BLF/UKPIN Consensus Statement on the Definition, Diagnosis and Management of Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD) in Common Variable Immunodeficiency Disorders (CVID).

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Abstract

A proportion of people living with CVID develop Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD). We aimed to develop a consensus statement on the definition, diagnosis and management of GLILD. All UK specialist centres were contacted and relevant physicians were invited to take part in a three-round on-line Delphi process. Responses were graded as Strongly Agree, Tend-to-Agree, Neither Agree-nor-Disagree, Tend-to-Disagree and Strongly Disagree, scored +1, +0.5, 0, -0.5 and -1 respectively. Agreement was defined as ≥80% consensus. Scores are reported as mean (±standard deviation (SD)). There was 100% agreement (score 0.92 (0.19)) for the following definition: '*GLILD is a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded*'. There was consensus that the work-up of suspected GLILD requires CT chest (0.98 (0.01)), lung function tests (e.g. gas transfer 0.94 (0.17)), bronchoscopy to exclude infection (0.63 (0.50)) and lung biopsy (0.58 (0.40)). There was not consensus on whether expectant management following optimisation of immunoglobulin therapy was acceptable: 67% agreed, 25% disagreed, score 0.38 (0.59). 90% agreed that when treatment was required, first line treatment should be with corticosteroids alone (score 0.55 (0.51)).

KEY WORDS: Common Variable Immunodeficiency; Lung Disease, Interstitial; complications

Introduction

Whilst Common Variable Immunodeficiency Disorders (CVID) are primarily characterised by hypogammaglobulinaemia and increased risk of infection, non-infectious auto-inflammatory, auto-immune and lymphoproliferative complications are also common [1]. Notably, 8-22% of people living with CVID develop an interstitial lung disease termed 'Granulomatous-Lymphocytic Interstitial Lung Disease' (GLILD) which is associated with reduced survival [2]. This important complication of GLILD has been little studied. Investigators have used different definitions, including diffuse radiological abnormalities and/or biopsy evidence of granulomatous inflammation, with lymphoproliferative changes including histologic patterns of Lymphoid Interstitial Pneumonia (LIP), follicular bronchitis and/or diffuse reactive lymphoid hyperplasia [3]. Impaired T-cell function leading to dysfunctional antigen handling has been proposed as a possible mechanism [4], perhaps in association with reduced switched memory B-cells [5, 6], and/or aberrant responses to viral infection [7]. Management is primarily based on small case series [8-10] and there have been no controlled trials. This is unsatisfactory both for people living with GLILD, and for health-care professionals.

In 2015, a UK consortium from London (UCL, Barts and Imperial), Cambridge and Oxford established a network of clinicians with an interest in GLILD, to develop patient literature, and to produce a consensus document on the definition, diagnosis and management of GLILD in adults. This was funded by the British Lung Foundation (BLF) and achieved in collaboration with the United Kingdom Primary Immunodeficiency Network (UKPIN), using Delphi methodology.

The Delphi technique, first used in the 1950s to assess the impact of new military technology, has been widely used in health-care to develop consensus documents. Key characteristics include anonymity of the participants, structured flow of information, and feedback to individuals of group data from previous rounds to inform subsequent responses [11].

We report the results of a Delphi consensus process providing a statement on the definition, diagnosis and management of GLILD in adults. This has not been previously performed and represents the largest report to date of collective clinical experience in GLILD. We provide a definition for future studies, illuminate current practice, and help to define future research priorities.

Method

A structured questionnaire containing a proposed definition of GLILD, and statements on diagnosis and management was developed by the Steering Committee (Delphi Round 1).

For Delphi Round 2, all UK centres providing specialist immunology services were contacted via the UK Primary Immunodeficiency Network (UKPIN) and asked to nominate interested Consultant Immunologists, Chest Physicians, Radiologists and Pathologists to take part. The role of Consultant in the UK signifies a senior physician who is on a national register in their respective specialty. Participants were therefore self-selected as those with an interest in GLILD. The number of participants was not restricted. These participants completed the questionnaire via a web-link (SurveyMonkey®). Participants did not have to answer all the questions thus, for example, a Radiologist might only answer sections on radiology. We report the number of respondents for each question.

Responses were graded, unless stated otherwise, as Strongly Agree, Tend to Agree, Neither Agree nor Disagree, Tend to Disagree and Strongly Disagree scored +1, +0.5, 0, -0.5 and -1 respectively. This is illustrated as Figure 1. *A priori*, agreement was defined as ≥80% consensus to Agree (Strongly or Tend to), or Disagree (Strongly or Tend to). Scores are reported as the mean and standard deviation (SD), on a scale of +1 to -1 with more extreme scores and lower SD indicating stronger consensus.

