On demand corticosteroid use in the syndrome of undifferentiated recurrent fever: a literature review and results from JIR-CLiPS survey study

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Abstract

Objective

We aimed to analyse the strategies of physicians regarding corticosteroid use in syndrome of undifferentiated recurrent fever (SURF) and examine the published data on this topic.

Methods

The JIR-CliPS questionnaire which addresses physicians' practices about on demand corticosteroid use in SURF was distributed via e-mail to potential respondents. We systematically reviewed the MEDLINE and Scopus databases and extracted the data about on demand corticosteroid use in SURF.

Results

One hundred thirty-seven physicians (F/M=2.5; 66.4% paediatric rheumatologists) from 45 countries responded to the survey. Around 70% of physicians prescribe corticosteroids for SURF flares. Most physicians (81.9%) do not use corticosteroids in SURF patients routinely, and this practice is more common among less experienced physicians ($p<0.001$). Prednisolone at a dose of 1 mg/kg (54.4%) was the most commonly preferred corticosteroid. The most common definition of response to corticosteroids was "response within 12 hours" (51.6%). Most respondents (59.5%) consider changing treatment if corticosteroids cause a decrease in quality of life.
We found 10 articles in the literature describing 239 SURF patients treated with on demand corticosteroids. The most frequently preferred corticosteroid was prednisolone (63.8%). The response to corticosteroids was 70.8% and an increase in attack frequency was observed in almost 40% of patients.

Conclusion

On demand corticosteroid use is not uncommon in the acute management of SURF attacks. However, most physicians do not use corticosteroids routinely and there is no consensus regarding the definition of response to treatment and when to change treatment neither in our survey results nor in the literature.

Key words

autoinflammatory disease, corticosteroid, steroid, syndrome of undifferentiated recurrent fever, treatment

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Introduction

Systemic autoinflammatory diseases (SAIDs) are characterised by inflammation driven by innate immunity dysregulation (1). The most common monogenic SAIDs are familial Mediterranean fever (FMF), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), cryopyrin associated periodic syndrome (CAPS), and tumour necrosis factor receptor associated periodic syndrome (TRAPS) (2, 3). On the other hand, periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome is the most frequent multifactorial SAID especially among children (4).

Despite great advances in genetic analysis during the last decades, a monogenic aetiology cannot be identified in almost two-thirds of SAIDs (3). While chronic inflammation predominates the phenotype in some undifferentiated SAIDs (USAIDs), recurrent fever episodes are the main common feature for others. The subgroup of USAIDs characterised with febrile flares of inflammation is called as syndrome of undifferentiated recurrent fever (SURF) (5). SURF patients lack specific features of PFAPA syndrome and pathogenic variants or VUS on periodic fever genes (5). There are no widely accepted treatment recommendations for SURF patients.

On demand corticosteroids form the mainstay of acute treatment in PFAPA episodes (4). In around 85-90% of PFAPA patients, single dose corticosteroids lead to an abrupt cessation of fever (4). On demand corticosteroids could also work for some patients with HIDS/MKD (6). Although the response rate does not seem to be as high as that observed in PFAPA patients, on demand corticosteroids may be beneficial during attacks in SURF patients.

There is no previous study that focused on demand corticosteroid use in SURF patients. Our aim was to evaluate the practices of physicians worldwide regarding on demand corticosteroid use in SURF and to analyse the published data on this topic.

Materials and methods

Questionnaire about on demand corticosteroid use in SURF

This study is an international, online, cross-sectional survey study included in the JIR-CliPS project. The general aim of this project is to analyse the real-life Clinical Practice Strategies (CliPS) in five conditions: paediatric vasculitis (Kawasaki disease and immunoglobulin A vasculitis), paediatric lupus nephritis, and three autoinflammatory diseases as systemic juvenile idiopathic arthritis/adult-onset Still's disease, biological treatment in monogenic autoinflammatory diseases, and PFAPA/SURF. The SURF questionnaire was developed by the JIR-CliPS PFAPA/SURF team, and it includes a total of 42 questions. Addressing the objectives of this study, we analysed the responses to nine questions of the survey that focused on corticosteroid use in SURF, in addition to the seven questions about the demographic features of the respondents (Supplementary Table S1). We evaluated the responses between January 27th and May 31st, 2024, but the survey is still accessible to new respondents. It is noteworthy that each respondent could fill the survey only once.

