

Early Response in Cellulitis: A Prospective Study of Dynamics and Predictors

Trond Bruun,^{1,2} Oddvar Oppegaard,^{1,2} Karl Ove Hufthammer,³ Nina Langeland,^{1,4} and Steinar Skrede^{1,2}

¹Department of Clinical Science, University of Bergen, ²Department of Medicine, ³Centre for Clinical Research, and ⁴National Centre for Tropical Infectious Diseases, Haukeland University Hospital, Bergen, Norway

Background. Skin and soft tissue infections are common reasons for medical care. Use of broad-spectrum therapy and costs have increased. Assessment of early treatment response has been given a central role both in clinical trials and everyday practice. However, there is a paucity of data on the dynamics of response, causes of early nonresponse, and how early nonresponse affects resource use and predicts outcome.

Methods. We prospectively enrolled 216 patients hospitalized with cellulitis. Clinical and biochemical response data during the first 3 days of treatment were analyzed in relation to baseline factors, antibiotic use, surgery, and outcome. Multivariable analysis included logistic lasso regression.

Results. Clinical or biochemical response was observed in the majority of patients the day after treatment initiation. Concordance between clinical and biochemical response was strongest at days 2 and 3. Female sex, cardiovascular disease, higher body mass index, shorter duration of symptoms, and cellulitis other than typical erysipelas were predictors of nonresponse at day 3. In contrast, baseline factors were not predictive of clinical failure assessed posttreatment. Among cases with antibiotic treatment escalation by day 2, 90% (37/41) had nonresponse at day 1, but only 5% (2/40) had inappropriate initial therapy. Nonresponse at day 3 was a predictor of treatment duration >14 days, but not of clinical failure.

Conclusions. Nonpharmacological factors had a major impact on early response dynamics. Delayed response was rarely related to inappropriate therapy but strongly predictive of early treatment escalation, suggesting that broadening antibiotic treatment may often be premature.

Keywords. cellulitis; skin infections; early response; treatment failure; outcome.

Skin and soft tissue infections (SSTIs) are common causes of medical care, and increasing frequency and costs are reported [1–3]. The SSTI that most often requires systemic antibiotics is cellulitis, a diffuse skin infection that includes the superficial subtype known as erysipelas [4]. Cellulitis is usually caused by β -hemolytic streptococci (BHS) that are susceptible to penicillin and other narrow-spectrum antibiotics [4]. However, there are significant treatment challenges, including overuse of broad-spectrum and intravenous antibiotics [5, 6], difficulties regarding when to initiate rescue therapy and when to stop treatment [7], and frequent recurrences [8]. Toxin effects and profound local inflammation, not necessarily corresponding to bacterial burden or antibiotic needs, may contribute to these problems [7, 9]. Also, host factors affecting the dynamics of treatment

response may adversely impact antibiotic choices and other resource use.

Increasing the knowledge on the clinical course, response dynamics, and associated factors may be important in dealing with the challenges of cellulitis care. Optimizing the assessment of treatment response may be a key factor, due to its major role in treatment decisions and clinical trials. The standard assessment of response in SSTI trials has been performed after end of treatment (EOT). However, clinical success posttreatment may often be the result of natural improvement, as demonstrated by high cure rates following nonantibiotic therapy in studies from the preantibiotic and early antibiotic eras [10]. Moreover, 2 studies published in 1937 comparing antibiotic and ultraviolet therapy found the difference between treatment arms to peak 2–3 days after start of treatment, suggesting that early response is a more treatment-specific measure than cure assessed posttreatment [11, 12]. Clinical response 48–72 hours after treatment initiation is therefore currently recommended by the US Food and Drug Administration (FDA) as the primary efficacy endpoint for clinical trials [13]. This has not been without controversy, however, primarily because early response is not the ultimate goal of antibiotic therapy [14]. European guidelines still recommend cure assessed after treatment as the primary endpoint [15].