The Steering Committee reviewed the Round 2 summary responses and where further clarification was required, the question was adapted and sent back to participants with feedback from Round 2 as the third and final round. The process was designed to complete after the third round, reporting consensus or otherwise.

Results

The Steering Committee that developed the questionnaire consisted of a facilitator (NV, a senior trainee in Immunology) and 12 Consultants: five Immunologists, four Chest Physicians, two Radiologists and one Pathologist.

Thirty-three Consultants completed the second round Delphi, consisting of 17 Immunologists, eight Chest Physicians, four Radiologists and four Pathologists. This included representation from 13 centres in total, including six of the 10 Royal College of Physicians 'QPIDS'-accredited centres. In total, the participating centres estimated that they currently cared for 112 patients with GLILD (median 4, inter-quartile range 5-9, minimum 2, maximum 24). Thirty-one Consultants completed the third and final round Delphi.

1. Definition of GLILD:

After revision for the final round Delphi, 24/29 strongly agreed and 5/29 tended to agree with the following definition of GLILD which we therefore present as a BLF/UKPIN consensus definition (100% agree, score 0.91 (0.19)):

"GLILD is a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded".

Importantly, there was also consensus that GLILD is usually seen in the context of multi-system granulomatous / inflammatory involvement that might include, for example, splenomegaly, lymphadenopathy and/or liver disease, even if these manifestations are not symptomatic (93% agree, score 0.66 (0.31)).

2. Diagnosis of GLILD:

There was not consensus that patients with GLILD must be symptomatic: 63% disagreed with this statement, score -0.27 (0.64). This was true for both major symptoms of GLILD: change in (or new) breathlessness (score -0.22 (0.61)) and change in (or new) cough (score -0.29 (0.61)). 96% agreed that the diagnosis of GLILD required a high index of suspicion, supporting a strategy of screening for respiratory complications of CVID.

88% agreed that the diagnosis of GLILD required discovery of new abnormalities on chest imaging (score: 0.65 (0.56)) and therefore all respondents felt a CT scan was essential in the diagnostic work up (score 0.98 (0.01)). The results of consensus opinion on other aspects of the diagnostic work-up are reported in Table 1.

The other tests considered essential in diagnostic work up were full lung function (spirometry 96% agreed, 0.88 (0.27); lung volumes 91% agreed, 0.76 (0.40); and gas transfer 100% agreed, 0.94 (0.17)), flexible bronchoscopy to exclude infection (83% agreed, 0.63 (0.50)) and surgical lung biopsy (83% agreed, 0.58 (0.46)). 96% preferred video-assisted thoracic surgical biopsy (VATS) to open thoracotomy (score 0.85 (0.28)). There were no radiological findings considered sufficiently diagnostic to avoid the need for biopsy (score -0.05 (0.61)). There was not consensus that there had to be new change on lung function tests to make the diagnosis (54% agreed, 33% disagreed, score 0.04 (0.67)) and therefore the value of lung function testing is primarily in assessing progression and treatment response rather than establishing the diagnosis (as described further below).

There was no consensus on the need to perform other imaging tests (including chest x-ray and MRI chest), functional tests (including oxygen saturation, 6 minute- or shuttle-walk, or cardio-pulmonary exercise testing), echocardiography, or blood tests (including inflammatory markers, β_2-microglobulin, serum ACE, or serum IgM). Despite GLILD usually being associated with multi-system involvement, there was not consensus for preference to biopsy another site in the presence of such manifestations even if that was more practical than surgical lung biopsy (score 0.27 (0.59)). This likely reflects the differential diagnosis in the lung discussed further below.

There was consensus that, where available, a diagnosis of GLILD should prompt a search for specific underlying genetic mutations, for example LRBA/CTLA-4 (81% agree, score 0.57 (0.36)).

2.1 Radiology

Regarding the CT-protocol, there was consensus that this should be thin slice (<2mm, 80% agree score 0.73 (0.47)) and contiguous (85% agree, score 0.77 (0.38)). There was not consensus about administration of IV contrast (62% agree, 8% disagree, score 0.40 (0.53)).

