommendations, was calculated in all rounds. Consensus was defined as more than 70% of participants agreeing or disagreeing with a recommendation in line with previously published Delphi studies [17, 25]. Qualitative data from the free-text responses to surveys and the round-table discussion were reviewed and independently thematically coded using the comparative method by 2 authors [26]. Themes were identified and agreed upon by both coders. Qualitative analysis was conducted after each round so themes could inform subsequent survey rounds [27].

Agreement on the final round was defined as a "yes" response to the question, "Do you agree with this recommendation?" Disagreement was defined as a "no" to the same question. Stability of responses was defined as a change of 15% or less in participant responses when consensus was achieved [27]. Gwet's agreement coefficient was used to quantify the strength of consensus agreement for rank-type responses to the recommendations, with Landis-Koch benchmarking used for validation of the degree of agreement [28]. Face validity for the recommendations was based upon the high qualitative acceptance of the recommendations by the expert group [29]. All quantitative analyses were conducted using R v4.0.2.

Results

The systematic literature review identified 16 infections across 68 publications identified as at risk of reactivation or exacerbation in the setting of immunomodulatory therapy (Table 1). Evidence of reactivation was identified in 55 of the 68 identified publications in 15 of 16 infectious diseases. The level of evidence as ranked by the SORT criteria indicated an overall low level of evidence with 5 "B" ratings in 3 distinct infections and 58 "C" ratings across all 16 infections. No "A" ratings were identified.

The expert group was comprised of 52 individuals including dermatologists, surgeons, infectious disease specialists, and translational scientists, all with clinical and academic exposure to HS. All expert members had a minimum of five peer-reviewed publications in HS and were considered among their peers to have a high level of clinical or investigative expertise in the disease. These individuals represented 11 countries and 5 continents. The response rate to participate in the Delphi consensus was 84.6% (44/52). Eight individuals from the expert group agreed to form the "core" expert group to refine recommendations based upon feedback from participants. 44/44 participants responded to the first Delphi survey round (100%), and 43/44 participants responded in the second Delphi round (97.7%).

A round-table discussion among the core expert group identified a number of tenets around which the guidelines were developed. These included:

- Guidelines need to be general yet flexible to account for regional endemicity and individuals with prior exposure to infectious diseases (migrants, refugees, etc). This was termed "*patient- or location-specific screening.*"
- Acknowledge the issue with availability and cost of serological testing, but recommendations should be independent of this.
- Vaccination recommendations to be the subject of a separate discussion.

Consensus was achieved after the second Delphi round. No changes to recommendations were found after the update round in 2023. The agreement statistics are presented in Table 2. The proposed therapies in which screening should be undertaken are presented in Table 3. The proposed screening recommendations are presented in Table 4. In the first round, consensus for screening was reached for 3 infectious diseases (hepatitis B, hepatitis C, and tuberculosis) prior to relevant therapy for all individuals. Consensus for patient- or location-specific screening was reached for 11 diseases. In the second round, consensus was reached for all identified infectious diseases. This was split into general screening recommendations (hepatitis B, hepatitis C, and tuberculosis) and patient- or location-specific screening recommendations (Table 2).

Regarding the specific therapies which require screening, In the first round, consensus was reached on screening prior to therapy with adalimumab, infliximab, anakinra, IL-17 inhibitors, IL-23 inhibitors, cyclosporine, and methotrexate. In the second round, consensus was reached on screening prior to all listed therapies (Table 3).

Free-text comments in both rounds pertained to the role of prophylactic vaccinations prior to commencing biologic therapy, SARS-CoV2, pneumococcal, hepatitis A, VZV

Table 1. Summary of a systematic review of the evidence pertaining to reactivation of infectious disease in the setting of immunomodulatory therapy

