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Etiology of Cellulitis and Clinical Prediction of Streptococcal Disease: A Prospective Study

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Background. The importance of bacteria other than group A streptococci (GAS) in different clinical presentations of cellulitis is unclear, commonly leading to treatment with broad-spectrum antibiotics. The aim of this study was to describe the etiological and clinical spectrum of cellulitis and identify clinical features predicting streptococcal etiology.

Methods. We prospectively enrolled 216 patients hospitalized with cellulitis. Clinical details were registered. Bacterial culture was performed from blood, cutaneous or subcutaneous tissue, and/or swabs from skin lesions. Paired serum samples were analyzed for anti-streptolysin O and anti-deoxyribonuclease B antibodies.

Results. Serology or blood or tissue culture confirmed β-hemolytic streptococcal (BHS) etiology in 72% (146 of 203) of cases. An additional 13% (27 of 203) of cases had probable BHS infection, indicated by penicillin response or BHS cultured from skin swabs. β-hemolytic streptococcal etiology was predominant in all clinical subgroups, including patients without sharply demarcated erythema. β-hemolytic group C or G streptococci (GCS/GGS) were more commonly isolated than GAS (36 vs 22 cases). This predominance was found in the lower extremity infections. Group C or G streptococci in swabs were associated with seropositivity just as often as GAS. *Staphylococcus aureus* was cultured from swabs as a single pathogen in 24 cases, 14 (64%) of which had confirmed BHS etiology. Individual BHS-associated clinical characteristics increased the likelihood of confirmed BHS disease only slightly; positive likelihood ratios did not exceed 2.1.

Conclusions. β-hemolytic streptococci were the dominating cause of cellulitis in all clinical subgroups and among cases with *S aureus* in cutaneous swabs. Group C or G streptococci were more frequently detected than GAS. No single clinical feature substantially increased the probability of confirmed BHS etiology.

Keywords. β-hemolytic streptococci; cellulitis; erysipelas; *Streptococcus dysgalactiae* subsp *equisimilis*; *Streptococcus pyogenes*.

Cellulitis is a common bacterial skin infection that spreads diffusely and often involves subcutaneous tissue [1–3]. The dermal, sharply demarcated variant, often called erysipelas, is almost always caused by β-hemolytic streptococci (BHS). Group A streptococcus ([GAS] *Streptococcus pyogenes*) is a major pathogen, but group B streptococcus (GBS), group C streptococcus (GCS), and group G streptococcus (GGS) may also cause erysipelas [4–6]. Studies of deeper cellulitis without sharp demarcation and studies of unspecified cellulitis indicate a more diverse etiology, and the relative importance of GAS compared with other streptococci, *Staphylococcus aureus*, and other bacterial agents is unclear [7, 8]. Furthermore, some cases present with signs of both erysipelas and deeper cellulitis [2]. To our knowledge, the etiology of these overlapping cases has not been thoroughly elucidated.

The use of different microbiological methods and inconsistent definitions of cellulitis have also contributed to the etiological uncertainty [1, 3, 9]. An important clarification states that cellulitis should not refer to the inflammation surrounding collections of pus [1, 3, 9]. Although most studies have identified BHS as the major cause of nondrainable cellulitis, the appropriateness of penicillin or other narrow-spectrum regimens as first-line treatment is still unclear, particularly for deeper cellulitis and infections requiring hospitalization [1, 10, 11]. Frequent use of broad-spectrum coverage, even for mild cases, as well as low frequency of de-escalation underscore the need for more precise knowledge of the etiology of cellulitis in different subgroups [12–14].

It is even more difficult to make a probable etiological diagnosis in every day clinical work than in a study setting. Culture is often not feasible, and if pathogenic bacteria are detected, it is often difficult to define their clinical significance [3]. Therefore, culture has been regarded as being of limited value. In addition, there is insufficient knowledge about how clinical features might be predictive of bacterial etiology in cellulitis. Purulence has been recognized as a sign that differentiates staphylococcal

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from streptococcal etiology [9]. However, purulence has neither been thoroughly evaluated nor is it a prominent sign in pure cellulitis.

The aim of this study was to describe the etiological spectrum of cellulitis and to investigate whether clinical and biochemical markers were associated with, and predictive of, BHS etiology.

PATIENTS AND METHODS

Study Population

Haukeland University Hospital is a tertiary care hospital in western Norway, and it also functions as a local hospital for approximately 300 000 inhabitants. Patients aged 18 years or older and admitted with possible skin or soft tissue infection between September 2010 and August 2014 were prospectively evaluated for inclusion. The study was approved by the Regional Committee for Ethics in Medical Research (REC West; approval no. 2010/1406). Written informed consent was obtained from all participants in the study.