2.2 Bronchoscopy

With regard to samples obtained at flexible bronchoscopy, the tests considered essential are reported in Table 2. There was consensus to perform microscopy and bacterial culture (96% agreement, score 0.93 (0.23)), *Mycobacterial* culture (96% agreement, score 0.93 (0.23)) and fungal culture (91% agreement, score 0.80 (0.33)). There was not consensus for other tests at bronchoscopy including trans-bronchial biopsy, PCR for *Mycobacteria*, atypical pathogens or viruses, routine tests for *Pneumocystis jirovecii*, or analysis of broncho-alveolar lavage fluid for cell differential or lymphocyte phenotyping.

2.3 Histopathology

There was ≥80% consensus (n=20) that biopsy specimens should be immuno-stained for CD3, CD4, CD8 and CD20, for the presence of bacteria including *Mycobacteria* and fungi, and for clonality to exclude lymphoma. Two respondents additionally mentioned staining for viral markers including cytomegalovirus (CMV) and Epstein Barr Virus (EBV).

3. Differential Diagnosis of GLILD:

Respondents were asked to rate a list of radiological features as 'necessary to make the diagnosis of GLILD', 'typical of the diagnosis of GLILD', or 'not typical of the diagnosis of GLILD'. No features were consistently rated as necessary to make the diagnosis. >80% of 22-25 respondents rated the presence of solid nodules (nodule defined as <3cm), semi-solid nodules, pure ground-glass opacities, enlarged thoracic (hilar and/or mediastinal) lymph nodes and splenomegaly as necessary or typical. >80% respondents rated the presence of cysts and bronchiectasis as not typical. There was no consensus for reticulation, traction bronchiectasis, honeycombing, masses (defined as >3cm), consolidation or upper abdominal adenopathy. When nodules were present, there was no consensus about their distribution.

Results of the consensus on radiological differential diagnosis are presented in Table 3. There was consensus that this includes infection, organising pneumonia, lymphoid interstitial pneumonia, sarcoidosis and lymphoma.

Respondents were also asked to rate a list of histo-pathological features as 'necessary to make the diagnosis of GLILD', 'typical of the diagnosis of GLILD', or 'not typical of the diagnosis of GLILD'. No features were consistently rated as necessary to make the diagnosis. >80% respondents rated the presence of granulomatous inflammation, peri-bronchiolar lymphoid proliferation, interstitial lymphoid proliferation and CD4-cell predominance as necessary or typical. There was consensus that eosinophils were not typical. There was no consensus for the presence of organising pneumonia, interstitial fibrosis or paucity of B-cells. 92% agreed that the biopsy features are sufficiently typical to make a confident diagnosis in a person known to have primary immunodeficiency.

Results of the consensus on histo-pathological differential diagnosis are also presented in Table 3. There was consensus that this includes infection, organising pneumonia, lymphoid interstitial pneumonia due to other causes/associations and sarcoidosis.

4. Management of GLILD:

There was strong support for decision making on management being led by a multi-disciplinary team including immunologists, chest physicians, radiologists and pathologists (n=26, 100% agree, score 0.90 (0.20)), for patients to be managed in a multi-disciplinary clinic comprising immunologists and chest physicians (n=25, 96% agree, score 0.90 (0.25)), and for patients to have access to a nurse specialist (n=25, 84% agree, score 0.70 (0.43)) and psychological support (n=24, 96% agree, score 0.79 (0.29)) as necessary.

91% (n=22, score 0.68 (0.33)) agreed that immunoglobulin therapy should be optimised to standard concentrations prior to initiation of specific therapy for GLILD, but there was not consensus about targeting a higher trough level (n=22, 64% agreed, 9% disagreed, score 0.39 (0.46)).

There was not consensus about the routine use of anti-microbial prophylaxis in patients with GLILD (n=21, 48% agreed, 19% disagreed, score 0.21 (0.56)). Where prophylactic antibiotics were given, the most commonly used agents were azithromycin and, particularly if there was a risk of *Pneumocystis*, co-trimoxazole. There was not consensus that macrolides should be the preferred agent because of potential anti-inflammatory activity.

There was no consensus about whether expectant management (monitoring without additional therapy) following optimisation of immunoglobulin therapy was an acceptable strategy: n=24, 67% agreed, 25% disagreed, score 0.38 (0.59). We went on to explore, having made a diagnosis, which features of GLILD were associated with a decision to commence additional therapy, examining the presence or absence of symptoms, normal vs. abnormal and stable vs. deteriorating lung function. There was consensus to start treatment when patients were symptomatic with abnormal and deteriorating lung function (n=17, complete agreement), asymptomatic with abnormal and deteriorating lung function (n=17, 100% agree, score 0.79 (0.25)) and symptomatic with normal but deteriorating lung function (n=16, 81% agree, score 0.63 (0.53)). There was consensus not to treat for a patient who was asymptomatic with normal and stable lung function (n=17, 94% agree, score -0.79 (0.40)). There was not consensus to treat or not for the remaining four options.