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Correspondence: T. Bruun, Department of Medicine, Haukeland University Hospital, Post Box 1400, Bergen 5021, Norway (trond.bruun@helse-bergen.no).

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The aim of this study was first to describe the early and late course after treatment initiation, including how rapidly the clinical and biochemical responses occur. Second, we wanted to examine early response dynamics in relation to underlying factors, etiology, and severity as well as antibiotic escalation and other outcomes. By limiting the study to cellulitis in a setting with low prevalence of BHS and *Staphylococcus aureus* resistant to first-line antibiotics [16], the study of early response in relation to baseline factors could be performed largely without influence of confounders such as need of surgical drainage or antibiotic resistance. The results may provide an improved basis for the assessment of early response and how initial response can be used in guiding continued treatment and predicting outcome.

PATIENTS AND METHODS

Study Population

The study population has been described previously [17]. In brief, patients (aged ≥ 18 years) with acute cellulitis admitted to Haukeland University Hospital (Bergen, Norway) were prospectively included. Patients with drainable collections of pus or other fluid were excluded.

Clinical Characteristics and Response

Data on underlying factors and clinical findings at admission were obtained by detailed history and clinical examination. Clinical evaluation of response after initiation of intravenous treatment at admission was performed daily until improvement or discharge from hospital; local inflammation intensity and spread of erythema and, in a subset of patients, the area of erythema (length times width) were registered. In addition, blood for measurement of leukocytes and C-reactive protein (CRP) was obtained daily until a reduction of at least 20% in 1 day was observed or the patient was discharged from hospital. A telephone consultation scheduled at approximately 2 weeks after cessation of therapy was used to register residual inflammation and increase in symptoms or new course of antibiotics posttreatment. Criteria for response and failure were defined as follows:

- Response at day 1: cessation of lesion spread and overall improvement of local inflammation (intensity of erythema, warmth, and tenderness) at the day 1 assessment compared to admission.
- Nonresponse at day 1: criteria for response day 1 not met.
- Response at day 3 (“early response”): local response (cessation of lesion spread and overall improvement of local inflammation) plus CRP reduction of $\geq 20\%$ by day 3, that is, at day 1 compared to admission, day 2 compared to day 1, and/or at day 3 compared to day 2.
- Nonresponse at day 3: criteria for response day 3 not met.
- Indeterminate response at day 1 or day 3: ≥ 1 response variable missing.
- Clinical failure posttreatment: increase in symptoms or new course of antibiotics between end of therapy and 2 weeks

after EOT, or death or readmission for SSTI within 30 days of discharge.

- Clinical cure posttreatment: absence of clinical failure posttreatment.
- Indeterminate outcome posttreatment: loss to follow-up or ≥ 1 posttreatment outcome variable missing.

Bacterial Etiology and Treatment

Bacterial culture and serological analyses were performed as described previously [17]. Confirmed BHS etiology was defined by streptococcal seropositivity according to specific criteria and/or growth of BHS in culture of blood or normally sterile tissue [18]. Probable BHS etiology was defined as BHS in cutaneous swabs or a satisfactory response to penicillin monotherapy, defined as clinical response at EOT in patients receiving no other antibiotics during the course. Cases lacking both 2 serology samples and a positive culture of blood or normally sterile tissue were considered nonevaluable regarding BHS etiology. Discordant or inappropriate treatment was defined as penicillin monotherapy as initial treatment in cases without confirmed or probable BHS etiology. Antibiotic treatment escalation was defined as addition of an antimicrobial agent or other change resulting in a regimen with broader antimicrobial spectrum. Surgical treatment escalation was defined as a first or more extensive surgery than performed before >1 day after start of treatment.