Case Definition

Patients were eligible if they were hospitalized with acute diffuse erythema of the skin of presumed bacterial origin and had the following: (1) fever, chills, or reduced general condition; or (2) facial infection site. Patients were excluded if they had postoperative surgical site infection, animal/human bite, impetigo, necrotizing soft tissue infection, arthritis, osteomyelitis, mastitis, wound or ulcer with erythema extending <5 cm beyond the skin defect, tenosynovitis, or nonbacterial disease underlying the findings. Patients with drainable abscess, bursitis, or other fluid/pus collection were also excluded, whereas patients with progressive erythema after proper drainage of small purulent lesions before admission were eligible.

Clinical Characteristics

Data were obtained by detailed clinical examination and history by an infectious diseases physician (T.B., O.O., or S.S.), including review of medical records. Age, gender, potential risk factors, symptoms and their duration, clinical findings on admission (within 24 hours), clinical chemistry results, and antibiotic treatment were registered.

Bacterial Culture and Identification

On admission, blood cultures and cutaneous swabs for bacterial culture from ulcers, wounds, abrasions, fissured toe webs, or other skin lesions were obtained. For some patients, samples from normally sterile tissue were obtained for culture, either a 4 mm cutaneous punch biopsy or surgical subcutaneous samples in cases where surgical exploration was performed to rule out necrotizing infection. Identification of the bacteria was performed as part of the routine diagnostic service at the hospital. Serogroups of BHS were identified using Streptococcal Grouping Kit (Oxoid, Cambridge, UK) on large β-hemolytic colonies or bacterial species identification using mass spectrometry (matrix-assisted laser desorption/ionization time of flight).

Streptococcal Serology

An acute serum sample for streptococcal serology was collected during the hospital stay, and a convalescent serum was collected approximately 1 week after the cessation of antimicrobial therapy. Anti-streptolysin O (ASO) and anti-deoxyribonuclease B (ADB) titers were measured using nephelometry (Siemens Healthcare Diagnostics, Marburg, Germany). Titers <200 IU/mL were considered normal. Seropositivity was defined as (1) a 0.2 $\log_{10}$ rise in titer and a titer ≥200 IU/mL in the convalescent serum or (2) titers of both acute and convalescent sera ≥200 IU/mL [15].

Classification of β-Hemolytic Streptococcal Etiology

Confirmed BHS etiology was defined as ASO and/or ADB seropositivity and/or BHS in culture of blood or normally sterile tissue. Probable BHS etiology was defined as BHS in cutaneous swabs or a satisfactory response to penicillin monotherapy, defined as clinical response at end of therapy in patients who were not given other antibiotics during the course. Response was assessed by a telephone consultation 1–2 weeks after cessation of therapy.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 22, except that diagnostic accuracy analyses were calculated using an online calculator (www.medcalc.org). Categorical data were analyzed using χ^2 test or Fisher's exact test. Continuous data were presented as median with range and compared using the Mann-Whitney *U* test. All statistical tests were 2-sided. *P* values were considered significant below .05. For multivariate logistic regression analysis, variables were dichotomized based on preliminary analyses, and *P* values were calculated using the likelihood test. Variables entered into the multivariate models were chosen on the basis of low unadjusted *P* values, low multicollinearity, and objectivity. In multivariate analysis of streptococcal etiology, adjustment was also made for factors that may affect serological sensitivity or admission findings. In order to have probability measures that can be used in clinical practice independently of prevalence, positive and negative likelihood ratios (LR^+ and LR^-) were calculated in addition to sensitivity, specificity, and predictive values [16].

RESULTS

Patients

In total, 216 patients were included, 203 of whom were evaluable for β-hemolytic streptococcal etiology (Figure 1). Median age was 54.5 years (range, 18–94 years); 58% were men. Lower extremity was the most common location (57%) followed by facial (24%), upper extremity (16%), and other sites (3%).

Culture and Serology Results

Of 127 cases with cutaneous swabs, 90 had growth of Gram-positive pathogens and 5 had growth of Gram-negative bacteria alone (Figure 2A). Among BHS, GCS/GGS were more prevalent