Data collection was in accordance with the General Data Protection Regulation (GDPR) law. And, ethical approval was not required for this study.

Systematic literature review

Two authors (EDB and SS) systematically searched the MEDLINE and Scopus databases from their inception until June 16th, 2024, according to the PRISMA guidelines (7). The following keywords were used during the literature search: syndrome of undifferentiated recurrent fever, SURF, undifferentiated systemic autoinflammatory disease, USAID, steroid, corticosteroid, glucocorticoid, prednisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, deflazacort, and hydrocortisone. We analysed only English articles and hand-searched the references of the included articles. The studies that included data regarding on demand corticosteroid use in SURF were included. Figure 1 shows the

flowchart of the systematic literature review.

The following data were extracted from the included articles: number of patients, demographic and clinical features, type of corticosteroid, dose, the number of doses per flare, treatment duration, response, and adverse events.

Statistical analysis

The descriptive analysis of the responses was performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Ratios and percentages were used to present categorical variables and continuous data were described in median and minimum-maximum values. The Chi-square test or Fisher's exact test were used to compare categorical variables, as appropriate. A *p*-value below 0.05 was regarded as statistically significant.

Results

Results of the JIR-CliPS survey

One hundred thirty-seven of 298 physicians who responded the PFAPA/SURF survey answered questions regarding on demand corticosteroid use in SURF (Table I). They were from 45 different countries (Supplementary Fig. S1) and 71.3% were female. The majority (85.4%) provided care for pediatric patients only. Most respondents were pediatric rheumatologists (66.4%), and 56.9% of them had ≥10-year experience with patients who have recurrent fever (Table I).

Ninety-seven participants (70.8%) prescribe corticosteroids at the onset of a SURF flare. Prednisolone was the most commonly used corticosteroid (62.8%), followed by prednisone (52.6%). The most frequently chosen prednisone equivalent dose was 1 mg/kg (54.4%), followed by 0.67 mg/kg (10.4%).

Most physicians (81.9%) state that they do not use corticosteroids in SURF patients routinely (Table II). Among them, the most common factor influencing the decision to use corticosteroids during a flare was the severity of the attack (54.1%). The frequency of physicians using on demand corticosteroids routinely in SURF management was higher among those with ≥10-year