Infectious disease	Reactivation in setting of biologic therapy	Specific biologics	Level of evidence (SORT)	References
HIV	No	Anti-TNF	C	Cepeda et al. [30] (2008)
	No	Infliximab	C	Rafael et al. [31] (2019)
	No	Secukinumab	C	Elewski et al. [32] (2021)
	No	Apremilast	C	Shah et al. [33] (2020)
Hepatitis B	Yes	Adalimumab, Etanercept, Infliximab, Ustekinumab	C	Solay et al. [34] (2018)
	Yes	Adalimumab, Etanercept, Infliximab	C	Navarro et al. [35] (2014)
	No	Adalimumab	C	Laurenti et al. [36] (2013)
	No	Adalimumab, Etanercept, Infliximab	C	Charpin et al. [37] (2009)
	Yes	Infliximab	C	Matsumoto et al. [38] (2010)
	Yes	Secukinumab	C	Megna et al. [39] (2022)
	No	Apremilast	C	Piascero et al. [40] (2019)
Hepatitis C	No	Adalimumab	C	Piaserico et al. [41] (2017)
	No	Adalimumab, Etanercept, Infliximab	C	Roux et al. [42] (2006)
	No	Adalimumab, Etanercept	C	Prignano et al. [43] (2011)
	No	Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab	B	Caso et al. [44] (2015)
	Yes	Adalimumab, Etanercept, Infliximab, Golimumab	B	Fiore et al. [45] (2018)
	Yes	Secukinumab	C	Megna et al. [39] (2022)
	No	Apremilast	C	Piascero et al. [40] (2019)
Tuberculosis	Yes	Adalimumab, Etanercept, Infliximab	B	Yonekura et al. [46] (2017)
	Yes	Adalimumab, Etanercept, Infliximab	C	Atteno et al. [47] (2014)
	Yes	Adalimumab, Etanercept	C	Medina-Gil et al. [48] (2015)
	Yes	Adalimumab, Etanercept	C	Lee et al. [49] (2018)
	Yes	Adalimumab, Etanercept, Infliximab	C	Sanchez-Moya et al. [50] (2011)
	Yes	Adalimumab, Infliximab	C	Kim et al. [51] (2015)
	Yes	Adalimumab	C	Kim et al. [52] (2018)
	Yes	Adalimumab	C	Asensio-Sanchez, [53] (2018)
	Yes	Adalimumab, Infliximab	C	Bernal et al. [54] (2016)
	Yes	Adalimumab	C	Azevedo et al. [55] (2009)
	No	Secukinumab	C	Elewski et al. [32] (2022)
	No	Apremilast	C	Hagberg et al. [56] (2020)
Atypical Mycobacteria	Yes – *Mycobacterium marinum*	Adalimumab	C	Timoney et al. [57] (2017)
	Yes – *M. marinum*	Adalimumab	C	Kaneko et al. [58] (2014)
	Yes – *M. marinum*	Adalimumab	C	Kump et al. [59] (2013)
	Yes – *Mycobacterium avium*	Adalimumab	C	Liakopoulou et al. [60] (2019)
	Yes – *M. avium*	Adalimumab	C	Kobayashi et al. [61] (2019)
	Yes – *Mycobacterium haemophilum*	Adalimumab	C	Navina et al. [62] (2019)
	Yes – *Neisseria meningitidis*	Adalimumab	C	Salinas et al. [57] (2019)
	Yes – *Streptococcus sanguinis*, *Fusobacterium nucleatum*, and *Parvimonas micra*	Adalimumab	C	Lo et al. [63] (2020)
	Yes – *Tropheryma whipplei*	Adalimumab, Etanercept, Infliximab, Tocilizumab, Golimumab	C	Ramos et al. [64] (2015)
	Yes – *Kocuria kristinae*	Adalimumab	C	Kolikonda et al. [65] (2016)
	Yes – *Mycobacterium chelonae*	Adalimumab	C	Diaz et al., 2008

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Table 1 (continued)