Statistical Analysis

Categorical data were analyzed using the χ^2 or Fisher exact test. Continuous data were compared using the Mann–Whitney *U* test. All reported statistical tests are 2-sided, and *P* values $< .05$ are considered statistically significant. For multivariable analyses, a logistic lasso regression model was used, due to a high number of predictors compared with the number of events/nonevents, and the risk of severe overfitting when using ordinary logistic models [19]. Lasso regression is a shrinkage method, and the coefficient estimates of predictors with little or no predictive value will be shrunk to zero (an odds ratio of 1). For comparison, we report results from normal univariate and adjusted logistic regression. For the latter model, we also report tests of the joint effect of all predictors, which tests if the predictors jointly have *any* predictive power. To evaluate the discriminative ability of the lasso model, we used leave-pair-out cross-validation of the entire model fitting procedure to estimate the area under the receiver operating characteristic curve (AUC/C-statistic) [20]. Details concerning the statistical methods, including regression methods and selection of predictors, are provided in the [Supplementary Methods](#).

RESULTS

Patients, Bacterial Etiology, and Antibiotic Treatment

Two hundred sixteen patients were included. Clinical characteristics and bacterial etiology have been published elsewhere [17].

In brief, median age was 54.5 years (range, 18–94 years), and 57% had lower extremity infection. Of 203 patients evaluable for assessment of BHS etiology, 72% had confirmed BHS, and an additional 13% had probable BHS infection. No cases with methicillin-resistant *S. aureus* were detected.

Dynamics and Concordance of Different Early Clinical and Biochemical Response Parameters

At day 1, 55% of evaluable cases (116/211) had cessation of lesion spread, and 52% (109/211) had improvement of local inflammation (Figure 1A), but 16% (34/211) had cessation only, and 13% (27/211) had improvement of inflammation only. Local clinical response defined by a combination of these 2

events was seen in 39% (82/212). Local clinical response or biochemical response was observed at day 1 in 74% (148/200) of cases (Figure 1B).

Concordance between different clinical measures and biochemical response was strongest at day 2 and 3 (Supplementary Table 1). In a subgroup of 57 patients, reduction of lesion size was measured but had a weaker association with biochemical response compared with other clinical response parameters.

An overall early response according to defined criteria—that is, local clinical response plus CRP response by day 3—was observed in 90% (170/190).

