SYSTEMATIC REVIEW

A systematic review and critical evaluation of inflammatory cytokine associations in hidradenitis suppurativa [version 1; peer review: 2 approved, 1 approved with reservations]

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Abstract
Background: The pathogenesis of hidradenitis suppurativa (HS) remains unclear. In order to develop effective treatment strategies, a deeper understanding of pathophysiology is needed. This is impaired by multiple small studies with inconsistent methodologies and the impact of co-occurring pro-inflammatory conditions such as smoking and obesity.

Methods: This systematic review aimed to collate all published reports of cytokine studies in tissue, blood, serum and exudate. It was registered with PROSPERO (Registration number CRD42018104664) performed in line with the PRISMA checklist.

Results: 19 studies were identified comprising 564 individual HS patients and 198 control patients examining 81 discrete cytokines. Methodology was highly varied and the quality of studies was generally low. There was a large degree of variance between the measured levels of cytokines. 78.2% of cytokines demonstrated heterogeneity by the chi-squared test for homogeneity and hence meta-analysis was not deemed appropriate. However, a strong and significant IL-17 signalling component was identified.

Conclusions: Cytokines consistently elevated in lesional, peri-lesional and unaffected tissue are identified and discussed. Areas for further investigation include the role of dendritic cells in HS; the contribution of obesity, smoking, diabetes and the microbiome to cytokine profiles in HS; and examining the natural history of this disease through longitudinal measurements of cytokines over time.

Keywords
Hidradenitis Suppurativa, Cytokines, Inflammation, Pathogenesis, IL-17, TNF-alpha
Introduction
Hidradenitis Suppurativa (HS) is a chronic inflammatory disease, the exact pathophysiology of which remains poorly defined. Dysregulation of the T<sub>H</sub>17: Treg axis, IL-36 signalling pathways and keratinocyte-mediated inflammatory cytokines have been demonstrated in lesional skin, blood, serum, and exudate although contradictory results exist. Given the variable and incomplete response of patients to treatment, including monoclonal antibodies, some authors have proposed clinical, and immunological subtypes of HS in an effort to better predict treatment outcome and response. Thus far, no current schema accurately predicts treatment efficacy.

In order to develop and implement effective treatment strategies in HS, a deeper understanding of the underlying inflammatory pathophysiology is needed. However, due to the heterogeneity of sampling methods, laboratory processing methods and data analysis, comparison across studies is problematic and potentially biased or inaccurate. Heterogeneity of tissue sampling and laboratory techniques alone may explain the inconsistent and conflicting results regarding specific cytokines, however, no systematic analysis of cytokine studies has been undertaken to compare results, methodology, and analytical techniques.

An additional complicating factor is that clinical comorbidities, which are strongly associated with disease activity in HS, such as obesity, diabetes, inflammatory bowel disease, and smoking, also produce pro-inflammatory cytokines, which affect multiple organ systems including the skin. Hence, it remains unclear whether the presence or absence of these conditions confound the findings of cytokine studies in HS, and whether clinical stratification of patients is necessary to identify significant pathogenic pathways, which may be amenable to pharmacological intervention. Critical evaluation and analysis of existing studies may also enable meta-analysis, which may identify cytokines, which, in smaller studies, do not have sufficient power to meet statistical significance when compared to controls.

Objectives
The objectives of this systematic review are:
1) To collate and describe all published reports of human cytokine studies in HS including those in skin, blood, serum and exudate.
2) To critically evaluate the sampling, laboratory and analysis techniques used in each study to assess whether comparisons can be made across individual studies.
3) To analyze the heterogeneity of published studies enable meta-analysis

Methods
This systematic review was registered with PROSPERO (Registration number CRD42018104664) and was conducted in line with the PRISMA checklist.

Data sources
Information sources for this review included PubMed (1946-July 1 2018), Scopus (2004- July 1 2018) and Web of Science (1990-July 1 2018) as shown in Figure 1. Search strategy is presented in Table 1

Study eligibility criteria
Eligibility criteria for this review included cohort studies, case-control studies and other observational studies with no restrictions of patient age, sex, ethnicity or language of publication. Eligible studies included:

1) Studies reporting the results of cytokine investigations (in cutaneous tissue, serum, blood or exudate) in human subjects clinically diagnosed with hidradenitis suppurativa.

Studies deemed not eligible included those which:
1) Provide no new data but a review or summary of previously published data
2) Provide no comparison with controls or non-lesional tissue

Appraisal and synthesis methods
Data collection was performed independently by 2 authors (JWF & JEH), with any disagreements regarding inclusion of citations being referred to a third author (JGK) for mediation. Information was collected using a standardized data collection form (available as Extended data) with the principal outcomes of interest being the cytokine of interest, measured level of cytokine in lesional HS skin or serum. Comparison data against either peri-lesional, unaffected or control skin or serum was also collated. If data from individual patients was not available then the aggregate data including average change and statistical analyses of the significance of change was collected.

For each individual cytokine, where more than one study reported results, heterogeneity was assessed using the chi-squared tests for homogeneity. Homogeneity was defined as a chi squared value >0.05. All statistical analysis was undertaken using R (version 3.5.1)

Potential sources of bias in the identified studies are acknowledged including the small size of patient cohorts, the variability in sampling, laboratory techniques and the inclusion of patients being treated with a wide-variety of medications including immunosuppressants. Bias was also assessed using the NIH quality assessment tool for observational studies.

Results
A total of 367 non-duplicated citations were identified in the literature review (Figure 1). 343 of these articles were removed upon review of titles and abstracts against the pre-defined eligibility criteria. Full text review of the remaining 24 articles excluded...
5 review articles providing no new data. The remaining 19 studies included the results of 564 individual HS patients and 198 control patients, which were included in this systematic review.

**Demographics**

The summarized demographic data of the patients and controls comprising this review are included in Table 2. The 564 reported cases comprised of 231 males (40.9% reported cases) and 333 females (59.0%). 24 cases were unreported (4.1%). The average age was 38.5 years (n=560, 18 cases unreported). 141 individuals were current smokers (82.4% reported cases), 8 ex-smokers (4.7% reported cases), 22 non-smokers (12.8% reported cases) and 407 unreported. Obesity (BMI>30) was reported in 85 individuals (42.5% reported cases), with 115 (57.5%) individuals non-obese (BMI<30) and unreported in 378 cases. 8 cases reported diabetes mellitus out of 24 reports (33% of reported cases). 12/38 cases reported a positive family history of HS (31.6% reported cases). Hurley Stage was reported as stage 1 in 68 individuals (17.4% reported), stage 2 in 199 individuals (51% reported cases) and stage 3 in 123 individuals (31.6% reported cases) with 188 cases going unreported. The average mHSS (modified hidradenitis suppurativa score) was 78.1 (n=247 cases). Biopsies were largely taken

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**Table 1. Search Strategy.**

| Resources: |
| --- |
| 1) Pubmed (1946-July 1 2018), |
| 2) Scopus (2004- July 1 2018) |
| 3) Web of Science (1990- July 1 2018) |
| 4) Published Abstracts |
| 5) Contact with Authors for abstracts without full text for clarification of data and methodology |

| Pubmed Search Strategy: |
| --- |
| acne inversa OR apocrine acne OR apocrinitis OR Fox-den disease OR hidradenitis axillaris OR HS OR pyoderma sinifica fistulans OR Velpeau's disease OR Verneuil's disease OR Hidradenitis Suppurativa AND Cytokine OR chemokine OR inflammatory mediator |

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**Figure 1. PRISMA Flowchart.**
| Number of HS Patients | Male | Female | Mean Age (Years) | Comorbidities | Biopsy Sites | Hurley Staging | mHSS Score (Mean) | Therapy | Study Reference |
|-----------------------|------|--------|------------------|---------------|--------------|----------------|-------------------|---------|----------------|
|                       |      |        |                  | Smoking       | Obesity (BMI>30) | Diabetes | Family History | Axillae | Groin | Genital | Serum Measurements |              |                  |                     |         |                  |
| 17                    | 1    | 1      | 45               | Ex            | Y             | N          | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 39               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 24               | N             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 41               | Y             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 23               | Ex            | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 35               | Y             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 30               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 41               | Y             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 35               | Y             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 47               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 19               | N             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 34               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 47               | N             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 32               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 38               | Y             | N             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 24               | Y             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 1                     | 1    | 1      | 26               | E             | Y             | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 18                    | 11   | 7      | (Range 19-62)    | NR            | NR           | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |
| 15                    | 6    | 9      | 38.7             | NR            | NR           | NR        | NR        | NR      | NR    | NR      | Serum Measurements |              |                  |                     |         |                  |