90% agreed that when specific treatment was required, first line treatment for GLILD should be with corticosteroids alone (n=21, score 0.55 (0.51)). Of these 21 respondents, all but one preferred oral prednisone (one preferred intravenous methylprednisone). Of the twenty using oral prednisone, the minimum dose used was 10-20mg day, and the maximum 1-2mg/kg/day. For a 70kg subject, the median (IQR) dose was 40 (30-70) mg/day. For respondents using prednisone with a second agent, the two most commonly used second agents were azathioprine (six respondents) and mycophenolate (four respondents).

The consensus results regarding second line drug therapy are reported in Table 4. There was ≥80% consensus for the following three drugs as second line agents, with or without steroids, in decreasing order of support: azathioprine (n=21, 100% agreed, score 0.71 (0.25)), rituximab (n=21, 90% agreed, score 0.67 (0.40)) and mycophenolate (n=21, 81% agreed, score 0.62 (0.44)). There was no consensus support for abatacept (though potential use in patients with specific genetic mutations was noted), anti-TNF agents, ciclosporin, hydroxyxchloroquine, methotrexate, sirolimus or tacrolimus. There was no consensus that biopsy at a single time-point could be used to guide future second line therapy decisions: 43% agreed with the statement that second-line therapy could be guided by lung biopsy results and 24% disagreed with this (n=21). The second line agents that had been used in clinical practice, in alphabetical order, were: abatacept, adalimumab, azathioprine, ciclosporin, hydroxychloroquine, infliximab, methotrexate, mycophenolate and rituximab. Of the 22

participants responding to the question “Would you consider bone-marrow transplantation for GLILD?” seven (32%) said yes, seven said no and eight were unsure.

Regarding opportunistic infections (OI) in the context of immunosuppression for GLILD, 55% of respondents had seen OI including *Pneumocystis*, non-tuberculous *Mycobacteria*, CMV, varicella zoster virus (VZV) and one case of possible progressive multifocal leucoencephalopathy (PML). Further research is required here as these data are not incidence rates.

There was consensus that treatment response (or progression) could be assessed using change in symptoms (n=22, 91% agreed, score 0.64 (0.38)), change in lung function (n=22, 91% agreed, score 0.75 (0.40)) and/or change in CT appearance (n=22, 91% agreed, score 0.77 (0.40)). The single preferred test in 82% of 17 respondents was change in gas transfer (DL_{CO} and/or K_{CO}). 63% of 19 respondents considered a change in gas transfer of 10-20% to be significant and 21% considered a change of 20-30% to be significant. After initiation of therapy, response was first assessed a median (IQR) of 3 (1.5-3) months later in 22 respondents. 9% of 22 participants would not repeat a CT, but in those that would the median (IQR) time to repeat was 5.5 (5.5-7.5) months.

There was not consensus about preferred maintenance therapy, or indeed the need for maintenance thereapy, in clinically stable disease. In 24 respondents 46% would prefer a second line (non-corticosteroid) agent alone, 21% preferred a second line agent with a minimum continuing dose of corticosteroid, 13% preferred corticosteroid alone, and 13% preferred to withdraw all therapy and monitor.

In clinically stable disease, 55% of 22 respondents monitored patients every 3-4 months, and 32% every 5-6 months. 55% of 22 respondents would consider a repeat lung biopsy in the event of relapse.

Discussion

We present the first consensus statement on the definition, diagnosis and management of adult GLILD. This is not an evidence based treatment guideline, but it does permit individual centres to compare their management against consensus. We hope that the statements made below will be supported or challenged by future research in this neglected condition. The consensus is derived from 33 consultants working across 13 centres currently providing care to over 100 patients with GLILD, with contributions from Immunology, Respiratory Medicine, Radiology and Pathology. It is therefore the largest record of shared experience in managing GLILD reported to date.

We propose that GLILD should be defined as ***“a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded”***. There was consensus that GLILD is usually seen in the context of multi-system granulomatous and/or inflammatory disease [6]. Only by agreeing a definition can the field move forward with rational experimental studies. Operationally, this implies that a confirmed diagnosis of GLILD requires both pertinent CT and histo-pathological abnormalities. The diagnosis may be suspected, but not confirmed, when the CT changes are considered typical but no biopsy has been performed.