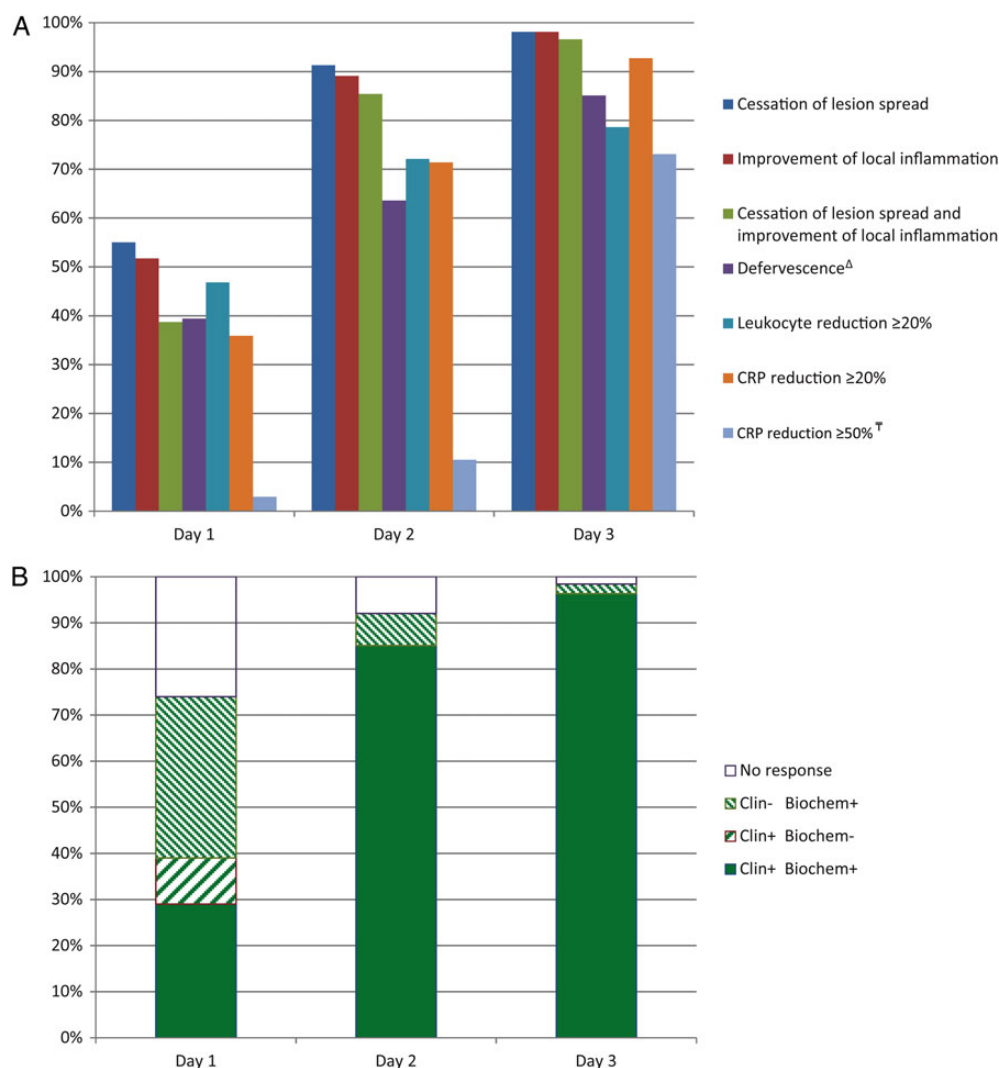


Figure 1. Clinical and biochemical response at days 1, 2, and 3. Response evaluation was based on comparison with findings the day before. Response at days 2 and 3 was defined as response by day 2 and 3, respectively. See the “Methods” section for further details. *A*, Different clinical and biochemical response parameters are presented. ^ABody temperature $\leq 37.5^{\circ}\text{C}$ in ≥ 2 separate measurements in 1 day (≥ 1 measurement if discharged) among cases with temperature $>37.5^{\circ}\text{C}$ the day before. ^TNot based on comparison with the day before but compared to the maximum value of all preceding days in hospital. *B*, Clinical and/or biochemical response using combined parameters. Clinical response was defined as cessation of lesion spread and overall improvement of local inflammation from one day to the next. Biochemical response was defined as at least 20% reduction of blood leukocytes or C-reactive protein (CRP) from one day to the next. The number of cases with indeterminate response (≥ 1 response parameter missing) at days 1, 2, and 3 were 16, 28, and 24, respectively. Abbreviations: Biochem+, biochemical response; Biochem-, no biochemical response; Clin+, clinical response; Clin-, no clinical response.

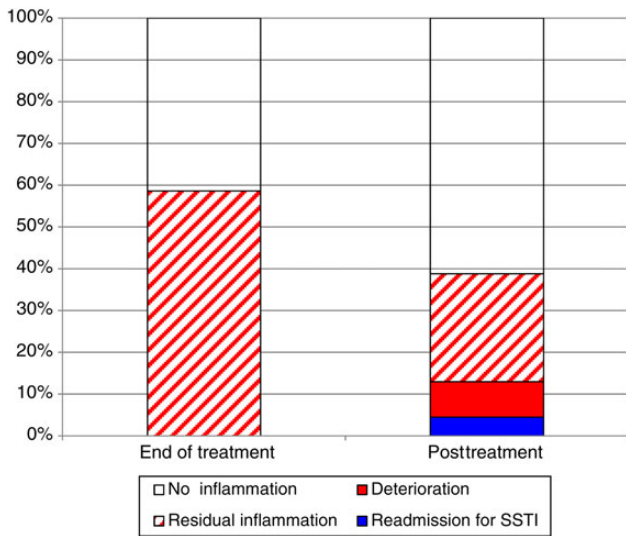


Figure 2. Clinical course after treatment. Status at end of treatment and post-treatment was determined by a telephone consultation scheduled approximately 2 weeks after cessation of therapy. Signs of residual inflammation (red/rose/purple discoloration, tenderness, warmth) and deterioration (symptom increase or new antibiotic course) after treatment were registered. Readmissions for skin and soft tissue infection (SSTI) within 30 days are also shown. The number of cases with indeterminate outcome (≥ 1 parameters missing) at end of treatment and posttreatment were 25 and 15, respectively.