N=9  N=4  N=2  Stage 1=0  Stage 2=10  Stage 3=5
| Number of HS Patients | Male | Female | Mean Age (Years) | Comorbidities | Obesity (BMI>30) | Smoking | Family History | Hurley Staging | Biopsy Sites | Therapy |
|-----------------------|------|--------|------------------|---------------|----------------|---------|----------------|---------------|-------------|---------|
| 18                    | 1    | 1      | 36               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 42               | Y             | N               | Y       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 30               | Y             | Y               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 43               | Y             | N               | Y       | Y              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 47               | N             | NR              | N       | Y              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 47               | N             | NR              | N       | Y              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 47               | N             | NR              | N       | Y              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 27               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 50               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 50               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 23               | N             | NR              | Y       | Y              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 54               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 56               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 65               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 44               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 68               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 35               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 44               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 29               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 31               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 30               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 26               | Y             | N               | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 36               | N             | NR              | N       | N              | NR            | N           | Tetracycline |
| 1                    | 1    | 1      | 29               | N             | NR              | N       | N              | NR            | N           | Tetracycline |

**Note:** NR indicates not reported.
| Number of HS Patients | Sex   | Age (Mean, Range) | Comorbidities | Smoking | Obesity (BMI>30) | Diabetes | Family History | Biopsy Sites | Hurley Staging | mHSS Score (Mean) | Study Reference |
|-----------------------|-------|-------------------|---------------|---------|-----------------|----------|---------------|--------------|----------------|-------------------|------------------|
| 24                    | Male  | 36.5 (Range 24-51) | N=16 (43.2%)  | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 74                    | Female| 37.4 (Range 21-30) | N=32 (91%)    | N=2     | N=14 (39.4%)    | N=16     | N=16          | NR           | NR             | NR                |                  |
| 8                     |       | 4                 | N=4           | NR      | NR              | NR       | NR            | NR           | NR             | NR                |                  |
| 19                    |       | 11                | N=14 (74%)    | NR      | NR              | NR       | NR            | NR           | NR             | NR                |                  |
| 120                   |       | 43                | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 44                    |       | 13                | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 22                    |       | 10                | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 3                     |       | 1                 | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 20                    |       | 8                 | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 25                    |       | 9                 | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 47                    |       | 19                | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 11                    |       | 9                 | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |
| 3                     |       | 2                 | N=16          | N=4     | N=14 (74.2%)    | N=13     | N=16          | NR           | NR             | NR                |                  |

**Study Reference**
- **Studie 1**: Mean=2.29 (SD=0.62) NR
- **Studie 2**: Mean=2.29 (SD=0.62) NR
- **Studie 3**: Mean=2.29 (SD=0.62) NR
- **Studie 4**: Mean=2.29 (SD=0.62) NR
- **Studie 5**: Mean=2.29 (SD=0.62) NR
- **Studie 6**: Mean=2.29 (SD=0.62) NR
- **Studie 7**: Mean=2.29 (SD=0.62) NR
- **Studie 8**: Mean=2.29 (SD=0.62) NR
- **Studie 9**: Mean=2.29 (SD=0.62) NR
- **Studie 10**: Mean=2.29 (SD=0.62) NR
- **Studie 11**: Mean=2.29 (SD=0.62) NR
- **Studie 12**: Mean=2.29 (SD=0.62) NR
- **Studie 13**: Mean=2.29 (SD=0.62) NR
- **Studie 14**: Mean=2.29 (SD=0.62) NR
- **Studie 15**: Mean=2.29 (SD=0.62) NR
- **Studie 16**: Mean=2.29 (SD=0.62) NR
- **Studie 17**: Mean=2.29 (SD=0.62) NR
- **Studie 18**: Mean=2.29 (SD=0.62) NR
- **Studie 19**: Mean=2.29 (SD=0.62) NR
- **Studie 20**: Mean=2.29 (SD=0.62) NR
- **Studie 21**: Mean=2.29 (SD=0.62) NR
- **Studie 22**: Mean=2.29 (SD=0.62) NR
- **Studie 23**: Mean=2.29 (SD=0.62) NR
- **Studie 24**: Mean=2.29 (SD=0.62) NR
- **Studie 25**: Mean=2.29 (SD=0.62) NR
- **Studie 26**: Mean=2.29 (SD=0.62) NR
- **Studie 27**: Mean=2.29 (SD=0.62) NR
- **Studie 28**: Mean=2.29 (SD=0.62) NR
- **Studie 29**: Mean=2.29 (SD=0.62) NR
- **Studie 30**: Mean=2.29 (SD=0.62) NR

**Therapy**
- Untreated
- Adalimumab
- Treatment withheld for 8 weeks prior
- Treatment withheld for 3 weeks prior
- N=15 Rifampicin, Clindamycin, Minocycline
- N=2 Infliximab
- N=24 untreated

**Disease**
- "Mod-Severe Disease"
| Study Reference | Number of HS Patients | Male | Female | Mean Age (Years) | Comorbidities | Biopsy Sites | Hurley Staging | Therapy | Reference |
|-----------------|-----------------------|------|--------|------------------|---------------|--------------|---------------|---------|-----------|
| 26              | 20                    | 6    | 14     | 38 (SD=15)       | NR            | NR           | Stage 1=11 Stage 2=3 Stage 3=5 | Treatment withheld 3 weeks prior | 26 |
| 33              | 10                    | 7    | 3      | 38.9 (SD=4.1)    | NR            | NR           | Stage 1=2 Stage 2=7 Stage 3=1 | Treatment withheld 3 weeks prior | 33 |
|                 | 10                    | 7    | 3      | 46.6 (SD=15.1)   | 4.5           | 3            | Serum         | Clindamycin+Rifampicin=18; Metformin=2; Treatment withheld=85; Thyroxine=1; Not Specified=12; No Treatment=86; Not Reported=258 | 33 |

BMI = Body Mass Index, mHSS = modified Hidradenitis Suppurativa Score, Sartorius Score NR = Not Reported SD = Standard Deviation Y = Yes N=No Ex = Ex Smoker
from the axillae (n=32, 43.8%) and groin (n=35, 48.0%), with a minority of samples being taken from the genital and perianal region (n=6, 8.2%). At the time of sampling patients were on treatment including Clindamycin+ Rifampicin (n=18); adalimumab (n=26); Metformin (n=2); levothyroxine (n=1); MABp1 (n=10); tetracyclines (n=12) Infliximab (n=2); other antibiotics (n=4). Treatment was not specified in 74 cases, with no treatment in 86 individuals and treatment withheld in 85 patients.

Only 5/19 (26.3%) studies analysed both lesional tissue and serum levels of cytokines, enabling direct comparison between these two compartments. 8/19 (42.1%) studies provided age and sex matched controls, 5/15 (33.3%) studies stratified by disease severity and no studies stratified by lesion site or comorbidities. 8/19 (42.1%) studies stratified or accounted for treatment or reported discontinuing treatment up to 3 weeks prior to sample collection (Table 3).

### Cytokine analysis

A total of 81 discrete cytokines were analysed over the 19 studies (presented in Table 4). 6 studies provided a total of 78 outcomes from tissue of lesional or peri-lesional biopsies, 4 studies provided a total of 30 results from serum analysis and 1 study provided 15 results from exudate analysis. The remaining 8 studies did not provide quantification of cytokine levels but did provide analysis of the change and significance between lesion and control samples. The degree of change between lesional and control samples varied widely from 1.5 times the control level (IL-1RA p=0.0112) to 149 times the control level (IL-17 p<0.05). 33 cytokines were evaluated in more than one study. Only IL-1β, IL-6, IL-8, IL-17A and TNF-α had data from 5 or more separate studies.

Cytokines and inflammatory proteins which were elevated in more than one study in lesional tissue included IL-1β, IL-6, IL-10, IL-17A, IL-36α, IL-36β, IL-36γ, IL-36RA, TNF-α, sTNFR2, hBD1, hBD2, hBD3, s100A7, LL37/Cathelicidin, CCL3, CCL5, CCL27 and BLC. Cytokines and inflammatory proteins evaluated in peri-lesional tissue included IL-1β, IL-17, IL-36β, IL-36RA, IL-37, IL-38 and TNF-α. IL-37 was the only cytokine identified which showed significant differences between lesional and peri-lesional tissue, with a 1.81 times elevation in lesion compared to peri-lesional tissue (p=0.0002). IL-17 was elevated in unaffected HS tissue compared to control patient tissue (p<0.05) in one study. In HS tissue, S100A9, hBD1 and hBD2 were reduced but this data did not meet statistical significance. Two studies measuring IL-1β levels showed no statistically significant difference between lesional and control skin. No significant elevation of IL-6 was seen in lesional tissue compared to control with the exception of 1 study. IL-8 levels only just made significance in two studies, with one study showing significant elevation of IL-8 in lesional compared to control tissue. Two additional studies showed no significant difference. TNF-α levels were significantly elevated compared to control tissue in two studies but not significantly in 2 additional studies. sTNFR1 was significantly elevated in one study whilst showing a non-significant difference in a second study. CCL5 was significant in 2 studies in lesional tissue compared with controls. One methodology using muramyl dipeptide (MDP) did not reach statistical significance compared to stimulation with Pam2CSK4 Lipopeptide, and non-treated (NT) cells. IFN-γ was elevated in lesional tissue with no significance in one study and significance in another.