Patients with GLILD may or may not be symptomatic. Only abnormalities on chest CT scan were felt essential for the diagnosis, with chest x-ray insufficiently sensitive. Our results support the need to screen patients with CVID for lung complications. The work-up of suspected GLILD requires contiguous thin-slice CT chest, full lung function tests (for subsequent monitoring), flexible bronchoscopy to exclude infection and surgical lung biopsy (VATS) to confirm the diagnosis and exclude differential diagnoses. There was not consensus around the use of BAL lymphocyte phenotyping, reflecting on-going controversy in the literature [12, 13], nor around the use of trans-bronchial biopsy for which yield has been reported to be variable [14] or endoscopic bronchial ultrasound (EBUS) for lymph node sampling. Further studies are required to establish the feasibility of less invasive diagnostic strategies.

The radiological, and histo-pathological differential diagnosis includes infection, organising pneumonia, LIP due to other causes/associations and sarcoidosis. Lymphoma is an additional radiological differential. These results are consistent with previous reports of the radiological features observed in GLILD [15], and a recent report describing the heterogeneity of histo-pathological findings in GLILD [16]. However, there was consensus that biopsy features were sufficiently typical to make a confident diagnosis in a person known to have primary immunodeficiency. We defined consensus that lung biopsy specimens should be stained for CD3, CD4, CD8 and CD20, for the presence of bacteria including *Mycobacteria* and for fungi, and for clonality to exclude lymphoma. The differential diagnosis of LIP and sarcoid emphasises the importance of assessing serum immunoglobulins in patients presenting with these conditions, to exclude primary immunodeficiency. In contrast to GLILD, sarcoid is typically associated with hypergammaglobulinaemia, hilar adenopathy and specific (upper zone predominant) distribution of nodules within the lung. Further work is required to confirm whether differences in BAL lymphocyte subsets are able to differentiate sarcoid from GLILD [12,13]. The diagnostic work up of granulomatous lung disease outside the context of known CVID would include a full occupational and exposure history, imaging, and autoimmune screen.

Immunoglobulin replacement should be optimised to standard guidelines prior to the initiation of therapy for GLILD. A major current limitation is the absence of information on the natural history of GLILD, but it has been reported that disease may progress despite optimal immunoglobulin replacement [17] which provides a rationale for active therapy. On-going observational studies such as STILPAD will inform further on this. We were not able to reach consensus on whether initial expectant management was an acceptable treatment option which therefore remains an open research question, of particular relevance for asymptomatic patients. There was consensus to treat patients irrespective of symptoms in the presence of abnormal and deteriorating lung function (as described further below, and of the order of a 20% reduction in gas transfer), and also to commence treatment in those who were symptomatic with normal but deteriorating lung function. Further work is required on biomarkers of disease progression, for example IgM and/or thrombocytopaenia [18]. We recognise that in current clinical practice, and the absence of screening for GLILD in CVID, many patients may have been managed 'expectantly' because their lung disease has not (yet) been recognised.

There was consensus that when specific treatment for GLILD was recommended, initial treatment should be with oral corticosteroids alone, despite a restricted evidence basis for such practice. Steroids have been used in GLILD for many years [9, 14]. The median (IQR) dose of prednisone equivalent deemed appropriate for a 70kg subject was 40 (30-70) mg/day. Preferred second line agents, alone or in combination with corticosteroids, were azathioprine, rituximab and mycophenolate. Published case series are available to support the use of combination azathioprine

and rituximab [8] and mycophenolate [19]. There was no consensus for other therapeutic approaches, including bone-marrow transplantation, and interventions for which case reports or case series do exist including ciclosporin [20], anti-TNF therapy [21, 22], and abatacept (in the context of LRBA/CTLA-4 deficiency [10]). However, no prospective randomised trials have been undertaken to date, and the largest case series of second line therapy describes only seven patients [8]. Our results suggest that many other therapies had been tried, without published evidence of success or otherwise. It is important that as a community we report the results of trials of novel agents, whether or not they are associated with therapeutic success. Immunosuppression appears to be associated with an increased risk of opportunistic as well as conventional infections in this already immunodeficient cohort but there was no consensus on the routine use of anti-microbial prophylaxis. There was also no consensus on the approach to management of disease that is clinically stable, with some clinicians preferring to continue treatment and others to withdraw, with continued treatment consisting of corticosteroids and/or second line agents. We recognise that treatment needs to be individualised, including taking account of co-morbidities, and that treatment of other manifestations of immune-mediated and inflammatory complications of CVID may complicate the treatment of GLILD.