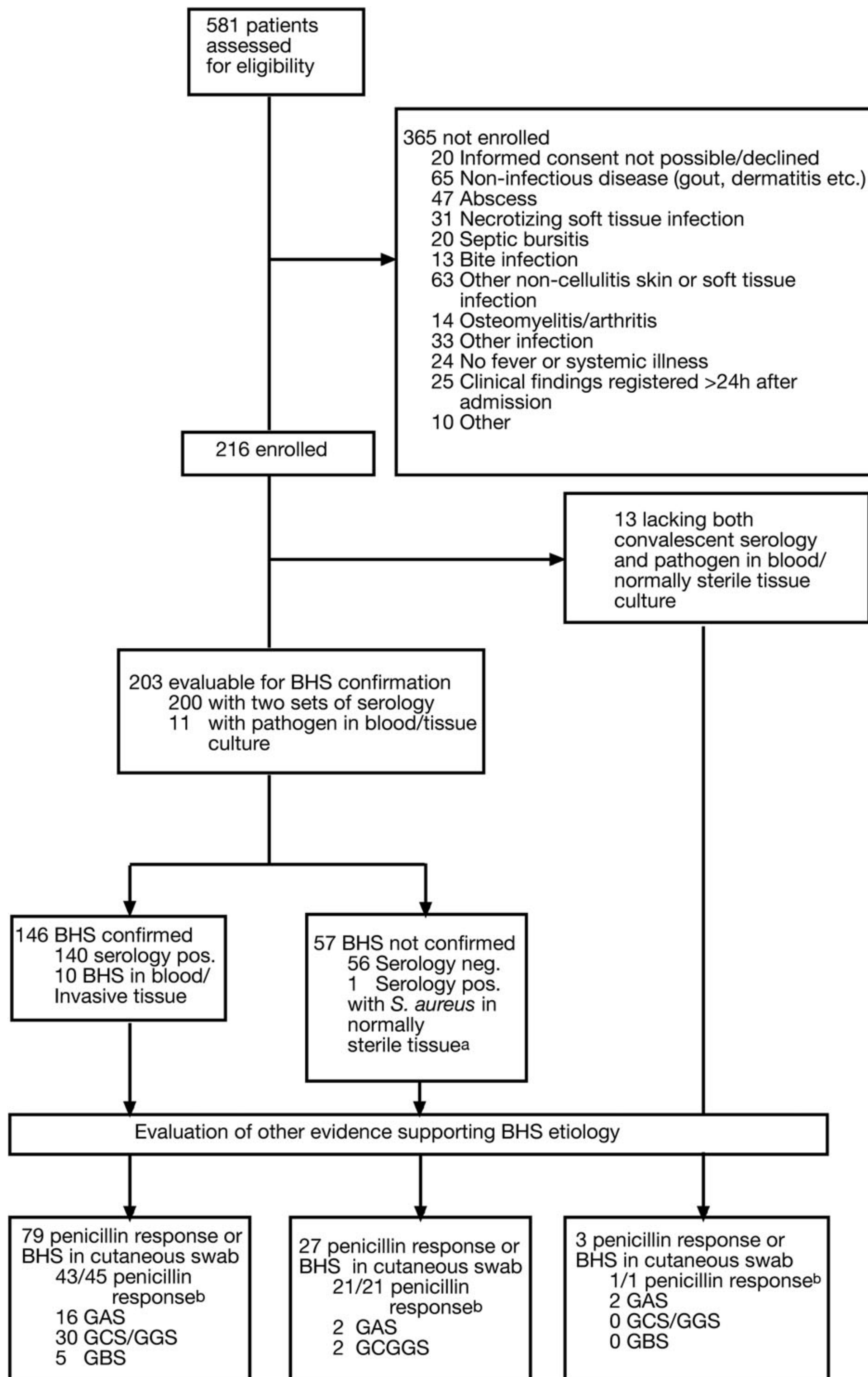
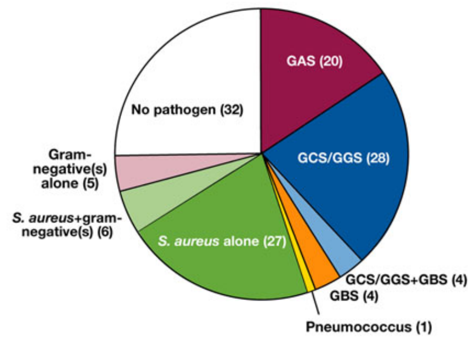


Figure 1. Flow chart of patient enrollment and evaluation for β-hemolytic streptococcal etiology. [a]One case with *Staphylococcus aureus* in culture of normally sterile tissue and 2 positive (pos.) anti-streptolysin titers without significant rise were classified as negative (neg.) concerning confirmed β-hemolytic streptococcal (BHS) disease. [b]Proportion with local clinical improvement at end of therapy among cases treated with penicillin only. Abbreviations: GAS, group A streptococcus; GBS, group B streptococcus; GCS/GGS, group C or G streptococcus.