Elevated cytokines and inflammatory proteins in HS serum included IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, sTNFR1, CRP, ESR, LC2, and MMP2. TNF-β, and IFN-γ were elevated in wound exudate from active HS lesions. IFN-γ was noted to be decreased in HS patient serum compared to healthy control serum, despite the elevation in wound exudate. Conflicting results were seen in serum findings in IL-10, IL-17 and IFN-γ. One study demonstrated elevated serum IL-10 levels compared to control whereas two other studies showed no significant difference. Whilst two studies illustrated elevated IL-17 Serum levels in HS patients, one study showed no significant difference between patients and controls. IFN-γ showed no statistically significant decrease in the serum of HS patients compared to control in one study but a significant difference in a larger, higher powered study.

Because adalimumab improves HS through TNF antagonism, this cytokine must be classified as pathogenic. TNF mediates inflammation in a classic “sepsis” cascade in tissues—in this pathway LPS from gram negative bacteria activates TNF release from cells, and then TNF stimulates production of IL-1β, IL-6, and IL-8, leading to neutrophil attraction into sites of infection. Increases in IL-1β and IL-8 measured in HS, as well as neutrophil accumulation, could result from this pathway. Alternatively, in psoriasis, TNF is a major cytokine that acts on the IL-23/Type 17 T-cell pathway at two points. First TNF induces IL-23 synthesis in myeloid (CD11c+) dendritic cells in the skin. Second, TNF (as well as other cytokines that also activate NF-kB) act synergistically with IL-17A or IL-17F to increase synthesis of many other cytokines, chemokines, and inflammatory molecules in keratinocytes and other cell types. There are several clues that an IL-23/Type17 T-cell pathway may be active in HS which include detection of T17 T-cells in skin infiltrates, increased production of IL-17A, and increased production of LL-37/cathecidin, S100A7, S100A8, S100A9, LCN2, IL-8, beta-defensins and IL-36; which are all molecules that may be active in HS which include detection of T17 T-cells in skin infiltrates, increased production of IL-17A, and increased production of LL-37/cathecidin, S100A7, S100A8, S100A9, LCN2, IL-8, beta-defensins and IL-36; which are all molecules induced by IL-17 in keratinocytes, as also the presence of psoriasis-like epidermal hyperplasia in some reports. The increased production of CCL20, would be predicted to increase tissue infiltration of both T17 T-cells and CD11c+ DCs, which have both been observed in HS, and increased production of TGF-β could increase differentiation of T17 T-cells from precursors and/or influence scarring in skin lesions. If IL-17 is driving inflammation in HS, one would expect to see increased production of additional chemokines that regulate neutrophil chemotraction (CXCL1, CXCL2, CXCL3). Epidermal hyperplasia is not presently explained in HS, but this could be related potentially to increased expression of IL-19, IL-20 or IL-22, which are associated with the IL-23/Type 17 T-cell axis. If IL-22 is produced in HS lesions, this would implicate T22 T-cells as a T-cell type also associated with the IL-23/Type 17
Table 3: Critical evaluation of methodology of studies included in this review.

| Study Reference | Cytokines Measured | Number of HS Patients | Number of Controls | Samples Analyzed | Age/Sex Matched Controls | Sample Types | Storage Time | Stratified by Treatment | Stratified by lesion site | Stratified by severity | Stratified by co-morbidities | Sample Storage
|----------------|-------------------|-----------------------|-------------------|-----------------|-------------------------|--------------|--------------|------------------------|------------------------|----------------------|----------------------------|-----------------
| 17             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 9                      | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 18             | S10A7, lysozyme, LL37, BD3 α-MSH, MIF, TNF-α, IL-8, MHC-1 | 12                     | L                 | NR              | N                       | Skin         | NR           | NR                     | NR                     | N                    | Y                          | NR            |
| 19             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 20             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 21             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 22             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 23             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 24             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 25             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 26             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 27             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 28             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 29             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 30             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 31             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 32             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
| 33             | IL-17, IL-22, FNG IL-2, IL-10, GM-CSF | 18                    | L, PL, U, C, S    | Y               | NR                      | Skin, Serum  | NR           | Y                      | NR                     | N                    | N                          | NR            |
### Table 4. Reported cytokine results of studies included in this systematic review.

| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Level in Uninvolved Tissue Levels (pg/mL) | Mean Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Comparison and Significance | Study Reference |
|-----------------|----------------------------------|----------------------------------|--------------------------------------|----------------------------------------|--------------------------------------------|--------------------------|---------------|--------------------------------|--------------------------------|------------------|
| IL-1α           | 1126                             | 2549                             | Le:Ce                               | P = 0.53                               |                                           |                          |               |                                |                                | 6                |
|                 | 0.2                              | 0.1                              | NR                                  |                                        |                                           |                          |               |                                |                                | 26               |
|                 | 772.0                            | 697.2                            |                                     |                                        |                                           |                          |               |                                |                                | 33               |
| IL-1RA          | 44.0                             | 29.6                             | L:C                                 | P = 0.0112                              |                                           |                          |               |                                |                                | 26               |
| IL-1β           | 0.9                              | 0.4                              | L:C                                 |                                        |                                           |                          |               |                                |                                | 8                |
|                 | 862.5                            | 1503                             |                                      |                                        |                                           |                          |               |                                |                                | 6                |
| SERUM ONLY      | 100                              | 10                               | 3                                   | 1                                      | 115 fold                                  | L:C                      | P = 0.001     |                                |                                | 31               |
|                 | 1.6                              | 0.0                              | 54.4                                |                                        |                                           | L:U                      | P = 0.01      |                                |                                | 7                |
| IL-4            | 6.56                             | 9.77                             | L:Ce                                | P = 0.54                               |                                           |                          |               |                                |                                | 6                |
| IL-5            | 0.2                              | 0.2                              | L:C                                 |                                        |                                           |                          |               |                                |                                | 7                |
| IL-6            | 30.15                            | 9.314                            | L:Ce                                | P = 0.17                               |                                           |                          |               |                                |                                | 6                |
| SERUM ONLY      | 6.2                              | 0.6                              |                                      |                                        |                                           | L:C                      | NS            |                                |                                | 4                |
|                 | 2377                             | 5451                             |                                      |                                        |                                           | L:Ce                     | NS            |                                |                                | 8                |
| IL-6            | 124.4                            | 101.9                            |                                      |                                        |                                           | L:C                      | NS            |                                |                                | 25               |
| sIL-6R          | 16.3                             | 4.4                              | L:C                                 | P = 0.0028                              |                                           |                          |               |                                |                                | 7                |
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Uninvolved Tissue Levels (pg/mL) | Mean Control Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Comparison and Significance | Study Reference |
|----------------|-----------------------------------|------------------------------------|--------------------------------------|------------------------------------------|----------------------------------------|----------------------------------|---------------|-----------------------------|-----------------------------|-----------------|
| IL-8           | NR                                | NR                                 | i69.6 / s67.6                         | 64.9                                     | L:C P<0.01                             | L:s C P<0.001                    |               |                             |                             | 24              |
|                |                                   |                                    |                                      |                                          | L:C**                                   |                                 |               |                             |                             | 4               |
|                |                                   |                                    |                                      |                                          | L:C***                                  |                                 |               |                             |                             |                 |
|                | 27.9                              | 36.3                               |                                      |                                          |                                        |                                 |               |                             |                             | 8               |
|                |                                   |                                    |                                      |                                          | L.C P= 0.05                            |                                 |               |                             | Lpa:C NS        | 25              |
|                | 1401                              | 12.0                               |                                      |                                          | L.C                                    |                                 |               |                             |                             | 7               |
|                | 1000                               | 3000                               |                                      |                                          |                                        |                                 |               |                             |                             |                 |
| IL-10          | 3.4                               | 3.3                                |                                      |                                          | L:C P<0.05                             |                                 |               |                             |                             | 4               |
|                |                                   |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 19.85                             | 34.74                              |                                      |                                          | L.C P= 0.05                            |                                 |               |                             | Lpa:C 0.05      | 25              |
|                |                                   |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | SERUM ONLY                         |                                    |                                      |                                          | Hs:Cs: P= 0.0001                       |                                 |               |                             |                             | 5               |
|                |                                    |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                |                                   |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 3.8                               | 1.1                               | 0.4                                  | 3-4                                      | L:C P= 0.01                            | PL:C NS                          |               |                             |                             | 31              |
|                |                                    |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                |                                   |                                    |                                      |                                          |                                        |                                 |               |                             | L:U P= 0.01     | NR              |
|                |                                   |                                    |                                      |                                          |                                        |                                 |               |                             | U:C NS          |                 |
| IL-11          | 78.6                              | 7.2                                | 11.0                                 |                                          | L:C P= 0.005                           |                                 |               |                             |                             | 7               |
| IL-12p40       | 488.3                             | 97.86                              |                                      |                                          |                                        |                                 |               |                             |                             | 6               |
|                |                                     |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 75                                 | 75                                 |                                      |                                          |                                        |                                 |               |                             |                             | 27              |
|                | 0.5                               | 0.4                                |                                      |                                          | L.C                                    |                                 |               |                             |                             | 7               |
| IL-12p70       | 3.4                               | 0.6                                |                                      |                                          |                                        |                                 |               |                             |                             | 8               |
|                |                                     |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 9.412                             | 15.02                              |                                      |                                          |                                        |                                 |               |                             | Le:Ce P= 0.609  | 6               |
|                |                                     |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 0.0                               | 0.0                                |                                      |                                          | L.C                                    |                                 |               |                             |                             | 7               |
| IL-13          | 70.98                             | 55.61                              |                                      |                                          |                                        |                                 |               |                             | Le:Ce P= 0.56   | 6               |
|                |                                     |                                    |                                      |                                          |                                        |                                 |               |                             |                             |                 |
|                | 0.0                               | 0.1                                |                                      |                                          | L.C                                    |                                 |               |                             |                             | 7               |
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Uninvolved Tissue Levels (pg/mL) | Mean Control Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Study Reference |
|----------------|------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------|--------------|-----------------------------|----------------|
| IL-15          | 24.5                               |                                    | 5.61                                 |                                        |                                     |                                  | Le:Ce        | P = 0.18                    | 6              |
|                | 1.9                                |                                    | 2.9                                  |                                        |                                     |                                  | L:C          | NS                          | 7              |
| IL-16          | 15277                              |                                    | 15586                                |                                        |                                     |                                  | Le:Ce        | P = 0.97                    | 6              |
|                | 22.3                               |                                    | 4.2                                  | 5.3                                    |                                     |                                  | L:C          | P = 0.0028                  | 7              |
| IL-17          |                                    |                                    |                                      |                                        |                                     |                                  | S:C          | P < 0.005                   | 4              |
|                | SERUM ONLY                         | SERUM ONLY                         | SERUM ONLY                           | HSs:Cs *                               | 0.014                                |                                  | L:PL         | NS                          | 5              |
|                | SERUM ONLY                         | SERUM ONLY                         | SERUM ONLY                           | HSs:Cs **                              | 0.005                                |                                  | L:PL         | NS                          | 5              |
|                | 150                                | 45                                 | 1                                     | 1                                      | 149 fold                             |                                  | L:C          | P = 0.05                    | 31             |
|                |                                    |                                    |                                      |                                        |                                     |                                  | PL:C         | 0.05                        |                |
|                |                                    |                                    |                                      |                                        |                                     |                                  | U:C          | 0.05                        |                |
|                | No Quantification                  |                                    |                                      |                                        |                                     |                                  | L:C          | ↑(NS)                       |                |
|                |                                    |                                    |                                      |                                        |                                     |                                  | L:PL         | No Diff                     | 30             |
|                |                                    |                                    |                                      |                                        |                                     |                                  | R = 0.66     | NS                          | 27             |
| IL-17A         |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | P < 0.005                   | 4              |
|                | 5.6                                | 0.3                                |                                      |                                        |                                     |                                  | HSs:Cs       | NS                          | 8              |
|                |                                    |                                    |                                      |                                        |                                     |                                  | L:PL         | NS                          |                |
|                | 1006                               |                                    | 32.7                                 |                                        |                                     |                                  | Le:Ce        | NS                          | 6              |
|                |                                    |                                    |                                      |                                        |                                     |                                  | L:PL         | NS                          |                |
|                |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | P = 0.05                    | 25             |
|                |                                    |                                    |                                      |                                        |                                     |                                  | Lpa:C        | NS                          |                |
|                | 4                                  | 5                                 |                                        |                                        |                                     |                                  | HSs:Cs       | NS                          | 27             |
| IL-22          |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | NS                          | 4              |
|                |                                    |                                    |                                      |                                        |                                     |                                  | HSs:Cs       | NS                          | 8              |
| IL-23          |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | NS                          | 25             |
|                |                                    |                                    |                                      |                                        |                                     |                                  | Lpa:C        | 0.05                        |                |
|                |                                    |                                    |                                      |                                        |                                     |                                  | R = 0.68     | NS                          | 7              |
| IL-32          | 50ng/mL                            | 1ng/mL                             | Only Normalised Values Provided       | 4 (skin)                               |                                     |                                  | L:C          | P = 0.01                    | 7              |
|                |                                    |                                    |                                      |                                     |                                     |                                  | HSs:Cs       | p < 0.05                    |                |
| IL-32α         |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | P = 0.01                    | 29             |
| IL-32β         |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | P = 0.05                    | 29             |
| IL-32g         |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | P = 0.001                   | 29             |
| IL-32d         |                                    |                                    |                                      |                                        |                                     |                                  | L:C          | NS                          | 29             |
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Level in Uninvolved Tissue Levels (pg/mL) | Mean Control Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Comparison and Significance | Study Reference |
|----------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------|-----------------------------|-----------------------------|------------------|
| IL-36α         | 0.4                               | 0.02                              | 0.02                              | 1                                | 45.07 fold                       | L:C                              | P=0.0174       | PL:C NS                     | PL:C NS                     | 3                |
|                | 250                               | 0                                 |                                   |                                   |                                   |                                   |                |                             |                             | 28               |
| IL-36b         | 4.33                              | 3.00                              | 0.51                              | 1                                | 1.45 fold                        | L:C                              | P = 0.0001     | PL:C 0.0035                 | PL:L 0.0302                 | 3                |
|                | 15                                | 4                                 | 1                                 | 1.96 fold                        |                                   |                                   |                |                             |                             | 28               |
| IL-36g         | 3.64                              | 0.83                              | 0.49                              | 1                                | 1.45 fold                        | L:C                              | P = 0.0161     | PL:L 0.0302                 | PL:C 0.0003                 | 3                |
|                | 100                               | 20                                | 1                                 |                                   |                                   |                                   |                |                             |                             | 28               |
| IL-36RA        | 0.46                              | 0.28                              | 0.06                              | 1                                |                                   |                                   |                |                             |                             | 3                |
|                | 50                                | 100                               | No Quantification                | No Increase                      |                                   |                                   |                |                             |                             | 28               |
| IL-37          | 3.24                              | 14.7                              | 1.81                              |                                   |                                   |                                   |                |                             |                             | 3                |
| IL-38          | 0.09                              | 0.19                              | 0.06                              |                                   |                                   |                                   |                |                             |                             | 3                |
| TNF-α          | ≥69.4                             | 66.6 †                           | NR                               | 65.8                             | NR                                |                                   |                |                             |                             | 24               |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 4                |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 6                |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 5                |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 31               |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 26               |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 6                |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 3                |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 26               |
|                |                                   |                                   |                                   |                                   |                                   |                                   |                |                             |                             | 25               |