Clinical Course Posttreatment

More than half of the patients had residual signs of inflammation at EOT (Figure 2). The median duration of the recall period (ie, the time from EOT to the telephone interview) was slightly longer in the cases with residual inflammation at EOT (22 days vs 20 days; $P = .09$). Signs of inflammation were still common at the posttreatment evaluation (Figure 2). Among 112 cases with residual inflammation at EOT, 18 (16%) had deterioration or re-admission posttreatment (as in the definition of clinical failure), compared with 2 of 79 (3%) cases without such residual inflammation (odds ratio, 7.4 [95% confidence interval, 1.7–32.8]; $P = .003$). Clinical course data limited to the cases without discordant initial therapy showed a pattern equal to cases overall (Supplementary Figure).

Factors Associated With Early Nonresponse and Failure Posttreatment

Univariate analyses of factors possibly associated to nonresponse at days 1 and 3 are shown in Supplementary Table 2. Only cases without evidence of initial discordant therapy were entered into multivariable models to identify nonpharmacological predictors of early nonresponse (see flowchart in Figure 3). The adjusted lasso model identified no predictors of nonresponse at day 1 (Table 1). Antibiotic therapy prior to admission was not associated with decreased risk of nonresponse at day 1

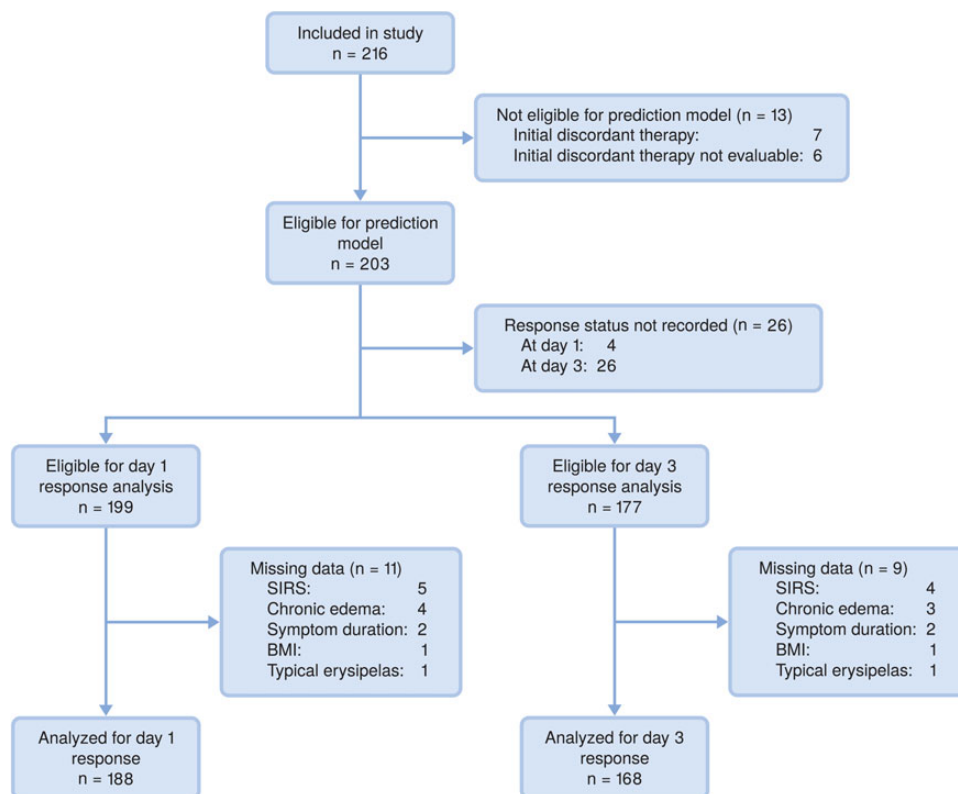


Figure 3. Flowchart of cases eligible for multivariable analyses to identify predictors of nonresponse at day 1 and day 3. Abbreviations: BMI, body mass index; SIRS, systemic inflammatory response syndrome.

Table 1. Regression Models for Nonresponse at Days 1 and 3 Among Cases Without Initial Discordant Therapy^a

Characteristic ^b	Nonresponse at Day 1					Nonresponse at Day 3				
	Univariate Model (n = 188)		Adjusted Model (n = 188)		Lasso Regression (n = 188)	Univariate Model (n = 168)		Adjusted Model (n = 168)		Lasso Regression (n = 168)