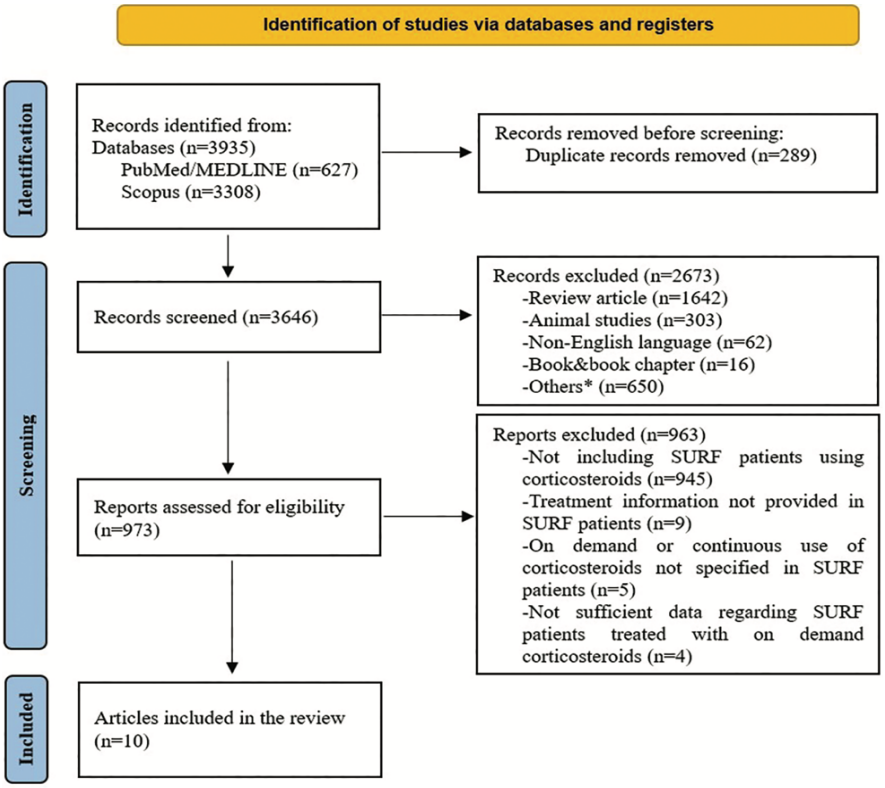

Fig. 1. The PRISMA flow diagram of literature screening regarding syndrome of undifferentiated recurrent fever (SURF) patients using on demand corticosteroids.
*Letter, editorial, conference paper, guideline, short survey, note, commentary, poster.
SURF: syndrome of undifferentiated recurrent fever.

Table I. General characteristics of the participants who responded to the questions of the JIR-CliPS survey regarding corticosteroid use in SURF (n=137).

Demographic features	n (%)
Sex, female	97/136 (71.3)
Country	
Turkey	29 (21.2)
France	21 (15.3)
Brazil	12 (8.8)
Germany	9 (6.6)
United Kingdom	6 (4.4)
Other countries*	60 (43.8)
Institution type	
University hospital	88 (64.2)
Tertiary hospital	21 (15.3)
Hospital	21 (15.3)
Private practice	5 (3.6)
Others*	2 (1.5)
Taking care of inpatients or outpatients	
Both outpatients and inpatients	130 (94.9)
Only outpatients	7 (5.1)
Taking care of paediatric or adult patients	
Only children	117 (85.4)
Both children and adults	14 (10.2)
Only adults	6 (4.4)
Specialty	
Paediatric rheumatology	91 (66.4)
Paediatric rheumatology and immunology	14 (10.2)
Paediatrician	7 (5.1)
Others*	25 (18.2)
Experience in the care of patients with recurrent fever	
≥10 years	78 (56.9)
5-9 years	40 (29.2)
0-4 years	19 (13.9)

SURF: syndrome of undifferentiated recurrent fever.
*less than five respondents per individual country.

Table II. The responses to the survey questions regarding on demand corticosteroid use in syndrome of undifferentiated recurrent fever (SURF).