**Note:** The table includes the mean levels of various cytokines in different tissues and serum samples, along with the fold increase and statistical significance for comparison between lesional and control tissues. The study references are indicated at the end of each row.
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Uninvolved Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Comparison and Significance | Study Reference |
|-----------------|-----------------------------------|------------------------------------|-------------------------------------|------------------------------------------|--------------------------------------|---------------|-----------------------------|-----------------------------|--------------------------|
| sTNFR2          | 927.9                             | 527.4                              |                                     |                                          |                                      |               | Hs:C:Cs P= 0.053            |                             | 8                        |
| hBD1            | 0.019                             | 0.021                              | 0.018                               | 0.058                                    | 0.077                                | 0.095         | L:C P= 0.05                | Lpa:C P= 0.0028           | 25                       |
| hBD2            | 0.013                             | 0.019                              | 0.058                               | 0.011                                    | 0.018                                | 0.067         | L:C*                       | L:C** P= 0.240 L:C*** P= 0.026 | 4                        |
| hBD3            | 76.9                               | 75.7                               | 72.5                                | 2.8                                      | 2.6                                   | 1.9           | L:C*                       | L:C** P= 0.485 L:C*** P= 0.485 | 4                        |
| S100A7          | i84.8                              | 77.8                               |                                     |                                          |                                      |               |                                | L:C P<0.05                | 24                       |
|                 | 1.516                              | 1.625                              | 2.297                               | 0.177                                    | 0.354                                 | 0.707         | L:C*                       | L:C** P= 0.009 L:C*** P= 0.132 | 4                        |
| S100A8          | 24.251                            | 25.992                             | 24.251                              | 4.925                                    | 11.314                                | 10.556        | L:C*                       | L:C** P= 0.240 L:C*** P= 0.393 | 4                        |
|                 | 0.003                             | 0.005                              | 0.003                               | 0.002                                    | 0.004                                 | 0.006         | L:C*                       | L:C** NS L:C*** NS         | 4                        |
| S100A9          |                                   |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
|                 |                                   |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
|                 |                                   |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| LL37            | 84.1 / 80.9                        |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| Lysozyme        | 55.2 / 52.7                       |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| MIF             | 77.8 / 77.8                       |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| αMSH            | NR                                | i74.6 / 73.1                       |                                    |                                          |                                      |               |                                |                             | 4                        |
| MHC1            | 75.5 / 74.7                       |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| RNase7          | 0.435                             | 0.330                              | 0.574                               | 0.063                                    | 0.077                                 | 0.109         | L:C*                       | L:C** P= 0.145 L:C*** P= 0.179 | 4                        |
| IP10            | 89.9                              |                                    |                                     |                                          |                                      |               |                                |                             | 4                        |
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Uninvolved Tissue Levels (pg/mL) | Mean Control Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Comparison and Significance | Study Reference |
|----------------|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------------|--------------------------------------|-----------------------------------|--------------|-----------------------------|-----------------------------|----------------|
| CCL3           | 0.4                               | 0.2                               | 2.0                                |                                          | L:C                                  | P = 0.0196                       | 26           |                             |                             |                |
| CCL5           | 46.1                              | 6.2                               | -                                  |                                          | L:C                                 | P<0.05                           | 4            |                             | P<0.05                     |                |
|                | 7.6                               | 1.4                               | 5.4                                |                                          | L:C                                  | P = 0.0112                       | 26           |                             |                             |                |
| CCL20          |                                   |                                   |                                    |                                          |                                     |                                   | 4            | L:C                         | <0.001                     |                |
| CCL27          |                                   |                                   |                                    |                                          |                                     |                                   | 4            | L:C                         | <0.05                      |                |
| CRP            | 13.4                              | 1.2                               |                                    |                                          |                                     |                                   | 8            | L:C                         | <0.001                     |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 8            | L:C                         | <0.05                      |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 25           | Lpa:C                       | 0.05                       |                |
| ESR            | 29.5                              | 10.2                              |                                    |                                          |                                     |                                   | 8            | L:C                         | <0.001                     |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 25           | Lpa:C                       | 0.05                       |                |
| IFNg           |                                   |                                   |                                    |                                          |                                     |                                   | 7            | R=0.7                       |                             |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 9            | L:C                         | <5% Normal                   |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 1418         | HSS:CS                       | <0.05                     |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 6            | L:C                         | <0.05                     |                |
|                |                                   |                                   |                                    |                                          |                                     |                                   | 6            | Lpa:C                       | 0.05                       |                |
| GMCSF          | 78.45                             | 82.13                             |                                    |                                          |                                     |                                   | 4            | L:C                         | <0.05                     |                |
|                | 0.4                               | 0.0                               | NR                                 |                                          |                                     |                                   | 26           | Le:Ce                       | P = 0.027                   |                |
| VEGF           | 632.1                             | 1544                              |                                    |                                          |                                     |                                   | 6            | Le:Ce                       | P = 0.23                   |                |
| sVEGFR1        | 60                                | 60                                |                                    |                                          |                                     |                                   | 27           | HSS:CS                       | NS                        |                |
| Caspase 1      | No Quanti                         | No Quanti                         |                                    |                                          |                                     |                                   | 30           | L:C                         | <5% Normal                   |                |
| NLPR3          | No Quanti                         | No Quanti                         |                                    |                                          |                                     |                                   | 30           | L:P:PL                       | <5% Normal                   |                |
| CAMP           | 4                                 |                                   |                                    |                                          |                                     |                                   | 7            | L:C                         | NS                        |                |
| Uteroglobin    | 20                                | 20                                |                                    |                                          |                                     |                                   | 27           | HSS:CS                       | NS                        |                |
| Cystatin C     | 0.85                              | 0.8                               |                                    |                                          |                                     |                                   | 27           | HSS:CS                       | NS                        |                |
| LCN2           | 90                                | 40                                | 0.5                                | 0.02                                     |                                     |                                   | 27           | HSS:CS                       | <0.001                     |                |
| BD2            | 0.9                               | 1                                 |                                    |                                          |                                     |                                   | 27           | HSS:CS                       | NS                        |                |
| MMP2           | 200                               | 210                               |                                    |                                          |                                     |                                   | 27           | HSS:CS                       | <0.05                     |                |
| BLC            | 8.1                               | 0.58                              | 10.5                               |                                          | L:C                                  | P = 0.0066                       | 26           |                             |                             |                |
| Target Cytokine | Mean Level in Patient Serum (pg/mL) | Mean Level in Control Serum (pg/mL) | Mean Level in Lesional Tissue (pg/mL) | Mean Level in Perilesional Tissue (pg/mL) | Mean Uninvolved Tissue Levels (pg/mL) | Fold Increase | Comparison and Significance | Key: L=Lesional; PL=Perilesional; C=Control; NS=Not Significant; HSs=HS Serum; Cs=Control Serum; HSe=HS Exudate; Cc=Control Exudate; I=Inflamed lesional skin, S=Scarred lesional skin, #=Vs CAMP, *=NT (Non-Treated) Samples, **=Stimulation by Pam2CSK4 Lipopeptide, ***=Stimulation by Muramyl Dipeptide (MDP), +Heat Killed Candida Albicans; ++Heat Killed Staph Aureus; +++ Lipopolysaccharide; |
|----------------|-----------------------------------|-----------------------------------|---------------------------------------|------------------------------------------|-------------------------------------|--------------|----------------------------|------------------------------------------|
| ICAM-1         | 98.7                              |                                   | 31.9                                  | 3.1                                      | L:C                                 | P= 0.0028    | 26                         |                                          |
| Eotaxin        | 0.1                               | 0.1                               | 0.1                                   | 0.1                                      | L:C                                 | NS           | 26                         |                                          |
| Eotaxin2       | 3.9                               |                                   | 2.5                                   | 0.6                                      | L:C                                 | NS           | 26                         |                                          |
| CXCL6          | 160                               | 140                               |                                       |                                          |                                     | NS           | 27                         |                                          |
| CXCL9          | 219.8                             |                                   | 13.8                                  | 16                                       | L:C                                 | P= 0.0028    | 26                         |                                          |
| CXCL11         | 0.4                               | 0.4                               |                                       |                                          |                                     | NS           | 27                         |                                          |
| CX3CL1         | 0.9                               | 1                                 |                                       |                                          |                                     | NS           | 27                         |                                          |
| I-309          | 0.4                               |                                   | 0.3                                   | 0.1                                      | L:C                                 | NS           | 26                         |                                          |
| MCP1           | 47.5                              |                                   | 37.1                                  | 0.1                                      | L:C                                 | NS           | 26                         |                                          |
| M-CSF          | 0.4                               |                                   | 0.2                                   | 0.2                                      | L:C                                 | NS           | 26                         |                                          |
| MIP1b          | 16.1                              |                                   | 5.8                                   | 0.9                                      | L:C                                 | NS           | 26                         |                                          |
| MIP1d          | 0.1                               |                                   | 0.1                                   | 0.1                                      | L:C                                 | NS           | 26                         |                                          |
| PDGF           | 0.5                               |                                   | 0.2                                   | 0.2                                      | L:C                                 | NS           | 26                         |                                          |
| TIMP1          | 260.1                             |                                   | 166.2                                 | 15.4                                     | L:C                                 | NS           | 26                         |                                          |
| TIMP2          | 989.2                             |                                   | 997.3                                 | 15.8                                     | L:C                                 | NS           | 26                         |                                          |
T-cell axis. There is an uncertain role for other T-cell subsets in HS. Increased production of CXCL9 and IP-10 (CXCL10) are often linked to production of IFN-γ from T,1 T-cells in inflammatory sites, but IL-26 or IL-29, which are also cytokines produced by T,17 T-cells are alternative activators of STAT1 and CXCL9 production. IL-32 production in HS may also be linked to a T-cell subset that produces this cytokine. Low production of T,2 associated cytokines (IL-4, IL-5, or IL-13) has been measured in HS, suggesting an unlikely role of this T-cell subset. Likewise, the presence and function of T regulatory cells (Tregs) in HS lesions needs further study. IL-10 which is elevated in HS could be produced by either Tregs or the cDC1 (BDCA3+) DC subset, but levels may be inadequate to control tissue inflammation. At present, dendritic cell subsets are also incompletely characterized in HS. Potential sources of IL-12 or IL-23 are CD11c+ DCs, which includes the tissue resident BDCA-1+ (cDC2) subset and less mature inflammatory DCs, which are abundant cells in inflammatory lesions of psoriasis or atopic dermatitis but have not been investigated in HS. Cytokine contributions by other cell types such as innate lymphoid cells, macrophages, mast cells, and other leukocytes also remains to be determined.

Cytokine analysis methods
The methodologies of cytokine analysis varied widely (Table 5). 92 results were produced using electrochemical luminescence (ECL) procedures from three separate systems and manufacturers. 62 results were produced using ELISA. 18 results were performed with either ELISA or ECL but not further specified. 15 results were produced using polymerase chain reaction (PCR) with three separate systems from three manufacturers. Four discrete cytokines (IL-10, IL-17, TNF-α and IFN-γ) were analysed using all three techniques (ECL, ELISA and PCR), whilst 15 discrete cytokines (IL-6, IL-8, IL12p40, IL-17A, IL-22, IL-23, S100A7, S100A8, S100A9, RNase7, IP-10, CCL5, CCL20, CCL27) were analysed using ELISA and ECL only. We note IL-17 levels may well be below the lower limit of quantification with ELC and ELISA based approaches, with only the Singulex platform having the ability to quantify levels of IL-17 present in blood and serum of normal subjects.