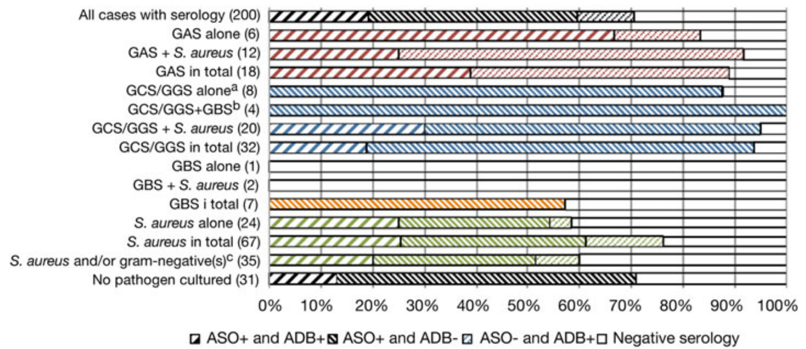


Figure 2. (A) Results of swab cultures of skin lesions in the affected body part. Coagulase-negative staphylococci, enterococci, and other bacteria interpreted as colonizers are not presented. Cases with *Staphylococcus aureus* found in addition to β-hemolytic streptococci (BHS) are not shown. This concerns 13 of 18 group A streptococcus (GAS) cases, 20 of 32 group C or G streptococcus (GCS/GGS) cases, and 4 of 8 group B streptococcus (GBS) cases. No Gram-negative bacteria were found in cases with BHS. (B) Seropositivity (see the Patients and Methods section) for streptococcal antibodies in relation to swab culture results. The number of cases (shown in parentheses) in each category of culture results is smaller than in A, because not all patients had 2 sets of serology. [a]The anti-streptolysin O (ASO)-positive/anti-deoxyribonuclease B (ADB)-negative serological pattern was specific for GCS/GGS among cases with BHS in culture. The titer rise was not significantly lower in cases with this pattern from whom GCS/GGS were not cultured. (median log rise 0.40 vs 0.47, $P = .369$). [b]Two of these cases also had growth of *S aureus*. [c]*Staphylococcus aureus* and/or Gram-negative bacteria found without other pathogens.

than GAS and GBS. *Staphylococcus aureus* was frequently isolated, often in combination with BHS (Figure 2). No methicillin-resistant *S aureus* isolates (MRSA) were found. β-hemolytic streptococci were cultured in 40% (28 of 70) of cases with swabs taken after antibiotics were started, compared with 49% (28 of 57) of cases with samples obtained before treatment ($P = .30$). Blood cultures were positive in 6 (3%) of 197 cases (GAS 3, GCS/GGS 2, GBS 1). Cultures of normally sterile tissue were positive in 6 cases (GAS 1, GCS/GGS 2, GBS 2, *S aureus* 1) and negative in 5 cases. Among the cases with tissue cultures, only the GBS case did not receive antibiotics before sampling.

Acute and convalescent sera were available in 200 cases. Positive BHS serology was found in 71% of cases; 60% of cases were positive for ASO, and 30% of cases were positive for ADB (Figure 2B). Seropositivity was 92% among cases positive for GAS or GCS/GGS in cutaneous swabs cultures compared with 63% among cases culture negative for these streptococci ($P < .0005$). The GCS/GGS cases were associated with seropositivity just as often as GAS cases (94% vs 89%) but were particularly associated with an ASO-positive/ADB-negative serological pattern. This GCS/GGS-associated pattern was also predominant among cases with cultures negative for BHS.

A multivariate analysis search for factors predicting low serological response during a streptococcal infection identified age ≥75 years (seropositivity odds ratio [OR], 0.026; 95% confidence interval [CI], .001–.479; $P = .007$) and blood leucocytes between 3.5 and 8 (OR, 0.008; 95% CI, .000–.220; $P = 0.001$) as independently associated with seronegativity in cases with GAS/GCS/GGS in culture. Immunosuppression (OR, 0.124; 95% CI, .005–2.840; $P = .173$) and area of erythema (percentage of total body surface area [TBSA%]) (OR, 1.187; 95% CI, .008–1.601; $P = .266$) were the nonsignificant factors in the model. Among cases with antibiotic treatment before admission, 93% had seropositivity compared with 88% among other cases. Therefore, this factor was not included in the model.

Confirmed and Probable Streptococcal Etiology

Serology, blood culture, and samples of normally sterile tissue confirmed BHS etiology in 146 (72%) of 203 evaluable cases (Figure 1). An additional 13% (27 of 203) had probable BHS defined by penicillin response or BHS in superficial culture, giving a total of 85% with confirmed or probable BHS etiology. Confirmed BHS etiology was found in the majority of both cases with swabs taken (92 of 121; 76%) and cases without such samples (54 of 82; 66%).

Of 35 cases with *S aureus* and/or Gram-negative bacteria as the only cultured pathogens from swab samples, 21 (60%) had BHS confirmed and 6 (17%) had probable BHS disease. *Staphylococcus aureus* was cultured as a single pathogen from 24 patients, 18 (75%) of which had confirmed or probable BHS infection. Twenty-one patients who had both penicillin-resistant *S aureus* in swabs and confirmed BHS disease were started on penicillin monotherapy. Thirteen of them continued penicillin monotherapy with good clinical response. The remaining 8 cases changed to therapy also covering *S aureus*, 5 of them within 2 days, ie, too early to indicate treatment failures.