	OR ^c	P Value	OR ^c	P Value ^d	OR ^c	OR ^c	P Value	OR ^c	P Value ^e	OR ^c
Age (years)	0.99	.50	0.99	.29	1	1.02	.14	0.97	.27	1
Female sex	0.80	.46	0.89	.73	1	4.01	.01	5.10	.03	2.09
Cardiovascular disease	1.19	.56	1.46	.38	1	5.05	.002	10.70	.006	2.83
Diabetes mellitus	1.56	.32	1.39	.51	1	1.47	.59	0.65	.60	1
Previous local surgery/radiation	0.81	.56	0.88	.77	1	1.77	.30	1.84	.40	1
Previous local cellulitis	0.94	.86	1.08	.84	1	1.06	.92	0.84	.82	1
Chronic edema	0.91	.76	0.49	.13	1	1.83	.23	0.53	.50	1
BMI (kg/m ²) ^f	1.04	.15	1.03	.36	1	1.08	.07	1.11	.08	1.03
Symptom duration (days) ^f	0.89	.17	0.90	.27	1	0.71	.03	0.79	.21	0.90
Prior antibiotic therapy ^{b,g}	0.55	.08	0.52	.10	1	1.17	.78	1.70	.48	1
Extremity infection	1.20	.57	1.30	.54	1	1.82	.34	1.57	.62	1
Typical erysipelas ^h	1.60	.12	1.46	.24	1	0.40	.07	0.23	.02	0.53
Sepsis (≥2 SIRS criteria)	1.75	.06	1.52	.20	1	1.63	.33	2.08	.25	1
TBSA% ^f	1.04	.51	1.11	.29	1	0.95	.61	0.90	.52	1

Abbreviations: BMI, body mass index; OR, odds ratio; SIRS, systemic inflammatory response syndrome; TBSA%, percentage of total body surface area with erythema.

^a Cases with initial penicillin monotherapy and either (1) streptococcal etiology not confirmed or probable or (2) streptococcal etiology nonevaluable were excluded from the analysis (in a total of 13 of 216 cases) see also Figure 3.

^b At admission.

^c OR values >1 indicate greater risk of nonresponse, and OR values <1 indicate greater probability of response.

^d Test of joint effect of predictors at day 1: $P = .34$.

^e Test of joint effect of predictors at day 3: $P = .008$.

^f The predictors were winsorized as follows: BMI at 40 kg/m², symptom duration at 6 days, and TBSA% at 10%.

^g Oral antibiotic treatment was started the day before admission or earlier.

^h Sharply demarcated, salmon-red erythema.