Assessment of bias
Assessment of bias is presented in Table 6. Two of the 14 questions regarding participation rate and loss to follow up were considered not applicable. All included studies identified clear objectives and a clearly defined study population. No clear inclusion or exclusion criteria were specified for 17 of the 19 studies. Power estimation was made for one study. 52.6% of the 19 studies included or exclusion criteria were specified for 17 of the 19 studies. In total, 18 individual cytokines (78.2%) were found to demonstrate heterogeneity. Only eight cytokines (Serum IL-10, Leional IL-10, IL-12p70, hBD1, hBD2, hBD3, S100A9 and GMCSF) illustrated homogeneity. Due to this high level of heterogeneity and concerns regarding the methodological quality of included studies, meta-analysis was not deemed appropriate to perform.

Discussion
The overall quality of reporting in the identified studies was low with little consistency between methodologies and cytokines examined. There was also great variability in the ages, genders, comorbidities, associated conditions and treatments of the patients included in these studies. This was again reflected in the high number of cytokines with statistical heterogeneity (Table 7). The studies presenting conflicting data are often those studies with lower numbers of patients as well as lack of matched controls and/or lack of stratification by treatment. Meta-analysis using individual patient data would be required in order to account for these factors and re-assess the relationship between lesional and control cytokine levels.

In assessing the relationship between lesional and peri-lesional tissue, it has been demonstrated by many authors that different cytokines are present in peri-lesional tissue as opposed to lesional tissue. The definition of peri-lesional tissue is fairly consistent in the studies examined being 2cm from an active HS nodule on unaffected skin. However, no studies reported ultrasound examination of the peri-lesional skin to ensure that subclinical extension of the adjacent nodule (either in the dermis or the subcutaneous tissue) was being inadvertently sampled. This is an important differentiation to make in terms of identifying the subclinical pathogenic processes that precipitate this disease.
Table 5. Cytokine analysis methodology of studies included in this review.

| Cytokine | Method | Details |
|----------|--------|---------|
| IL-1α    | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD), MSD V-Plex cytokine panel 1 and the V-Plex proinflammatory panel 1. Analysis: FACScan (BD Biosciences). |
| IL-1β    | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD) MSD V-Plex cytokine panel 1 and the V-Plex proinflammatory panel 1. Analysis: FACScan (BD Biosciences). |
| IL-1ra   | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). Analysis: FACScan (BD Biosciences). |
| IL-1β    | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). Analysis: FACScan (BD Biosciences). |
| IL-4     | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). Analysis: FACScan (BD Biosciences). |
| IL-5     | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). Analysis: FACScan (BD Biosciences). |
| sIL-6R   | ECL    | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). Analysis: FACScan (BD Biosciences). |
| IL-6     | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-8     | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-10    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-12    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-13    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-17    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-18    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| NLRP3    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| TNFα     | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IFNβ     | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-23    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-28    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IFNγ     | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-27    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-21    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-22    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-25    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |
| IL-24    | ELISA  | Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN). |

Methodology:
- **ECL**: Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD).
- **ELISA**: Cytokines were measured in duplicate by ELISA (R&D Systems, Minneapolis, MN).
- **PCR**: Cytokines were measured in duplicate by RT-PCR (Applied Biosystems) on a Roche Light Cycler (Roche, Pleasanton, CA, USA).
- **xMAP technology** (Luminex Corporation, Austin, TX, USA).
- **FACScan**: FACScan (BD Biosciences, Franklin Lakes, NJ, U.S.A.)
| Cytokine | Method | Details |
|----------|--------|---------|
| IL10, IL1A, IL1B, IL18 and NLRP3 | ELISA | ECL (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analysis: FACSCalibur (BD Biosciences) xMAP technology (Luminex Corporation, Austin, TX, USA) Analyse: FACSCalibur (BD Biosciences) |
| IL10, IL1A, IL1B, IL18, IL12p40, IL12p70, IL15, IL16, IL17A, IL17B, IL17E and NLRP3 | PCR | IL10, IL1A, IL1B, IL18 and NLRP3 was performed with pre-designed Taqman gene expression assays (Applied Biosystems) on a Roche Light Cycler (Roche, Pleasanton, CA, U.S.A.) Analysis: FACSCalibur (BD Biosciences) xMAP technology (Luminex Corporation, Austin, TX, USA) Analyse: FACSCalibur (BD Biosciences) Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD MSD V-Plex cytokine panel 1 and the V-plex proinflammatory panel 1) Analysis: FACSCalibur (BD Biosciences) ECL (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analysis: FACSCalibur (BD Biosciences) Quantikine enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA) ECL (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analysis: FACSCalibur (BD Biosciences) |
| Cytokine | Method | Details | Study |
|---------|--------|---------|-------|
| IL-22   | ELISA  | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). eBioscience, Paris, France | 4     |
| IL-23   | ECL    | xMAP technology (Luminex Corporation, Austin, TX, USA) | 8     |
| IL-32   | PCR    | IL-32 (Hs00992441_m1), ABI-Prism 7300 Sequence Detector System | 25    |
| IL-32a  | PCR    | IL-32a (Hs04353657_gH), ABI-Prism 7300 Sequence Detector System | 29    |
| IL-32b  | PCR    | IL-32b (Hs04353658_gH), ABI-Prism 7300 Sequence Detector System | 29    |
| IL-32g  | PCR    | IL-32c (Hs04353656_g1), ABI-Prism 7300 Sequence Detector System | 29    |
| IL-36α  | ELISA  | Rabbit polyclonal anti-IL-36a (C-terminal; ab180909), from Abcam, Cambridge, U.K. at 1 : 500 dilution. | 3     |
| IL-36β  | ELISA  | Rabbit polyclonal anti-IL-36b (C-terminal; ab1809890) from Abcam, Cambridge, U.K. at 1 : 500 dilution. | 3     |
| IL-36G  | ELISA  | Mouse monoclonal anti-IL-36c ab156783; (Abcam, Cambridge, U.K.) at 1 : 500 dilution. | 3     |
| IL-36RA | ELISA  | Rabbit polyclonal from Abcam, Cambridge, U.K. at 1 : 500 dilution. | 3     |
| IL-37   | ELISA  | Rabbit polyclonal Abcam, Cambridge, U.K. at 1 : 500 dilution. | 3     |
| IL-38   | ELISA  | Rabbit polyclonal Abcam, Cambridge, U.K. at 1 : 500 dilution. | 3     |
| TNF-α   | ELISA  | TNF-alpha: 559071 mABG 1:10 mouse anti human | 24    |
| ELISA/ECL | ELISA | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). | 4     |
| ECL     | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD MSD V-Plex cytokine panel 1 and the V-plex proinflammatory panel 1 | 6     |
| PCR     | Taqman gene expression assays (Applied Biosystems) on a Roche Light Cycler | 31    |
| ECL     | (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analyysi: FACSCalibur (BD Biosciences) | 26    |
| ECL     | Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD MSD V-Plex cytokine panel 1 and the V-plex proinflammatory panel 1 | 6     |
| ECL     | (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analyysi: FACSCalibur (BD Biosciences) | 26    |
| ECL     | xMAP technology (Luminex Corporation, Austin, TX, USA) | 8     |
| ECL     | (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analyysi: FACSCalibur (BD Biosciences) | 26    |
| ECL     | xMAP technology (Luminex Corporation, Austin, TX, USA) | 8     |
| ECL     | (CBA Human Inflammation kit and CBA Human TH1/TH2 Cytokine kit; BD Biosciences, Franklin Lakes, NJ, U.S.A.) Analyysi: FACSCalibur (BD Biosciences) | 26    |
| ECL     | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). | 4     |
| Cytokine | Method | Details |
|----------|--------|---------|
| hBD2     | ELISA/ | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| hBD3     | ECL    | S100A8:
|          |        | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A7   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A8   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A9   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A8   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A9   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A8   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| S100A9   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| LL37     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| MIF      | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| MHC1     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| RNase7   | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| IP10     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| CCL3     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| CCL5     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| CCL20    | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| CCL27    | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| CRP      | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| ESR      | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |
| IFAg     | ECL    | ELISA (Quantikine; R&D Systems) or Luminex assay (Millipore, Billerica, MA). |

**Note:** The table includes various methods such as ELISA, ECL, Luminex assay, and more specific assays like the Quantikine kit. The details column specifies the specific antibodies or reagents used for detection, and the Assay column indicates the type of assay used for quantification.
| Cytokine | Method | Details |
|----------|--------|---------|
| GMCSF    | ECL    | Kelly et al. used a meso-scale discovery electrochemiluminescence assay (MSD, Meso Scale Diagnostics, Rockville, MD) for GMCSF analysis. |
| VEGF     | ECL    | Kelly et al. used a meso-scale discovery electrochemiluminescence assay (MSD, Meso Scale Diagnostics, Rockville, MD) for VEGF analysis. |
| Caspase 1 | ELISA  | Kelly et al. used a Kelly et al. Caspase-1 fluorochrome inhibitor of caspases (FLICA) (ImmunoChemistry Technologies, Bloomington, CA) for Caspase 1 analysis. |
| NLRP3    | PCR    | Kelly et al. performed with predesigned Taqman gene expression assays (Applied Biosystems) on a Roche LightCycler 480 (Pleasanton, CA) for NLRP3 analysis. |
| CAMP     | PCR    | Kelly et al. used a CAMP enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for CAMP analysis. |
| Cystatin C | ECL    | Kelly et al. used a Cystatin C enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for Cystatin C analysis. |
| LCN2     | ECL    | Kelly et al. used a LCN2 enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for LCN2 analysis. |
| B2D2     | ELISA  | Kelly et al. used a B2D2 enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for B2D2 analysis. |
| MMP2     | ECL    | Kelly et al. used a MMP2 enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for MMP2 analysis. |
| PDGF-BB  | ECL    | Kelly et al. used a PDGF-BB enzyme-linked immunosorbent assay (ELISA) systems from Bio-Techne for PDGF-BB analysis. |