Parameters, n (%)	All responders (n = 137)	Responders with <10-year experience (n = 59)	Responders with ≥10-year experience (n = 78)	*p*-value*
How do you prescribe a treatment with a steroid dose at flare-onset?				
Routinely	24/133 (18.1)	6/58 (10.3)	18/75 (24)	0.042
Not routinely	109/133 (81.9)	52/58 (89.7)	57/75 (76)	0.042
Depending on attack severity	72/133 (54.1)	28/58 (48.3)	44/75 (58.7)	0.098
When antipyretics are not enough to control fever	41/133 (30.8)	17/58 (29.3)	22/75 (33.3)	0.435
Depending on attack frequency	38/133 (28.6)	16/58 (27.6)	22/75 (33.3)	0.357
Depending on family preferences	28/133 (21.1)	11/58 (18.9)	17/75 (22.7)	0.309
Only once, to confirm diagnosis	23/133 (17.3)	13/58 (22.4)	9/75 (12)	0.074
Others	11/133 (8.3)	5/58 (8.6)	6/75 (8)	0.981
How many doses per flare?				
1 or 2, depending on the response	100/127 (78.7)	36/54 (66.7)	64/73 (87.7)	0.015
Only 1 dose	27/127 (21.3)	18/54 (33.3)	9/73 (12.3)	0.015
Do you use any forms of steroids that are suitable for young children (*e.g.*, suspension, drops, etc.)?				
Yes	101 (73.7)	32 (54.2)	69 (88.5)	<0.001
No	36 (26.3)	27 (45.8)	9 (11.5)	<0.001
What is the maximum steroid uses that you recommend per year?				
<5	50/136 (36.8)	27 (46.6)	23/77 (29.9)	0.217
5 to 10	66/136 (48.5)	25 (43.1)	41/77 (53.2)	0.138
>10	20/136 (14.7)	7 (12.1)	13/77 (16.9)	0.243
When do you consider that the patients responded to a steroid dose at flare-onset?				
Response within 3-4 hours	17/128 (13.3)	9/55 (16.4)	8/73 (10.9)	0.341
Response within 12 hours	66/128 (51.6)	23/55 (41.8)	43/73 (58.9)	0.103
Response within 24 hours	45/128 (35.1)	23/55 (41.8)	22/73 (30.1)	0.297
On which criteria would you consider that the patient did not respond?				
Need for more than 2 doses of steroid per episode	69/133 (51.9)	27/57 (47.4)	42/75 (56)	0.194
No improvement in fever within 24 hours	68/133 (51.1)	31/57 (54.4)	37/75 (49.3)	0.562
Improvement in fever but fever recurs within the same episode after the steroid dose	49/133 (36.8)	26/57 (45.6)	23/75 (31.9)	0.081
No improvement in fever within 12 hours	26/133 (19.5)	11/57 (19.3)	15/75 (20)	0.835
Need for more than 1 dose of steroid per episode	11/133 (8.3)	5/57 (8.8)	6/75 (8)	0.649
No improvement in fever within 3-4 hours	9/133 (6.8)	5/57 (8.8)	4/75 (5.3)	0.672
Others	4/133 (3.1)	1/57 (1.5)	3/75 (4)	0.153
If steroids at flare-onset decrease the intervals between the flares, based on which criteria would you consider another treatment?				
If decreased the quality of life	78/131 (59.5)	33/57 (57.9)	45/74 (60.8)	0.716
Flare interval shorter than 2 weeks	47/131 (35.9)	21/57 (36.8)	26/74 (35.1)	0.902
Decrease in attack intervals persisting for >3 months	40/131 (30.5)	19/57 (33.3)	21/74 (28.4)	0.357
Only if severe attacks	33/131 (25.2)	16/57 (28.1)	17/74 (22.9)	0.741
Flare interval shorter than 3 weeks	29/131 (22.1)	9/57 (15.8)	21/74 (28.4)	0.069
Flare interval shorter than 4 weeks	29/131 (22.1)	17/57 (29.8)	13/74 (17.6)	0.094
Decrease in attack intervals persisting for >6 months	27/131 (20.6)	11/57 (19.3)	16/74 (21.6)	0.643
Decrease in attack intervals persisting for >1 year	5/131 (3.8)	2/57 (3.5)	3/74 (4)	0.947
Others	7/131 (5.3)	2/57 (3.5)	5/74 (6.8)	0.183

*p-values are for the comparison between respondents with <10-year and ≥10-year experience.

experience compared to less experienced ones (24% *vs*. 10.3%; $p<0.001$) (Table II).

Most of the respondents prefer 1 or 2 doses of corticosteroids, depending on the response (78.7%) (Table II). The percentage of physicians preferring 1 or 2 doses over single dose was higher among those with ≥10 years of experience than less-experienced respondents (87.7% *vs*. 66.7%; $p=0.015$) (Table II). The most common maximum number of corticosteroid doses per year was 5 to 10 (48.5%).