Infectious disease	Reactivation in setting of biologic therapy	Specific biologics	Level of evidence (SORT)	References
	Yes – *M. chelonae*	Adalimumab	C	Adenis-Lamarre et al., 2009
	Yes – *Legionella pneumophila*	Adalimumab	C	Kaku et al. [66] (2013)
	Yes – *Listeria monocytogenes*	Adalimumab	C	Willson et al. [67] (2012)
	No	Apremilast	C	Brunasso et al. [68] (2021)
Leprosy	Yes	Infliximab, Adalimumab	C	Freitas et al. [69] (2010)
	Yes	Etanercept, Infliximab	B	Cogen et al. [70] (2020)
	Yes	Adalimumab, Etanercept, Infliximab, Tocilizumab	B	Barroso et al. [71, 72] (2021)
	No	Apremilast	C	Narang et al. [73] (2021)
	No	Secukinumab	C	Kurizky et al. [74] (2021)
Brucellosis	Yes	Infliximab	C	Ozgur & Ozgocmen, [75] (2011)
	Yes	Infliximab	C	Jimenez et al. [76] (2005)
Salmonellosis	Yes	Adalimumab	C	Eke et al. [77] (2014)
	Yes	Adalimumab	C	Shivaprasad et al. [78] (2011)
	Yes	Etanercept	C	Sky et al. [79] (2013)
Leishmaniasis	Yes	Adalimumab	C	Berry et al. [80] (2013)
	Yes	Adalimumab	C	Catala et al. [81] (2015)
	Yes	Adalimumab	C	Plachouri et al. [82] (2020)
	Yes	Adalimumab, Etanercept, Infliximab, Golimumab	C	Bosch-Nicolau et al. [83] (2019)
	Yes	Adalimumab	C	Henchiri et al. [84] (2016)
	Yes	Adalimumab	C	Balta-Cruz et al. [71] (2009)
	Yes	Infliximab	C	Xynos et al. [85] (2009)
Lymphatic filariasis	Yes	Infliximab	C	Liyanage et al. [86] (2019)
Strongyloidiasis	Yes	Adalimumab	C	Krishnamurthy et al. [87] (2007)
	Yes	Adalimumab	C	[88]
	Yes	Etanercept	C	Boatright et al. [89] (2005)
Chagas disease	No worsening of disease but disease de-stabilizing inflammatory arthritis	Adalimumab	C	Navarrete-Dechent et al. [62] (2015)
	Yes	Infliximab	C	Vacas et al. [90] (2017)
Hepatitis E	Development of chronic HEV infection	Adalimumab	C	van Bijnen et al. [91] (2017)
	Yes	Etanercept	C	Behrendt et al. [92] (2016)
HTLV-1	Yes	Adalimumab	C	Bittencourt et al. [93] (2013)
Chromoblastomycosis	Yes	Adalimumab	C	Otto-meyer et al. [94] (2021)
	Yes	Adalimumab	C	Chou et al. [95] (2016)
Scabies	Yes	Adalimumab	C	Markovic et al. [96] (2015)

The level of evidence is evaluated using the SORT criteria. Level of evidence: A: recommendation based on consistent and good quality patient-oriented evidence; B: recommendation based on inconsistent or limited-quality patient-oriented evidence; C: recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series.

Table 2. Percentage Agreement and Gwet's Coefficient (with benchmarking as per the Landis-Koch benchmarking system) of Delphi Rounds of Screening Recommendations for infectious diseases and treatment-specific screening

	Delphi round 1 (% agreement)	Gwet's coefficient (benchmarking)	Delphi round 2 (% agreement)	Gwet's coefficient (benchmarking)
Infectious disease				
Hepatitis B	87.5	0.531 (95% CI = 0.477–0.585)	97.6	0.723 (95% CI = 0.539–0.908)
Hepepatitis C	81.3	$p < 0.001$ moderate (Landis-Koch)	95.2	$p < 0.001$ substantial (Landis-Koch)
TB	87.5		97.6	
HIV	75		64.3	
Leprosy	93.8		92.8	
Atypical mycobacteria	87.5		90.4	
Brucellosis	87.5		97.6	
Salmonellosis	87.5		100	
Leishmaniasis	87.5		95.2	
Strongyloidiasis	81.3		90.4	
Chagas disease	87.5		100	
Hepatitis E	87.5		97.6	
Chromoblastomycosis	87.5		90.4	
Scabies	75		90.4	
Treatment				
Adalimumab	95.8	0.587 (95% CI = 0.462–0.712)	97.6	0.634 (95% CI = 0.420–0.849)
Infliximab	90.5	$p < 0.001$ moderate (Landis-Koch)	95.8	$p < 0.001$ substantial (Landis-Koch)
Anakinra	87.0		92.8	
IL-17 inhibitors	91.7		92.8	
IL-23 inhibitors	73.8		87.5	
Cyclosporine	83.3		85.7	
Methotrexate	80.9		87.5	
JAK inhibitors	75.0		100	
Oral steroids	58.3		70	
Intralesional steroids	83.3		100	
Retinoids	73.8		87.5	
Antibiotics	73.8		95.8	
Apremilast	73.8		83.3	
Laser surgery	87.5		97.6	
Deroofing	91.7		97.6	
Wide excision	87.0		97.6	