**Table 4:** Antibodies Used for Identification of Cytokines in Studies Included in this Systematic Review. ECL: Electrochemiluminescence

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Table 6. Risk of bias across studies included in this review.

| Study Reference | 1. Was the research question or objective in this paper clearly stated? | 2. Was the study population clearly specified and defined? | 3. Was the participation rate of eligible persons at least 50%? | 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | 5. Was a sample size justification, power description, or variance and effect estimates provided? | 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | 10. Was the exposure(s) assessed more than once over time? | 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | 12. Were the outcome assessors blinded to the exposure status of participants? | 13. Was loss to follow-up after baseline 20% or less? | 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? |
|----------------|-------------------------------------------------|-----------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Moran et al.²   | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | Y                                               | Y                                               | Y                                               | Y                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Emelianov et al.²⁴ | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | N                                               | Y                                               | N                                               | Y                                               | Y                                               | NR                                              | N/A                                             | N                                               |
| Hessam et al.³   | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | N                                               | Y                                               | N                                               | Y                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Hotz et al.³     | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | Y                                               | N                                               | Y                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Thomi et al.⁷    | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | Y                                               | Y                                               | N                                               | N                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Jimenez-Gallo et al.⁸ | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | Y                                               | Y                                               | N                                               | Y                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Banerjee et al.⁸ | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | Y                                               | N                                               | Y                                               | N                                               | Y                                               | N                                               | NR                                              | N/A                                             | N                                               |
| Jimenez-Gallo et al.²⁶ | Y                                               | Y                                             | N/A                                            | N                                                | N                                               | N                                               | Y                                               | Y                                               | N                                               | N                                               | Y                                               | N                                               | Y                                               | Y                                               | NR                                              | N/A                                             | N                                               |
| Study Reference | 1. Was the research question or objective in this paper clearly stated? | 2. Was the study population clearly specified and defined? | 3. Was the participation rate of eligible persons at least 50%? | 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | 5. Was a sample size justification, power description, or variance and effect size estimates provided? | 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | 10. Was the exposure(s) assessed more than once over time? | 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | 12. Were the outcome assessors blinded to the exposure status of participants? | 13. Was loss to follow-up after baseline 20% or less? | 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? |
|-----------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Kanni et al[33] | Y | Y | N/A | N | N | Y | Y | Y | Y | Y | Y | Y | NR | N/A | N |
| Kelly et al[31] | Y | Y | N/A | N | N | Y | Y | N | Y | N | Y | NR | N/A | N |
| Lima et al[28] | Y | Y | N/A | N | N | Y | Y | N | Y | N | Y | NR | N/A | N |
| Ten Oever et al[9] | Y | Y | N/A | N | N | Y | Y | N | Y | N | Y | NR | N/A | N |
| Schlapbach et al[32] | Y | Y | N/A | N | N | Y | Y | Y | Y | Y | N | Y | NR | N/A | N |
| Thomi et al[29] | Y | Y | N/A | N | N | Y | Y | Y | Y | Y | N | Y | NR | N/A | N |
| Thomi et al[30] | Y | Y | N/A | N | N | Y | Y | Y | Y | N | Y | NR | N/A | N |
| Wolik et al[27] | Y | Y | N/A | N | N | Y | Y | N | Y | N | Y | NR | N/A | N |
| Van der Zee et al[26] | Y | Y | N/A | N | N | Y | Y | Y | Y | N | Y | NR | N/A | N |
| Kanni et al[33] | Y | Y | N/A | N | N | Y | Y | Y | Y | Y | N | Y | NR | N/A | N |

Key: Y = Yes; N= No, NR= Not Reported N/A = Not Applicable
## Methodological quality

Regarding methods of cytokine analysis, a number of authors have identified variability in cytokine levels measured with different forms of multiplex assays as well as traditional ELISA methods. Different methods of cytokine analysis are known to be prone to variability, with some cytokines more sensitive than others. For example, IFN-γ and IL-1β were overestimated compared with ELISA methods, whilst IL-6 levels were underestimated. IL-6 levels when compared across four different multiplex assays showed significant variation in detectable range, accuracy and responsiveness. The correlation of TNF-α between ELISA and Multiplex assays was also poor ($r=0.31$). Issues also exist with minimum detectable levels of cytokines with specific bead-based arrays. As an example, minimal detectable dose readings reported for IL-12p70 using some multiplex arrays are higher than the levels reported in lesional HS samples. Therefore, whilst the general trends in the level of consistently elevated or suppressed cytokines in HS are reliable, the quantification of individual cytokines as well as the relationship between comorbidities and cytokine levels requires further research with consistent, reliable and accurate methodologies in order to further dissect the inflammatory cascade in this disease.

### Keratinocyte mediated inflammatory pathways

The majority of elevated cytokines and inflammatory proteins identified in lesional skin of HS (TNF-α, IL-1β, IL-6, IL-8, IL-11, IL-23, IL-17A, IL-33, IL-36, IL-37, S100A7, S100A8, S100A9, GM-CSF, TGF-β, hBD2, hBD3, CCL3, CXCL9, CXCL11, PDGF, CCL5, CCL-20, MIF, GM-CSF and LCN2) are those known to be produced by keratinocytes, as well as perpetuating a self-amplification pathway (Figure 2). Additionally T-cells produce IL-17A, IL-17F, IL-26, IL-29, and IFN-γ; dendritic cells produce IL-12, IL-23 and possibly IL-39; neutrophils produce S100A8

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### Table 7. Table of heterogeneity of cytokine studies by chi-squared tests for homogeneity.

| Cytokine       | Chi Squared | P       |
|----------------|-------------|---------|
| IL1a Lesional  | 0.3525      | $p=0.552705$ |
| IL1b Lesional  | 153.5947    | $p<0.00001$ |
| IL4 Lesional   | 4.3992      | $p=0.035955$ |
| IL5 Lesional   | 15.1692     | $p=0.000098$ |
| IL6 Lesional   | 461.9724    | $p<0.00001$ |
| IL8 Lesion     | 846.6251    | $p<0.0001$ |
| IL8 Serum      | 94.4212     | $p<0.0001$ |
| IL10 Lesion    | 90.3211     | $p<0.0001$ |
| IL10 Serum     | 0.1595      | $p=0.689624$ |
| IL12p40 Lesional | 4.9618     | $p=0.025913$ |
| IL12p70 Lesional | 2.2116     | $p=0.136973$ |
| IL13 Lesional  | 5.4163      | $p=0.019949$ |
| IL15 Lesional  | 39.2837     | $p<0.00001$ |
| IL16 Lesional  | 126.1959    | $p<0.00001$ |
| IL17A Lesional | 22.6668     | $p<0.00001$ |
| IL17A Serum    | 19.1621     | $p=0.000012$ |
| TNFa Lesional  | 6.9761      | $p=0.030561$ |
| TNFb Lesional  | 7.4004      | $p=0.006521$ |
| hBD1 Lesional  | 2.3317      | $p=0.311156$ |
| hBD2 Lesional  | 0.6488      | $p=0.722954$ |
| hBD3 Lesional  | 1.0314      | $p=0.597084$ |
| S100A7 Lesional| 621.2537    | $p<0.00001$ |
| S100A8 Lesional| 19.6371     | $p=0.000054$ |
| S100A9 Lesional| 1.27        | $p=0.529927$ |
| RNAse 7        | 6.7263      | $p=0.034626$ |
| GMCSF Lesional | 1.9405      | $p=0.163611$ |
Figure 2. Inflammatory pathways in hidradenitis suppurativa, a schematic representation of the results identified in this systematic review. Immunological ‘priming’ occurs due to the contribution of adipose tissue, genetic susceptibility, smoking-related inflammatory mediators and obesity related pro-inflammatory signals and the composition of the microbiome. Increased activity of cDC1, cDC2 and T cells lead to both keratinocyte hyperplasia via the actions of IL-12 and IL-23, as well as a Th17 predominant immune response. Alterations of antimicrobial peptides (AMPs) also occur throughout the epidermis. The dermal inflammation interacting with the hyperplastic epidermis result leads to a self-perpetuating inflammatory feed forward mechanism mediated by IL-36, IL-1B and TNF-a. The development of scarring and sinus tracts is associated with MMP2, ICAM-1 and TGF-Beta, with possible augmentation of ICAM-1 and TGF-B signaling via specific components of the microbiome. TNF-a, PGE2 and CXCL2 then lead to additional feed forward mechanisms perpetuating the inflammatory cycle.