''Response within 12 hours'' (51.6%) was the most frequent definition for response to corticosteroid dose at flare onset (Table II). Around half of the physicians agreed that the patient was not responding to corticosteroids if the patient needed >2 doses of corticosteroids per flare (51.9%) or there was no improvement in fever within 24 hours (51.1%). When corticosteroid use leads

Table III. General characteristics of patients with syndrome of undifferentiated recurrent fever (SURF) treated with on demand corticosteroids in the literature.

Characteristics	n (%) or median (min-max)
Total number of patients	498
Number of patients treated with CS	239
Age at diagnosis, years	3.7 (0-35)
Sex, female	12/32 (37.5)
Clinical features	
• Fever	32/32 (100)
• Abdominal pain	18/32 (56.3)
• Headache	14/32 (43.8)
• Nausea/vomiting	11/32 (34.4)
• Pharyngitis/tonsillitis	10/32 (31.3)
• Cervical lymphadenopathy	8/32 (25.8)
• Aphthous stomatitis	8/32 (25.8)
• Arthralgia	7/32 (21.9)
• Ocular symptoms	6/32 (18.8)
• Rash	6/32 (18.8)
• Myalgia	3/32 (9.4)
• Constitutional symptoms	3/32 (9.4)
Duration of febrile episode, days	4.3 (2-30)
Interval between febrile episodes, weeks	7.8 (2-25.7)
Type of CS	
• Prednisolone	30/47 (63.8)
• Betamethasone	16/47 (34.1)
• Methylprednisolone	1/47 (2.1)
Doses of CS*	
• 0.5 mg/kg	1/81 (1.2)
• 0.5-1 mg/kg	46/81 (56.8)
• ≤1 mg/kg	29/81 (35.8)
• >1 mg/kg	5/81 6.2)
Response to CS in a SURF episode	
Improvement	136/192 (70.8)
No improvement	56/192 (29.2)
Concomitant therapy with CS	
Colchicine	15/25 (60)

CS: corticosteroid; SURF: syndrome of undifferentiated recurrent fever.
*prednisone equivalent.

to an increase in flare frequency, a decrease in patient's quality of life is the most common reason for preferring a different treatment (59.5%).

Results of the literature review

We reviewed the literature and identified 10 articles containing 239 SURF patients treated with on demand corticosteroids (Fig. 1) (5, 8-16). The definitions of SURF and the inclusion/exclusion criteria for SURF patients are presented in Supplementary Table S2, while Supplementary Table S3 details these patients' characteristics.

Age and sex were reported in only four studies (11-14); the median (min.-max.) age of the patients was 3.7 (0-35) years and 37.5% of the patients were female (Table III). Among the patients whose clinical features were specified, all had fever (100%), and other common symptoms included abdominal pain (56.3%), headache (43.8%), nausea/vomiting (34.4%) and pharyngitis/tonsillitis (31.3%) (11-14).

In the five articles where corticosteroid type and dose were reported, the most commonly used corticosteroid type was prednisolone (63.8%), while the most commonly preferred corticosteroid dose was 0.5-1 mg/kg prednisone equivalent (56.8%) (8, 10, 11, 13, 14). The number of corticosteroid doses per SURF flare was reported as 1 dose in only one article (13). The definition of response to corticosteroids during a SURF flare was given in only one article as "resolution of symptoms with a single dose of steroid" (13). The corticosteroid response rate which was reported in seven articles was 70.8% (5, 8, 9, 12-15). An increase in attack frequency after on demand corticosteroid use was mentioned only in one case reported by Harrison *et al*. (11) and in eight of 21 cases (38.1%) reported by De Pauli *et al*. (8). Corticosteroid side effects were not addressed in any of the articles except one where the authors stated that no side effects were observed in a SURF patient using on-demand corticosteroids (11). Colchicine (60%) was the most common concomitant therapy (8, 11, 12, 14).