Treatment response or progression should be assessed using change in symptoms, lung function and imaging. There are no currently accepted scores to measure symptoms (if present) in GLILD (although validated scores exist for both breathlessness (such as the MRC scale) and cough (such as the Leicester Cough Questionnaire). We suggest the need for a validated Patient-Reported Outcome Measure in GLILD. Although there was most support for imaging as the optimal modality to detect treatment response or progression, a reluctance to perform repeat CT scanning meant the preferred test to assess progression and/or response to therapy was gas transfer. A change in gas transfer of the order of 20% was generally considered significant, assessed not more than three months after starting therapy. It is important to note that a 'normal' lung function measurement does not exclude significant deterioration if a patient previously had supra-normal physiology. What little data have been published would suggest that vital capacity in GLILD remains stable over time [6]. CT, if repeated, was generally performed after 4-6 months of therapy. It was noted that chest x-ray may be used to monitor disease, if changes are initially visible. Monitoring in stable disease was typically every 3-6 months.

Reflecting the complexity of management decisions, and the uncertainty inherent in treatment and monitoring, there was strong support for management decisions being made in a multi-disciplinary meeting and clinic, with access to specialist nursing and psychological support as necessary. Uncertainty in management also mandates the need for further research. This Delphi process has been necessary because of the current absence of robust evidence on which to base clinical decisions in GLILD. We included an additional question on research priorities in our survey. The two most frequent responses were a trial of expectant versus immediate management and, for immediate management, a randomised trial of corticosteroid versus combination therapy, or a second line agent alone, most frequently rituximab.

There are strengths and weaknesses of the Delphi method. Key strengths include participant anonymity, and the opportunity to revise opinions in the light of group results. Delphi is well suited to the development of consensus documents [11]. Potential disadvantages include low response rates, the time taken to complete the questionnaires (typically 20 minutes for Round 2 in this case), and the risk that the way feedback is presented can lead to convergence. Our participants were a large group of self-selected experts involved in the management of GLILD, including consultant immunologists, chest physicians, radiologists and pathologists. All UK centres managing GLILD were

invited to take part. However, individual experience remains limited, even in larger centres, and the process reports an average of such limited experience with the potential for convergence of opinion. It must also be recognised that the definition of consensus used, although defined *a priori*, is arbitrary [23], and this is why we have elected to present the actual scores with standard deviation in this report. Our definition of consensus at ≥80% is above, and therefore more robust than the 75% median reported in a systematic review [23].

GLILD is not new, with the first report of LIP in the context of hypogammaglobulinaemia dating back to 1973 [24]. However, whilst previously neglected, there is now increasing interest. We recognise it is likely that on-going genetic studies will dissect the heterogeneity of CVID, and may provide the basis for a future 'precision medicine' approach to treat the complications of CVID, including interstitial lung disease. Already this is reaching the clinic, for example GLILD in the context of CTLA4 deficiency [25, 26] being treated with abatacept [10]. The future may therefore see a move away from the term GLILD, and it is already recognised that a subset of patients with CVID are more likely to experience lung complications: those with LOCID (Late-Onset Combined Immunodeficiency) [27]. However, the timeframe and feasibility of novel approaches remain undefined, and there is a current clinical imperative to establish the optimal treatment for GLILD for the benefit of our patients. As noted above, important observational cohort studies in GLILD, notably STILPAD, are currently in progress and these will also inform future treatment and management strategies. Finally, it is possible that a deeper understanding of the pathogenesis of auto-immune / auto-inflammatory pathology in GLILD may inform on the pathogenic mechanisms of other interstitial lung diseases. Meanwhile, we present this consensus statement to the community to promote debate. Most importantly, we aim to facilitate and support further research. Only by doing this can we move from this initial iteration of a consensus document to evidence-based treatment guidelines for people living with this neglected and challenging condition.

Conclusion

We present a consensus statement on the definition, diagnostic criteria, treatment and monitoring of GLILD in CVID, which can serve as a rational basis for experimental studies. This is the largest collection of shared clinical experience in GLILD ever recorded.