(online suppl. material), which the core group agreed should be the topic of a separate consensus process. The role of clinical screening (vs. serological screening) in regions with limited diagnostic equipment availability for certain diseases (leprosy, leishmaniasis) was discussed and acknowledged. Additionally, the need for flexibility with regards to patient and location-specific screening for endemic diseases (e.g., strongyloidiasis in Australia [97] and Chagas disease in South America [98]) was acknowledged. Many participants acknowledged their lack of exposure to and awareness of rarer infectious diseases not endemic in their local area and commented that addressing these conditions would increase awareness and potential screening in migrant or refugee populations prior to therapy in HS.

Discussion

The proposed recommendations for infectious disease screening prior to immunomodulatory therapy include mandatory screening for hepatitis B, hepatitis C, and tuberculosis, with patient and region-specific recommendations based upon the individual patient and proposed therapy (Tables 3, Table 4).

Evidence-based guidelines are vital to direct appropriate infectious disease screening in the setting of immunomodulatory and immunosuppressive therapies in HS. Clinical trials of novel immunomodulatory agents are often the major source of information regarding infectious complications in systemic inflammatory disease. However, monoclonal antibody

Table 3. Treatment-Specific Infectious Disease Screening Recommendations as determined by Delphi Consensus

Infectious disease	Adalimumab	Infliximab	Anakinra	IL-17 inhibitor	IL-23 inhibitor	Cyclosporine	Methotrexate	JAK inhibitors	Oral steroids*	Intralesional steroids	Retinoids	Antibiotics	Apremilast	Laser Surgery	Deroofing	Wide excision
Recommended																
Hepatitis B	x	x	x	x	x	x	x	x	x				x			
Hepatitis C	x	x	x	x	x	x	x	x	x				x			
TB	x	x	x	x	x	x	x	x	x							
Patient-specific																
HIV	x	x	x	x	x	x	x	x	x							
Leprosy	x	x	x	x	x	x	x	x	x							
Atypical mycobacteria	x	x	x	x	x	x	x	x	x							
Brucellosis	x	x	x	x	x	x	x	x	x							
Salmonellosis	x	x	x	x	x	x	x	x	x							
Leishmaniasis	x	x	x	x	x	x	x	x	x							
Strongyloidiasis	x	x	x	x	x	x	x	x	x							
Chagas disease	x	x	x	x	x	x	x	x	x							
Hepatitis E	x	x	x	x	x	x	x	x	x							
Chromoblastomycosis	x	x	x	x	x	x	x	x	x							
Scabies	x	x	x	x	x	x	x	x	x							

*Only applicable for prolonged (>14 days) or high dosages (>0.5 mg/kg) of oral steroids.

therapy is increasingly being used on a global scale where unique endemic diseases and complications may arise [99]. Additionally, significant numbers of participants with disease reactivation may not be identified until many years after a medication has been widely used [100]. The systematic literature review undertaken as background to this guideline development identified numerous infections with low level of evidence of reactivation, particularly in the setting of TNF-α inhibition (Table 1). Evidence for reactivation in the setting of IL-17 and apremilast therapy was relatively sparse. Therefore, guidelines for infectious disease screening need to not only consider diseases of the urban environments of North America and Europe but also endemic diseases in other global regions including the Asia-Pacific, Africa, and South America [101].

The regional differences regarding infectious diseases of concern have been identified in recent rheumatological guidelines regarding migrant populations [102]. Anecdotally, this is reflected in rates of occult infections identified in countries such as Australia (including a recent report of an 11% incidence of positive Strongyloides serology in an Australian biologics cohort [103]) among migrant populations and the exposure of travelers to tropical diseases. There is also future expectation that climate change may alter and expand the geographic regions of tropical and subtropical infections, meaning that screening recommendations for various locations may change in the setting of ongoing climate change [104]. Specific recommendations regarding which patients/locations are candidates for specific disease screening are beyond the scope of this paper, and the prevalence of infectious diseases is in constant flux. Hence, future endeavors will aim to develop living recommendations regarding specific population groups and locations at risk of relevant infectious disease reactivation. Currently, we recommend all physicians encountering patients from endemic areas consult the most up-to-date information from the World Health Organization (https://www.who.int/data/gho/publications/world-health-statistics).