Discussion

To our knowledge, this is the first study in the literature that focus on on-demand corticosteroid use in SURF. Our results show that on demand corticosteroid use is not uncommon in SURF management. However, most physicians do not use corticosteroids routinely and the most important factor affecting this treatment decision is the attack severity. On the other hand, quality of life of the patients is a significant consideration for physicians while deciding to switch to another treatment. The presented literature review revealed a response rate of 70.8% for on-demand corticosteroids in SURF.

SURF is defined as a subgroup of USAIDs primarily characterised by recurrent fever episodes, while USAIDs include systemic inflammation that may affect multiple organ systems (5). Both are diagnosed by exclusion of other SAIDs, meaning other causes of recurring fever or inflammation must be ruled out before reaching a diagnosis (17). They both lack specific genetic or clinical markers, making classifying them under established autoinflammatory diseases challenging (17). Their management focuses on controlling inflammation and symptoms, treatment plans are often personalised.

There are no clear recommendations regarding SURF management since its aetiopathogenesis remains unknown. On demand corticosteroids, colchicine, and biologic drugs (mainly anti-interleukin 1 agents) are among the main

therapeutic options (5). Our results show that more than two-thirds of physicians use on demand corticosteroids in SURF treatment. Previous studies showed that colchicine was one of the most frequently used drugs in SURF treatment with a complete response rate higher than 50% (5, 18). While colchicine is mainly used for preventing attacks, on demand corticosteroids are a more acute treatment which aims to abort inflammatory flares. We know that successive corticosteroid use may cause an increase in attack frequency in PFAPA syndrome (4, 19). Whether the same impact is present in SURF patients remains to be elucidated. There are a few reports of increased attack frequency after on demand corticosteroid use in SURF (8, 11). However, long term data is not present.

The corticosteroid response rate derived from the literature review was 70.8% in our study. In PFAPA syndrome, on the other hand, a response rate around 85-95% is observed (4, 19). Although it is challenging to make a direct comparison between these rates, inconsistent response to on demand corticosteroids could be counted among the features differentiating SURF from PFAPA syndrome. PFAPA represents a more homogeneous phenotype with specific clinical features compared to SURF. SURF is a less well-defined and heterogeneous entity which may involve more complex or diverse immune mechanisms that do not respond to corticosteroids. Also, although a specific monogenic cause has not been identified in SURF patients, there could still be an overlap with monogenic SAIDs where corticosteroids are less effective than they are in PFAPA syndrome. Previous studies showed that more than half of SURF patients respond well to colchicine (5, 18). SURF patients with a good colchicine response may represent a more homogeneous subgroup of SURF. For instance, generalised lymphadenopathy was less frequently observed among colchicine-responsive SURF patients (18).

The main limitation of this study is inherent to the bias introduced by the characteristics of the respondents. Since the majority of the respondents were paediatric rheumatologists and physicians who take care of only children, the perspectives of general practitioners, paediatricians, and adult care specialists are not equivalently represented. However, paediatric rheumatology is currently the main subspecialty that focus on the care of SURF patients. Therefore, analysing paediatric rheumatologists' perspectives is valuable. Regarding literature review, possible overlap of cohorts from same center, underrepresentation of adult patients, the lack of specification of on demand or continuous corticosteroid use, and the absence of a widely accepted definition for SURF were the main limitations. Also, some of the studies included from the literature review are from papers published before the definition of SURF in the literature. Furthermore, while most included papers defined SURF patients in similar terms, there is no widely accepted standard for determining the 'extent' of genetic testing required before classifying patients as having SURF. Thus, SURF still represents a heterogeneous group of disorders which makes it difficult to draw strict conclusions based on the literature data.

In conclusion, the results of this study may provide some guidance for the physicians taking care of SURF patients, in the absence of clear recommendations. The presented data may also serve as a reference to be communicated to the families while prescribing on demand corticosteroids. Although the response rate is not as high as that observed in PFAPA syndrome, on demand corticosteroids seem to work for more than two-thirds of SURF patients. Prospective studies with long term follow-up will be invaluable and can shed more light to the benefits and risks of on demand corticosteroid use in SURF treatment.

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