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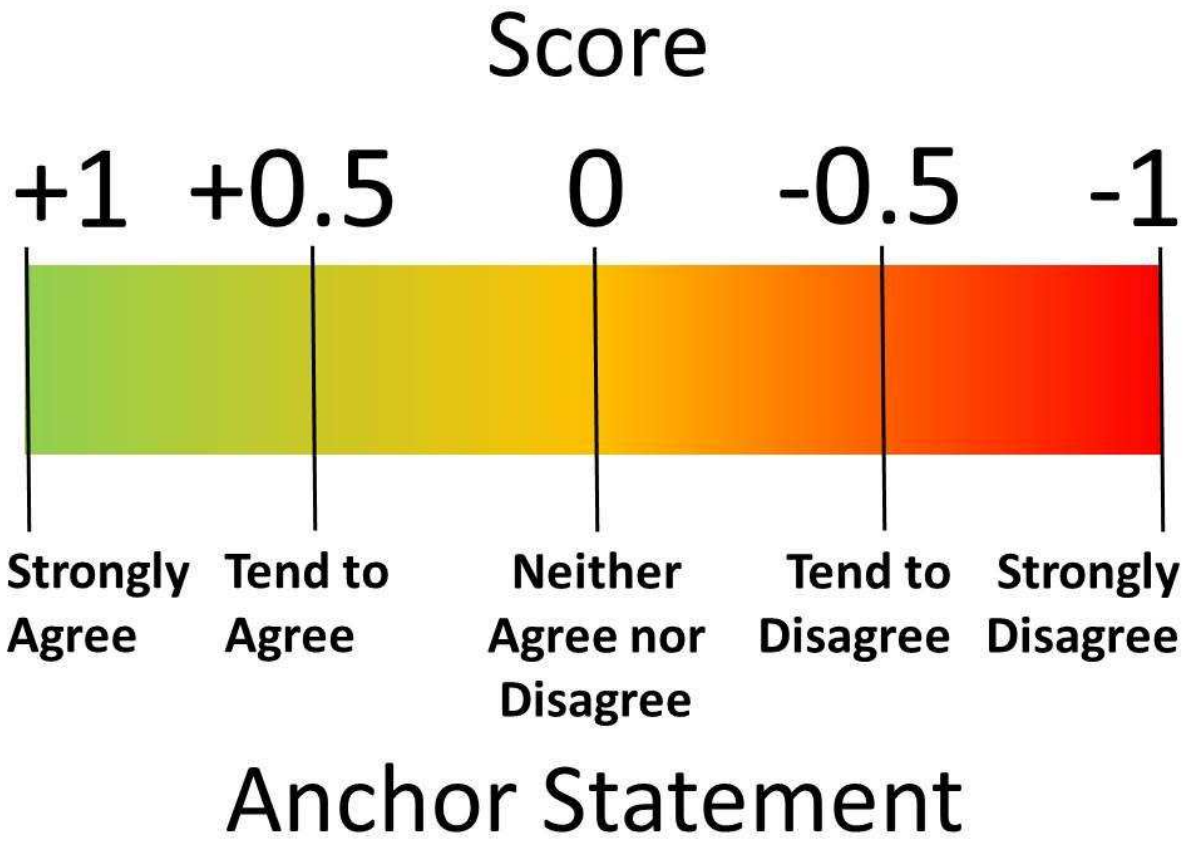
Acknowledgements

We are grateful to the British Lung Foundation for funding this work (grant reference PPRG15-7), and the UK Primary Immunodeficiency Network for facilitating the consensus process. We thank the Peer Reviewers for the helpful comments received.

Figure Legend

FIGURE 1: *Anchor Statements and Scoring.*



Tables

TABLE 1: *Consensus on diagnostic work-up of GLILD.*

Criteria	Number of Respondents	% Agree	% Disagree	Mean (SD) Score*
"The following tests are essential in the work-up of suspected GLILD":				
CONSENSUS				
CT Thorax	24	100	0	0.98 (0.01)
Spirometry	24	96	0	0.88 (0.27)
Lung Volumes	23	91	4	0.76 (0.40)
Gas Transfer	24	100	0	0.94 (0.17)
Flexible Bronchoscopy to exclude Infection	23	83	4	0.63 (0.50)
Surgical Lung Biopsy	24	83	8	0.58 (0.46)
NO CONSENSUS				
Chest Radiograph	23	65	9	0.48 (0.57)
MRI Chest	21	0	48	-0.40 (0.46)
Peripheral Oxygen Saturation	23	74	13	0.52 (0.65)
6 minute or Shuttle Walk Test	24	58	17	0.31 (0.57)
Cardio-Pulmonary Exercise Test	23	0	57	-0.39 (0.40)
Echocardiogram	24	33	29	0.06 (0.60)
Serum CRP	23	52	26	0.15 (0.65)
Serum β2-microglobulin	24	29	38	-0.06 (0.58)
Serum ACE	24	50	25	0.25 (0.68)
Serum IgM	24	29	25	0.04 (0.55)
Percentage $CD21^{low}$ B Cells	24	33	25	0.02 (0.40)
Trans-Bronchial Biopsy	23	61	17	0.39 (0.62)
Broncho-Alveolar Lavage Cell Differential	24	63	4	0.44 (0.52)
Broncho-Alveolar Lavage Immuno-phenotyping	23	30	17	0.00 (0.48)