A number of the identified infectious diseases in these guidelines (including leprosy, etc.) do not have simple, cheap, objective, and widely available diagnostic tests appropriate for low-resourced health settings. Yet, these infectious diseases are more prevalent in said locations. In these instances, the use of clinical suspicion with targeted clinical examination and diagnosis may be required to prescreen populations, with the more expensive diagnostic procedures requiring further evaluation of utility and cost effectiveness [104]. Given the expanding use of

Table 4. Screening recommendations for infectious diseases in HS as developed by Delphi consensus

Infectious disease	Guideline screening recommendation	Candidate(s) for screening	Type of screening
Hepatitis B	Yes	All patients	Serum surface antigen, surface antibodies, core antibodies)
Hepatitis C	Yes	All patients	Serum (surface antibodies)
Tuberculosis	Yes	All patients	IGRA (if not available, then TST). If high risk, then add on CXR
Human immunodeficiency virus (HIV)	Limited*	High-risk	Serum (ELISA and/or Western blot for confirmation)
Leprosy	Yes*	Originating form high prevalence country/unexplained cutaneous lesions/peripheral neuropathy	Lesion biopsy, Wade-Fite stain, and slit skin smear
Atypical mycobacteria	Yes*	High-risk occupations/regions, unexplained respiratory symptoms/skin lesions	CXR, tissue biopsy, GeneXpert/ TB PCR, BAL
Brucellosis	Yes*	Febrile patients, consumption of unpasteurized milk, exposure to infected animals	Serology/culture
Salmonellosis	Yes*	High prevalence region, fever and diarrhea, defects in urinary tract	Stool/urine culture
Leishmaniasis	Yes*	Endemic countries, fever, hepatosplenomegaly	Clinical/tissue
Strongyloidiasis	Yes*	Endemic areas, unexplained eosinophilia	Serology/stool
Chagas disease	Yes*	Endemic areas, blood transfusion in endemic area	Serology
Hepatitis E	Yes*	Unexplained liver abnormalities	Serology
Chromoblastomycosis/ histoplasmosis/coccidiomycosis	Yes*	High-risk occupations/regions, unexplained respiratory symptoms/skin lesions, erythema nodosum	CXR, tissue biopsy, BAL urinary antigen testing
Scabies	Yes*	High-risk individuals (long-term care facilities), known endemic populations	Clinical
Schistosomiasis	No	N/A	N/A
Lymphatic filariasis	No	N/A	N/A
Cysticercosis	No	N/A	N/A
HTLV-1	No	N/A	N/A
Chikungunya	No	N/A	N/A
Yaws	No	N/A	N/A
Onchocerciasis	No	N/A	N/A
Rabies	No	N/A	N/A

CXR, chest X-ray; TST, tuberculin Skin test; BAL, bronchioalveolar lavage; IGRA, interferon gamma release assay; N/A, not applicable; HTLV-1, human T-lymphotropic virus-1). * Screening recommended only for individuals from known endemic regions/individuals at high risk of disease.

monoclonal antibody therapy globally, acknowledgment of novel challenges in the reactivation of various infectious diseases is required for appropriate screening and management.

The role of vaccinations in the setting of biologic therapy in HS is a complex topic and has been addressed in recent publications [105] with regards to COVID-19. A number of experts commented on the role of ensuring "routine" recommended vaccinations are up to date as per the local vaccination guidelines. Additionally, therapy-specific vaccination recommendations (such as varicella vaccination prior to JAK inhibition) were mentioned by a number of experts (online supplementary material). Future guideline development is required in order to establish recommendations based upon therapy-specific risks in the setting of HS.

Additionally, the role of bacterial colonization, biofilm formation, and the pathogenic role of bacteria in HS raises the question of whether bacterial pathogens should be screened prior to immunomodulatory therapy in HS. This would be linked to concepts of the "window of opportunity" in treating chronic wounds and other conditions such as periodontitis and cystic fibrosis [106, 107]. While none of the experts identified this as a potential issue, it would be a topic for further mechanistic-focused research as to the role of such organisms in the inflammatory pathogenesis of disease. Overall, this would be linked to the concept of disease-associated infections rather than therapy-associated infections.