Comorbidity and Risk Factors

Comorbidity and other risk factors were identified in the majority of cases with and without confirmed BHS (Table 1). In each subgroup of underlying factors, confirmed BHS etiology was found in half or more of the cases. Confirmed BHS etiology

Table 1. Demographics and Underlying Factors by Etiology[a]

		BHS⁺ vs BHS⁻[b]			GCS/GGS vs GAS[c]		
Characteristic	All Cases (n = 216)	BHS⁺ (n = 146)	BHS⁻ (n = 57)	*P* Value	GAS (n = 22)	GCS/GGS (N = 36)	*P* Value
Demographics							
Age ≥75 y	32 (15)	17 (12)	14 (25)	.021	2 (9)	6 (17)	.697
Male gender	126 (58)	92 (63)	27 (47)	.042	10 (46)	27 (75)	.023
Underlying condition							
Cardiovascular disease	82 (38)	60 (41)	21 (37)	.578	10 (46)	17 (47)	.896
Diabetes mellitus	28 (13)	21 (14)	7 (12)	.696	2 (9)	11 (31)	.103
Previous or active malignancy	35 (16)	21 (14)	13 (23)	.149	4 (18)	2 (6)	.187
Immunosuppression	21 (10)	12 (8)	9 (16)	.111	2 (9)	4 (11)	.589
Other general somatic disease[d]	78 (36)	49 (34)	26 (46)	.110	6 (27)	14 (39)	.366
General somatic disease in total	134 (62)	90 (62)	40 (70)	.255	15 (68)	23 (64)	.739
IDU	13/214 (6)	4/144 (3)	4 (7)	.227	0/21 (0)	1/35 (3)	1.000
Alcoholism	8/214 (4)	7/144 (5)	1 (2)	.445	1/22 (5)	1/34 (3)	1.000
BMI ≥ 30	75 (35)	55 (38)	15 (27)	.126	4 (18)	18 (50)	.015
None of the conditions above	45 (21)	28 (19)	12 (21)	.763	6 (27)	6 (17)	.505
Skin barrier impairment							
Chronic skin disease locally	60/215 (28)	46/145 (32)	11 (19)	.077	5 (23)	9 (25)	.844
Wound/ulcer before infection	87 (40)	64 (44)	19 (33)	.171	17 (77)	21 (58)	.141
Other skin barrier impairment[e]	106/215 (49)	74/145 (51)	25 (44)	.359	6/21 (29)	22 (61)	.018
No identified skin barrier impairment	40 (19)	22 (15)	16 (28)	.033	1 (5)	2 (6)	1.000
Other local factors							
Chronic edema[f]	74/155 (48)	57/108 (53)	14/37 (38)	.117	5/16 (31)	18/29 (62)	.048
Peripheral vascular insufficiency	7 (3)	6 (4)	1 (2)	.368	1 (5)	2 (6)	1.000
Previous local erysipelas/cellulitis/NSTI	62 (29)	37 (25)	19 (33)	.252	1 (5)	11 (31)	.021
Previous local radiation/surgery	51 (24)	32 (22)	15 (26)	.504	5 (23)	8 (22)	1.000
None of the local factors above	100 (46)	67 (46)	28 (49)	.678	15 (68)	13 (36)	.018

Abbreviations: BHS⁺, β-hemolytic streptococcal etiology confirmed; BHS⁻, BHS not confirmed; BMI, body mass index; GAS, group A streptococcus; GCS, group C streptococcus; GGS, group G streptococcus; IDU, previous or active intravenous drug use; NA, not applicable; NSTI, necrotizing soft tissue infection.

[a] Data are presented as No. (%) or No./evaluable cases (%).

[b] Cases with BHS etiology confirmed by serology or culture of blood or normally sterile tissue compared with cases with BHS not confirmed.

[c] Cases with GCS/GGS compared with GAS cultured from blood, normally sterile tissue, or cutaneous swabs.

[d] Rheumatic disease or chronic disease of lungs, gastrointestinal tract, liver, pancreas, kidney, or nervous system.

[e] Includes fissured toe web/tinea pedis, intertrigo, excoriations.

[f] Calculated for extremity infections only.

was positively associated with male gender and skin barrier impairment and negatively associated with older age, probably reflecting lower serological sensitivity in the elderly. Compared to the cases that were culture-positive for GAS, the GCS/GGS cases had more often male gender, obesity, chronic edema, minor skin breaks, or previous cellulitis. Several risk factors were significantly more frequent among patients with recurrent cellulitis compared with patients experiencing their first episode (Supplementary Table 1); however, in a multivariate analysis, only chronic edema was independently associated with recurrence ($P < .0005$). Among cases with streptococcal seropositivity, a lower rise in antibody titer was significantly associated with recurrence, also when adjusted for other factors, including baseline antibody level (Supplementary Table 2).

Findings Upon Admission and Diagnostic Accuracy

Several clinical variables on admission were significantly associated with BHS in general or with GAS compared with GCS/GGS (Table 2). β-hemolytic streptococcal etiology was not significantly more common in cases with typical erysipelas signs. In addition, among the cases without any typical erysipelas sign and cases with an overlapping clinical presentation (erysipelas/deeper cellulitis), two thirds or more had confirmed BHS disease.

Diagnostic accuracy of clinical and biochemical parameters in predicting confirmed BHS disease is shown in Supplementary Table 3. Several clinical variables significantly increased the likelihood of BHS disease, but the increase was small; positive likelihood rates (LR^+) ranged from 1.5 to 2.1, and the sensitivity was low (30%–65%). A patient profile of rigors, percentage of total body surface with erythema (TBSA%) ≥3, skin bruising, and leucocytes ≥13.0 gave an LR^+ of 4.0 but a sensitivity of 7%.