Figure 3. Funnel plot of selected cytokine in lesional and control samples of hidradenitis suppurativa. IL-1a = Red, IL-10 = Blue, IL-12p70 = Green, hBD1 = Purple, hBD2 = light purple, hBD3 = Black, S100A9 = White, GMCSF = Yellow.
and S100A9 (calgranulin); and innate lymphoid cells also contribute IFN-γ, IL-17A and IL-17F. This inflammatory model has been well documented and explored in both psoriasis and atopic dermatitis. The psoriasis form epidermal hyperplasia seen in HS (mediated by IL-17 and maintained by IL-23-mediated T₃₁₇ stimulation) reflects this common inflammatory pathway.

The other elevated non-keratinocyte produced cytokines in HS (IL-4, IL-5, IL-10, IL-16, IL-17A, IL-22, IL-32, IL-36, hBD1), are produced by a combination of dendritic cells, monocytes, neutrophils and CD4+ T cells. IL-4 and IL-5 as key cytokines in the T₃₂ axis are consistent with the findings of Mast cells in HS, as well as the pruritus, which is frequently reported by patients. IL-10 in HS is produced by Treg cells (although dendritic cells may also be a source), and whilst quantitatively the IL-10 signal appears paradoxically elevated, it can be explained by the up-regulation of T cells including Treg cells, which although significantly elevated from baseline, are not elevated enough in comparison to T₃₁₇/IL-17/IL-22 signal to counteract this strong pro-inflammatory cascade. Further exploration of these cytokines may reveal the initial trigger(s) of the inflammatory cascade in HS, or correlations with known pro-inflammatory comorbidities.

Insights into pathogenesis of HS

In light of investigations in psoriasis and atopic dermatitis, the role of dendritic cells in HS needs to be clarified, as dendritic cell influx has been reported in histological studies, and they may contribute to the high IL-10 and IL-15 levels reported. IL-32 is a second cytokine produced by dendritic cells, but has only been reported in one study. Further research into the functional role of IL-32 in the activity of dendritic cells in HS would be of value. The role of IL-20, IL-22, IL-24 and IL-26 needs further clarification. IL-19, TSLP and CCL17 (TARC) have not yet been examined in HS and this is required in order to further explore the role of dendritic cell, monocyte and T cell activation and migration in this disease.

It is well established that smoking, obesity and diabetes are strongly associated with HS. The immunological effects of smoking include increase in number and responsiveness of dendritic cells, altered function of Treg cells and activation of Th17 pathways, whilst obesity and diabetes can result in production of IL-1β, IL-6 and TNF-α through activated macrophages in adipose tissue. These potential mechanistic pathways (which may prime or contribute towards inflammation in HS) require validation in functional studies. However, if they are a significant contributor to inflammation, the presence or absence of these comorbidities need to be considered in future cytokine studies as confounding variables in order to identify significant biochemical markers independent of these other pro-inflammatory states that reflect the pathogenesis of HS.

The role of the microbiome in stimulating chronic inflammation has parallels in diabetes and colonic inflammation, and the presence of Porphyromonas and Peptostreptococcus species has been associated with a subpopulation of patients with HS. Porphyromonas has been associated with systemic inflammation and atherosclerosis through aberrant toll-like-receptor 4 signalling and is not part of the natural cutaneous flora. Altered cutaneous and gastrointestinal microbiome can also act via microbiome metabolites (including lipopolysaccharides, short chain fatty acids and bile salts) through stimulation of myeloid dendritic cells via G Protein Coupled Receptors (including GPR41, GPR43 and GPR109A). The microbiome may be implicated as a trigger factor for the initial inflammatory cascade in HS in a proportion of patients. Similarly, the presence of genetic polymorphisms as reported in HS have the potential to up-regulate inflammatory activity through shedding of IL-6R, IL-15R, TNF-α, as well as up-regulating the response of dendritic cells to LPS stimulation via ADAM17 (which has been demonstrated to be elevated in a published gene expression study of HS). These pathways may be involved prior to the activation of keratinocyte-mediated inflammation, and hence, may reveal novel targets for new interventions to control the disease prior to the onset of destructive inflammation.

Limitations, interpretation and generalisability

The limitations to this study include the high degree of methodological variability (Table 5) and high impact of bias (Table 6) within the included studies. The lack of individual patient data has also prevented any further analysis into the contribution of comorbidities such as smoking and obesity to variable levels of cytokines in lesional tissue and/or serum. This, along with the high level of heterogeneity in many cytokines (Table 7), has resulted in analyses of the collated data being limited to descriptive analyses only and limited the generalisability of results.

Conclusions

Through this review we have catalogued the various cytokines that have been reported as elevated in lesional, peri-lesional tissue, serum or exudate of HS patients. We have also identified those cytokines with inconsistent results and identified methodological factors that may explain variability in findings. We have identified a number of missing links in disease pathogenesis with respect to cytokine actions and pathways that must be addressed in future work. Areas for further investigation include the role of dendritic cells in HS, the contribution of obesity, smoking, diabetes and the microbiome to cytokine profiles in HS, and examining the natural history of the disease through longitudinal measurements of cytokines over time.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

OSF: Extend data. Data Collection Sheet Cytokine. Review HS. https://doi.org/10.17605/OSF.IO/N2E7A
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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Version 1

Reviewer Report 04 March 2019

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Evangelos Giamarellos-Bourboulis
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2 National and Kapodistrian University of Athens, Athens, Greece

This is a long time needed review trying to shed light in the pathogenesis of hidradenitis suppurativa (HS). My concerns are coming from the biggest hurdle the authors had to overcome from the very beginning of their attempt i.e. the great heterogeneity of the existing evidence. Due to this, I find over-exaggerated the conducted approach to set-up a mechanistic interpretation for the disease. I believe that the heterogeneity is so vast that it is almost impossible to suggest the pathways implicated in the pathogenesis of HS. To this end, I suggest that the mechanistic parts are omitted and Figure 2 as well.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology, genetics, hidradenitis, anti-cytokine therapies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have
significant reservations, as outlined above.

Reviewer Report 25 February 2019

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Aude Nassif
Institut Pasteur, Medical Center, Paris, France

This very instructive study aims at analyzing previous cytokine studies in HS patients, in skin tissue, blood, serum and exudates, to assess relevancy and reliability of these studies.

The authors have performed an extensive work, methods seem perfectly appropriate. The authors are very critical and rigorous in their approach, looking for confounding factors, which is highly desired.

The authors could also mention that genetic heterogeneity may play a role in the diversity of results and encourage using similar phenotypes for future studies.

This analysis brings up a very important and honest contribution to the current knowledge in cytokines involved in HS and therefore deserves indexing.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: microbiology, genetics, therapeutics, clinical forms of HS and associated diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Thank you for the opportunity to review this manuscript and congratulations to the authors for their great efforts in putting this systematic review together. Research on the role of cytokines in HS is important, as it may lead to new targets for therapy and a better understanding of the pathophysiology of HS.

Summary

This systematic review focused on collecting all data published on cytokine studies in tissue, blood, serum and exudate in hidradenitis suppurativa. 81 discrete cytokines were examined in HS patients (n=564) and control patients (n=198) in 19 studies. Methodology varied greatly among studies, which were generally of low quality. When measuring levels of cytokines, substantial variance was found and the majority of cytokines showed heterogeneity. IL-17 signalling appeared to be a significant component. Suggestions for further research were discussed.

Questions

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes.

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes. However, I wonder why the term ‘hidradenitis suppurativa’ is not in the search strategy and ‘hidradenitidis suppurative’ is? ‘Hidradenitidis’ is not an existing word, as far as I know and will not provide any search results. Please adjust.

Is the statistical analysis and its interpretation appropriate?
Yes, as far as I can judge as a non-statistician. The analyses used are ones I have little experience with myself. I'll refrain from commenting on this section.

Are the conclusions drawn adequately supported by the results presented in the review?
Partly. The last conclusion ‘examining the natural history of the disease through longitudinal measurements of cytokines over time’ is not discussed anywhere else in this article. First, I suggest changing ‘history’ to ‘course’. Moreover, I am wondering, how the authors propose to do this. Monitoring the natural course of the disease, would mean patients cannot receive any treatment for their HS, during this proposed study. Depending on how long the natural course is meant to
be monitored, I don't think it is ethical to withhold patients from treatment. Please elaborate on this conclusion with a specific proposal or otherwise rephrase or maybe leave out this conclusion.

**Other comments**

Page 9 last paragraph/Page 28 – 1st paragraph: You state that ‘psoriasiform epidermal hyperplasia is seen in HS’. Please provide a reference for this statement. The reference provided only references to the pathway likely responsible for this in psoriasis.

Page 28 – 4th paragraph: ‘These potential mechanistic pathways (which may prime or contribute towards inflammation in HS) require validation in functional studies.’ Could you please provide an example on how such a functional study should be designed to produce reliable results?

Table 4: the abbreviation ‘Lpa’ is not clarified in the key section of the table. Does ‘Le’ (page 11, IL-1a, first row) mean lesion exudate?

Table 6: the number four of question four is missing in the top row of the table on both pages (24-25). Please insert.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**
Yes

**Is the statistical analysis and its interpretation appropriate?**
Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Hidradenitis suppurativa

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
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