Strengths and Limitations

This Delphi consensus process aimed to develop evidence-based guidelines for infectious disease screening in HS based on a systematic review of documented infections in the setting of TNF-α inhibitors (currently the only FDA/European Medicines Agency [EMA]-approved biologic therapy in the setting of HS), IL-17 inhibitors, and apremilast. While a number of other systemic therapies are used in the setting of HS, the involvement of a large expert panel across five continents enabled this project to draw upon the experience of multiple experts in the field to identify other potential infectious risks in the setting of HS therapy. Additionally, many neglected tropical diseases are documented to be reactivated in the setting of immunosuppressive and immunomodulating therapy. Given the increase in the use of biosimilars in countries outside of North America and Europe, consideration should be given to the safety and appropriate screening for individuals with HS in these settings. The expert group in this consensus process did not represent all possible regions and nations, and hence may be limited in its external validity. The inclusion of a broad range of clinicians from 5 continents as well as physicians, surgeons, and infectious disease clinicians was attempted to have the highest levels of external validity possible. Additionally, the appropriateness of screening an individual patient is based upon the clinical judgment of the individual in the context of the endemic diseases of the country/region under consideration. Additionally, the history of the individual patient (particularly emigrants and refugees) plays a strong role in the need for consideration of previously neglected tropical diseases when commencing systemic therapy as has been seen in rheumatology [102].

Future efforts are needed to discuss the role and recommendations for vaccination coverage prior to systemic therapy in HS. Given the complexity of this issue, discussion of vaccination recommendations was flagged for development in a separate consensus process.

Conclusions

The proposed recommendations for infectious disease screening in HS are the first evidence-based guidelines to be developed independently of recommendations for chronic plaque psoriasis. They are useful in promoting awareness of infectious disease which require screening in emigrant and refugee populations as well as promoting safety in HS biologic therapy internationally. With the emergence of novel therapeutics for HS, these recommendations will require re-evaluation and updating as new evidence comes to light.

Key Message

This article provides consensus guidelines for infectious disease screening prior to immunomodulatory therapy in HS.

Statement of Ethics

The study protocol was reviewed and approved by the Human Research Ethics Committee of Sydney South-West Area Health Service and complied with the Declaration of Helsinki (approval code 2021/ETH00387). All participants provided informed consent at the beginning of the study.

Conflict of Interest Statement

S.Y.P. has been an investigator for Avillion, Abbvie, BMS, and Novartis; a consultant for Abbvie, Janssen, Novartis, and Sanofi Genzyme; and a speaker for Abbvie and Janssen. M.P. has been a consultant and/or an investigator for Abbvie, Janssen, UCB, Eli Lilly, Incyte, Trifecta Clinical Novartis, Pfizer, and Anaptys Bio. H.H.O. has been a speaker, advisory

board member, and researcher for Janssen, Novartis, and Galderma. She has also been a clinical investigator for Pfizer and a speaker and advisory board member for AbbVie. J.W.F. has conducted advisory work for Janssen, Boehringer-Ingelheim, Pfizer, Kyowa Kirin, LEO Pharma, Azora Pharmaceuticals, CSL, Regeneron, Chemocentryx, AbbVie, and UCB; participated in trials for Pfizer, UCB, Boehringer-Ingelheim, Azora Pharmaceuticals, Eli Lilly, and CSL; and received research support from Ortho Dermatologics and Sun Pharma. E.K.K., D.M., N.S.C., E.K.M., K.G., and H.C.R. have no conflicts of interest to declare.

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Author Contributions

Emily Kay Kozera: investigation, writing – original draft, and writing – review and editing. So Yeon Paek, Martina Porter, Dillon Mintoff, Hazel H Oon, Nisha Suyien Chandran, Erin K McMeniman, Katalin Glasenhardt, and Hans Christian Ring: investigation, writing – review and editing. John Walter Frew: conceptualization, supervision, funding, investigation, and writing – review and editing.

Data Availability Statement

Data supporting the findings of this study are included as supplementary material. Further inquiries can be made to the corresponding author.

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