Independent Predictors of Etiology

Multivariate logistic regression analysis identified lower extremity location, TBSA% ≥3, and skin barrier impairment as the

Table 2. **Symptoms, Signs, and Biochemical Findings by Etiology**[a]

		BHS+ vs BHS−[b]			GCS/GGS vs GAS[c]		
Characteristic	All Cases (n = 216)	BHS+ (n = 146)	BHS− (n = 57)	*P* Value	GAS (n = 22)	GCS/GGS (N = 36)	*P* Value
Symptoms before admission							
Symptom duration ≥3 d	83/214 (39)	58/144 (40)	22 (39)	.826	9 (41)	17/35 (49)	.572
Rigors	96/212 (45)	74/143 (52)	19/56 (34)	.023	11 (52)	15 (43)	.489
Affected site							
Head	51 (24)	29 (20)	19 (33)	.042	5 (23)	5 (14)	.481
Upper extremity	35 (16)	14 (10)	16 (28)	.001	5 (23)	0 (0)	.011[d]
Lower extremity	123 (57)	97 (66)	21 (37)	<.0005	12 (55)	30 (83)	.017
Other	7 (3)	6 (4)	1 (2)	.676	1 (0)	1 (3)	1.000
Signs at admission							
Erythema sharply demarcated	161/215 (75)	112/145 (77)	43 (75)	.785	15 (68)	29 (81)	.285
Erythema salmon red	142 (66)	105/146 (72)	33 (58)	.054	14 (64)	28 (78)	.242
Erythema salmon red and sharply demarcated	121/215 (56)	90/145 (62)	27 (47)	.057	12 (55)	24 (67)	.356
Erythema with palpable edge	109/209 (52)	76/141 (54)	31/55 (56)	.756	9/21 (43)	19 (53)	.470
No typical erysipelas signs[e]	30/209 (14)	17/141 (12)	7/55 (13)	.898	5/21 (24)	2 (6)	.088
Erysipelas-cellulitis overlap[f]	95/209 (46)	58/136 (43)	29/57 (51)	.295	8/21 (38)	19 (53)	.284
TBSA%, median (range)	3 (1–40)	3 (1–21)	2 (1–40)	.007	2 (1–20)	4 (1–20)	.014
Skin bruising	52 (24)	43 (30)	8 (14)	.023	5 (23)	14 (39)	.203
Bullae	20 (9)	15 (10)	5 (9)	.747	2 (9)	9 (25)	.178
Pus[g]	27 (13)	17 (12)	7 (12)	.900	8 (36)	4 (11)	.042
Easily defined portal of entry	105 (49)	72 (49)	24 (42)	.355	15 (68)	25 (69)	.920
Biochemistry at admission							
Leucocytes (×10^9/L), median (range)	11.7 (3.2–37.4)	12.1 (3.2–37.4)	10.9 (3.8–23.3)	.014	15.5 (4.5–31.4)	13.1 (3.2–25.6)	.177
CRP (mg/L), median (range)	97 (<1–426)[h]	108 (<1–426)	78 (4–399)	.029	98 (3–426)	148 (6–407)	.501
PCT (µg/L), median (range)	0.19 (<0.10–86.20)	0.27 (<0.10–86.20)	0.12 (<0.10–14.20)	.011	0.13 (<0.10–36.00)	0.43 (<0.10–86.20)	.038

Abbreviations: BHS+, β-hemolytic streptococcal etiology confirmed; BHS−, BHS not confirmed; CRP, C-reactive protein; GAS, group A streptococcus; GCS, group C streptococcus; GGS, group G streptococcus; PCT, procalcitonin; TBSA%, percentage of total body surface with erythema.

[a] Data are presented as No. (%) or No./evaluable cases (%) unless otherwise specified.

[b] Cases with BHS etiology confirmed by serology or culture of blood or normally sterile tissue compared with cases with BHS not confirmed.

[c] Cases with GCS/GGS compared with GAS cultured from blood, normally sterile tissue, or cutaneous swabs.

[d] Fisher's exact test was used, and 1 observation was added to each cell, due to 1 zero cell.

[e] Sharply demarcated erythema, palpable edge, or salmon red erythema.

[f] Neither all erysipelas signs (salmon red erythema, sharply demarcated erythema, palpable edge) nor none erysipelas signs.

[g] Cases with drainable abscess or other drainable fluid collection were not included in the study.

[h] Seven cases had CRP <5 mg/L at admission, but all except 1 case had CRP > 5 mg/L the day after.

only independent predictors of confirmed BHS etiology, when adjusted for that may have affected admission findings and sensitivity of serology (Table 3). For confirmed and probable BHS combined, multivariate analysis identified intravenous drug use as a negative predictor of BHS etiology (OR, 0.075; 95% CI, .013–.438; $P = .005$). A multivariate analysis of GCS/GGS compared with GAS etiology based on culture results (blood/tissue/swabs) identified skin barrier impairment other than wound, ulcer, or chronic skin disease (OR, 8.884; 95% CI, 1.479–53.347; $P = .009$) as an independent predictor of GCS/GGS infection.