Table 2. Treatment Resources and Outcome in Relation to Response at Days 1 and 3

Treatment Resource or Outcome	Day 1			Day 3			Delayed Early Response		
	Response	Nonresponse	P Value	Response	Nonresponse	P Value	Response Day 3, Not Day 1	Response Day 3 and Day 1	P Value
Antibiotic treatment duration									
Days, total, median (range)	11.5 (6–31)	12 (2–44)	.80	11 (2–39)	15.5 (8–44)	<.01	12 (8–39)	12 (6–31)	.48
≥14 d, total	15/82 (18)	23/130 (18)	1.00	23/170 (14)	11/20 (55)	<.01	13/99 (13)	10/71 (14)	.86
Days of IV therapy, median (range)	3 (0–21)	3 (0–22)	<.01	3 (0–22)	4 (0–22)	.13 ^a	3 (1–22)	3 (1–21)	<.03^a
Antibiotic treatment escalation^b									
Within 2 d	4/81 (5)	37/129 (29)	<.01	27/170 (16)	9/20 (45)	<.01^a	24/99 (24)	3/71 (4)	<.01^a
Within 3 d	9/81 (11)	40/127 (32)	<.01	32/168 (19)	11/20 (55)	<.01^a	26/97 (27)	6/71 (9)	<.01^a
Overall	19/80 (24)	48/122 (39)	.02	50/163 (31)	11/19 (60)	.02^a	34/93 (37)	16/70 (23)	.06 ^a
Surgical treatment escalation^c									
2/80 (3)	3/121 (3)	1.00	2/161 (1)	3/20 (15)	.01^a	1/91 (1)	1/70 (1)	1.00 ^a	
Clinical failure^d									
Deterioration within 2 wk posttreatment ^e	7/80 (9)	15/117 (13)	.37	17/159 (11)	3/18 (17)	.43	11/89 (12)	6/70 (9)	.44
Readmission within 30 d	4/82 (5)	5/129 (4)	.74	8/169 (5)	0/20 (0)	1.00	5/98 (5)	3/71 (4)	1.00
Clinical failure, total ^d	8/79 (10)	16/116 (14)	.44	18/157 (12)	3/18 (17)	.46	12/89 (14)	7/70 (10)	.50
Resource-demanding course^f									
40/79 (51)	66/115 (57)	.35	80/156 (51)	15/18 (83)	.01	45/87 (52)	35/69 (51)	.90	

Data are presented as No./evaluable cases (%) unless otherwise specified. Boldface indicates statistical significance ($P < .05$).

Abbreviation: IV, intravenous.

^a Response at day 3 (and delayed response) may have been affected by early treatment escalation, IV therapy, or surgery and is therefore not a true predictor variable regarding these outcomes. However, increasing the response by such treatment escalation would not have strengthened the statistical association between nonresponse and escalation, but the opposite. Response at day 3 and delayed response are therefore included as predictor variables, despite the fact that these variables are also based on data not preceding outcomes.

^b Addition of an antimicrobial agent or other change giving a regimen with broader antimicrobial spectrum.

^c First surgery or more extensive surgery than before performed >1 day after start of in-hospital antibiotic treatment.

^d Increase in symptoms or new course of antibiotics between end of therapy and 2 weeks after end of treatment or death or readmission for skin and soft tissue infection within 30 days of discharge.

^e Increase in symptoms or new course of antibiotics between end of therapy and 2 weeks after end of treatment.

^f Surgical treatment escalation, antibiotic treatment escalation after 3 days, intravenous treatment >3 days, total treatment duration >14 days, or clinical failure.

or 3. As predictors of nonresponse at day 3, female sex, cardiovascular disease, higher body mass index, shorter symptom duration, and cellulitis other than typical erysipelas were identified. The model-based predicted probabilities of nonresponse at day 3 ranged from 2% to 42% (median, 8%; interquartile range, 5%–13%). The apparent AUC for the lasso model was 0.82. Leave-pair-out-cross-validation was used to correct for optimism, that is, to adjust for possible overestimation of the predictive ability of the model, reducing the AUC to 0.67. Sensitivity analysis with replacement of missing response data identified the same predictors (Supplementary Table 3).