**: see text. Scale of -1 (strongly disagree) to +1 (strongly agree), more extreme scores and smaller standard deviation indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.*

TABLE 2: *Consensus on diagnostic testing of broncho-alveolar lavage fluid obtained at flexible bronchoscopy for the investigation of suspected GLILD.*

Criteria	Number of Respondents	% Agree	% Disagree	Mean (SD) Score*
The following tests are essential in analysis of broncho-alveolar lavage from suspected GLILD:				
CONSENSUS				
BAL Microscopy and Culture	23	96	0	0.93 (0.23)
BAL *Mycobacterial* Culture	23	96	0	0.93 (0.23)
BAL Fungal Culture	23	91	0	0.80 (0.33)
NO CONSENSUS				
BAL PCR for *Mycobacteria*	23	61	9	0.46 (0.58)
BAL PCR for atypical bacteria	23	70	9	0.50 (0.50)
BAL PCR for respiratory viruses	23	74	4	0.61 (0.48)
BAL PCR for *Pneumocystis jirovecii*	22	64	14	0.36 (0.56)
BAL Silver stain or immunofluorescence for *Pneumocystis jirovecii*	21	48	10	0.31 (0.49)

**: see text. Scale of -1 (strongly disagree) to +1 (strongly agree), more extreme scores and smaller standard deviation indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.*

TABLE 3: *Differential Diagnosis of GLILD.*

Criteria	Number of Respondents	% Agree	% Disagree	Mean (SD) Score*
"The differential diagnosis of GLILD on Radiology includes":				
CONSENSUS				
Infection	25	96	4	0.72 (0.36)
Organising Pneumonia	26	92	4	0.65 (0.37)
Lymphoid Interstitial Pneumonia	26	81	12	0.52 (0.54)
Sarcoidosis	26	88	12	0.62 (0.48)
Lymphoma	26	96	0	0.69 (0.29)
NO CONSENSUS				
Non-Specific Interstitial Pneumonia	24	63	17	0.31 (0.55)
Vasculitis	25	40	32	0.12 (0.55)
Invasive Mucinous Adenocarcinoma	25	32	32	0.04 (0.54)
Pulmonary Metastases	25	28	64	-0.16 (0.55)
"The differential diagnosis of GLILD on Histo-Pathology includes":				
CONSENSUS:				
Infection	26	94	6	0.81 (0.39)
Organising Pneumonia	20	95	5	0.63 (0.43)
Lymphoid Interstitial Pneumonia	20	80	5	0.70 (0.47)
Sarcoidosis	22	95	5	0.75 (0.37)
NO CONSENSUS				
Non-Specific Interstitial Pneumonia	19	63	0	0.47 (0.42)
Usual Interstitial Pneumonia	19	42	37	0.11 (0.70)
Follicular Bronchitis	18	72	6	0.53 (0.47)
Hypersensitivity Pneumonia	20	70	15	0.38 (0.56)

**: see text. Scale of -1 (strongly disagree) to +1 (strongly agree), more extreme scores and smaller standard deviation indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.*

TABLE 4: *Consensus on second line drug therapy in GLILD.*

Criteria	Number of Respondents	% Agree	% Disagree	Mean (SD) Score*
Which of the following drugs would you consider as second line therapy in GLILD?				
CONSENSUS				
azathioprine	21	100	0	0.71 (0.25)
rituximab	21	90	5	0.67 (0.40)
mycophenolate	21	81	5	0.62 (0.44)
NO CONSENSUS				
abatacept	18	33	28	0.03 (0.50)
anti-TNF agents	17	29	47	-0.12 (0.57)
ciclosporin	16	25	25	0.00 (0.48)
hydroxyxchloroquine	19	42	32	0.07 (0.56)
methotrexate	17	35	29	0.03 (0.51)
sirolimus	18	28	28	0.03 (0.53)
tacrolimus	18	22	33	-0.08 (0.43)

**: see text. Scale of -1 (strongly disagree) to +1 (strongly agree), more extreme scores and smaller standard deviation indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.*