DISCUSSION

This comprehensive investigation demonstrates BHS as the major etiological agents in a representative group of cellulitis patients without drainable foci. By combining serology, culture, and response to penicillin treatment, our results suggest that more than 80% of the cases were of streptococcal origin, including the majority of patients without typical signs of streptococcal erysipelas and those with purulence and comorbidities such as diabetes mellitus.

Previous studies including streptococcal serology have also demonstrated a predominance of BHS in the etiology of cellulitis. However, these studies were restricted to nonculturable or sharply demarcated superficial cellulitis (erysipelas) [4, 6, 15, 17].

The relative importance of GCS/GGS (*Streptococcus dysgalactiae* subsp *equisimilis*) compared with GAS (*S pyogenes*) in skin infections has been unclear. In general, invasive GCS/GGS infections are increasing [18, 19], and in cellulitis other than erysipelas a predominance of GCS/GGS bacteremia has been demonstrated [8]. Such predominance has also been

Table 3. Clinical Predictors of Confirmed β-Hemolytic Streptococcal Etiology[a] in Cellulitis

	Unadjusted Models (n = 203[b])		Adjusted Model[c] (n = 198)	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age <75 y[d]	2.471 (1.125, 5.428)	.021	3.523 (1.313, 9.455)	.012
Male gender	1.893 (1.019, 3.516)	.042	0.961 (.448, 2.065)	.919
Skin barrier impairment	2.200 (1.055, 4.584)	.033	2.419 (1.027, 5.699)	.045
Antibiotics before admission[e]	0.561 (.286, 1.104)	.092	0.343 (.147, 0.801)	.012
Immunosuppression	0.478 (.189, 1.204)	.111	0.179 (.146, 1.433)	.184
Affected site		<.0005		.031
Lower extremity	1.00 (Reference)		1.00 (Reference)	
Upper extremity	0.189 (.080, 0.447)	<.0005	0.255 (.092, 0.705)	.008
Head	0.330 (.157, 0.697)	.004	0.453 (.161, 1.274)	.133
Other	1.299 (.148, 11.365)	.813	1.737 (.141, 21.380)	.667
TBSA% ≥3	2.754 (1.468, 5.166)	.001	2.549 (1.044, 6.222)	.038
Skin bruising	2.557 (1.117, 5.851)	.023	1.495 (.521, 4.290)	.450
Leucocytes ($\times 10^9$/L) ≤3.5 or ≥8.0[d]	3.342 (1.491, 7.490)	.002	2.426 (.950, 6.194)	.065

Abbreviations: CI, confidence interval; OR, odds ratio; TBSA%, percentage of total body surface with erythema.

[a] Defined by serology or culture of blood or normally sterile tissue.

[b] For some variables, the number of evaluable cases were lower than 203 (see Tables 1 and 2 for details).

[c] Adjustment was made for all factors listed in the table (Hosmer-Lemeshow's χ^2 = 13.166, df = 8, *P* = .068).

[d] The association of this characteristic to confirmed BHS etiology is probably mainly due to increased serological sensitivity (see text).

[e] Included in the adjusted model to correct for the possibility that antibiotics may have affected admission findings.

found for superficial cultures in some studies of cellulitis [20–22]. However, in the latter studies, serology was not used, and the causal role of GCS/GGS was therefore uncertain. In addition, GCS/GGS have primarily been associated with older age or comorbidities [4, 18, 19, 21, 23, 24]. Our study supports that GCS/GGS has a dominant role in cellulitis; they accounted for the majority of BHS in culture and were strongly associated with a serological profile predominant also among the culture negative BHS infections. The GCS/GGS were not confined to elderly or patients with comorbidities, underscoring the pathogenic significance of these bacteria in cellulitis. It is interesting to note that GCS/GGS were particularly associated with the lower part of the body and GAS was associated with the upper part, possibly related to differences in carriage, spread, or pathogenicity of streptococci in carriage sites such as anus, toe webs, and throat [21, 25–27].

Previous reports have suggested an important role also for *S aureus*, and occasionally also Gram-negative bacteria, in cellulitis [7, 8]. These studies are hampered by retrospective design or heterogeneous patient populations. Furthermore, these bacteria are frequent colonizers of skin and common in abscesses, and in a recent biopsy study of cellulitis patients, *S aureus* DNA was also frequently detected in samples from uninfected tissue [28]. In our study, cases with *S aureus* or Gram-negative bacteria in swabs were common. However, the great majority, including those with *S aureus* or Gram-negative bacteria as the only detected pathogens, had confirmed or probable BHS disease. This has also been reported previously for *S aureus* [6]. The results are in line with other studies demonstrating frequent colonization and dubious clinical significance of such pathogens when detected in wounds, ulcers, or interdigital fissures of cellulitis patients [26, 29]. Moreover, a recent randomized clinical trial indicates that MRSA coverage is unnecessary in treatment of uncomplicated nonpurulent cellulitis, adding to the evidence that nonstreptococcal etiology in cellulitis is relatively rare [30].

The use of bedside cultures from nonsterile sites in the diagnostic work-up of cellulitis is usually not recommended [1, 3, 31]. Our findings support that *S aureus* or Gram-negative bacteria in swabs from cellulitis patients is of doubtful significance and most often does not mandate antibiotic coverage against these microbes. In contrast, we found a strong correlation between identification of both GAS and GCS/GGS in culture and positive serology. A relative high proportion of "swab-positive" BHS infections was also documented, indicating that cutaneous swabs may be more useful in streptococcal cellulitis than previously thought [17].

Our study also demonstrated that underlying factors known to be associated with cellulitis, such as obesity and edema, were common not only in patients with confirmed BHS disease, but also among cases where other etiology is not unlikely. Some factors were particularly common in cases with recurrence, in line with other studies [32]. Our data also support recent investigations that have found GCS/GGS to be more associated with recurrence than GAS [21, 22].

To our knowledge, associations between bacterial etiology and a detailed spectrum of clinical findings at admission previously have not been prospectively examined in cellulitis patients. We found that some signs, such as skin bruising and extensive erythema, were related to BHS in this hospital setting. However, as demonstrated by low positive likelihood ratios, the

correlation between clinical signature and BHS etiology was not strong. This supports current recommendations using severity and risk factors associated to specific microbes rather than the clinical differentiation of erysipelas and deeper cellulitis as the basis for empiric therapy [1]. However, a combination of some severe symptoms and signs increased the positive likelihood ratio for BHS etiology in our study. This suggests that severe cases in some instances have a typical streptococcal profile that may justify narrow-spectrum therapy. Low negative predictive values and high LR^- values of BHS-related clinical signs implies that these markers should be used to confirm rather than to disprove BHS disease.

The limitations of our study are mainly due to the lack of a highly accurate "gold standard" for BHS etiology in nonbacteremic cellulitis [3, 9]. Biopsy studies have shown diverging results [5, 7]. In addition, recent studies using current molecular technology have failed in defining the etiology of cellulitis [28, 33]. Furthermore, biopsy procedures are not feasible for a large representative population. Likewise, culture of swab samples has low sensitivity [6], and BHS in swabs of healthy controls do occur, although rarely [26, 27]. We found serology to be the most appropriate method for a large representative study. The sensitivity is relatively good [9], but not optimal, as suggested by streptococcal seronegativity in some of our cases with typical erysipelas, BHS culture positivity, or penicillin response. As observed, reduced sensitivity appears to be particularly related to older age and low systemic response. Culture positive throat infections with significant titer increases not reaching the standard upper limit of normal have demonstrated how sensitivity is also dependent on the predefined diagnostic criteria [34]. In addition, GBS infections are not detected by the serology assays used. Sensitivity and specificity are also influenced by population-dependent differences in normal values [35]. In a group of healthy adults, the frequency of antibody levels above the upper limit of normal (200 U/mL) was low, suggesting relatively high specificity [15]. Nonetheless, recent or concurrent BHS infections of the throat or other sites would influence serology results. Another concern recently pointed out is the lack of specificity data regarding serology in skin and soft tissue infections [28]. Such specificity data were available from cases that were noneligible in the cellulitis part of our study. Fifteen cases with acute noncellulitis skin infection (abscess, bursitis, infectious phlebitis, animal bite, osteomyelitis with skin infection, or viral infection) with systemic illness and confirmed etiology other than BHS had 2 sets of serology obtained. Streptococcal seropositivity was demonstrated (data not shown) in only 1 of these patients. These data as well as the strong correlation between serological patterns and streptococcal species found in culture suggest relatively high specificity. Our study was a single-center cohort that was carried out in a population with low MRSA prevalence. Therefore, the results are not generalizable to all settings, but the minor role of MRSA and other staphylococci suggested by this and other studies increase the relevance [1, 9, 30, 36].

Strengths of our study include prospective design, low number of investigators, detailed and early registration of clinical signs, and inclusion of cases representing the most important subgroups of pure cellulitis. Finally, the combination of different methods enabled us to evaluate the etiology in a large proportion of patients.

CONCLUSIONS

In conclusion, this study confirms GAS and GCS/GGS as the primary causes of cellulitis. This not only includes erysipelas but also deeper cellulitis, overlapping conditions and cases with *S aureus* cultured from cutaneous swabs. Knowledge of the predominance of BHS in most subgroups of cellulitis constitutes an important basis for empiric therapy. However, more accurate tools are needed in the clinical setting to identify nonstreptococcal cases and establish etiological diagnoses. This may also improve appropriate and pathogen-directed antibiotic therapy for this large patient group.

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