Clinical failure posttreatment could not be predicted by the baseline factors included in the models of early nonresponse; the corresponding lasso model for clinical failure showed shrinkage to zero for all predictor coefficients and an AUC of 0.5. The test of joint effect of all predictors showed a *P* value of .87, compared with a *P* value of .008 for the model of nonresponse at day 3. AUC was 0.5 also if antibiotic or surgical treatment escalation was included in the definition of failure posttreatment, and the *P* value then was .37.

Treatment Escalation, Other Resource Use, and Outcome in Relation to Early Response

Antibiotic treatment escalation was observed in 34% (69/205) of cases, mostly within 2 days of treatment initiation (Table 2). Among cases with such early escalation, 90% (37/41) had nonresponse at day 1. Most cases with nonresponse at day 1 and treatment escalation within day 2 had response within day 3, but not as often as those without escalation (73% [24/33] vs 91% [75/82]; *P* = .009). Treatment escalation within day 2 was rarely associated with inappropriate initial therapy (2/40 [5%]) and was common both in cases with confirmed or probable BHS etiology (32/173 [19%]) and other cases (8/39 [27%]). Long duration of therapy was strongly associated with nonresponse at day 3, but not with nonresponse at day 1 (Table 2). Surgical treatment escalation was clearly more common in cases with nonresponse at day 3.

Nonresponse at day 1 and day 3 was not significantly associated with clinical failure, but nonresponse at day 3 was predictive of a complicated, resource-demanding course (Table 2). Sensitivity analysis with replacement of missing response data gave similar results (Supplementary Table 4).

DISCUSSION

The present study gives a detailed description of early response dynamics in cellulitis. A majority of patients responded, clinically or biochemically, the first day after treatment initiation. Improvement of local inflammation frequently preceded cessation of lesion spread, a pattern that has been reported before [9]. The ambiguous relation between extension of erythema and state of the infection was also demonstrated by the high frequency of residual inflammation signs at end of treatment. This discrepancy was also evident

in another study reporting resolution of symptoms with prednisolone treatment without increased risk of relapse [21]. Interestingly, a combined clinical parameter was more strongly associated with biochemical parameters than the FDA-recommended endpoint, which is reduction in lesion size. Supplementing endpoints relying on erythema size with other early response parameters may be warranted, as also discussed previously [22, 23].

Several factors were associated with nonresponse at day 3, demonstrating that factors other than antibiotic choice and discordant therapy are important. The impact of comorbidity has also been demonstrated recently in a large retrospective study of SSTIs [24]. Additionally, randomized clinical trials have showed a tendency toward lower early response rates for patients with high age, high body mass index, and diabetes mellitus [25–30]. Prior antibiotic therapy was not a predictor of early response, probably related to the fact that these patients were admitted to hospital due to an unsatisfactory response. Furthermore, we found no association between cellulitis severity and early nonresponse, in accordance with the findings reported by Talbot et al [31]. In contrast, 2 other studies found somewhat higher rates of early nonresponse among the more severe cases [24, 30].

Longer duration of symptoms before admission was among the factors related to early response. This association has, to our knowledge, previously not been demonstrated. Like the response seen after nonantibiotic treatment [10], this may be related to the natural course of disease; many of those with longer duration may have passed the maximum intensity of infection and inflammation.

Impact of treatment choice on early response was demonstrated as early as the 1930s [11, 12]. However, recent clinical trials using early clinical response as the primary endpoint have not demonstrated significant differences between the drugs tested [26–30, 32, 33], apart from a difference in early response found in a study assessing this new outcome measure retrospectively [25]. In our study, discordant treatment was infrequent as a result of the predominance of streptococcal etiology and rare resistance among these microbes. We found no correlation between discordant treatment and early nonresponse, but the effective sample size was small. However, antibiotic choice may be important beyond its relation to in vitro sensitivity. A recent retrospective study demonstrating an association between early clinical response and higher vancomycin trough concentration illustrates that drug-specific factors are also important for early response [34]. The paucity of reports showing significant associations between initial treatment and early response underscores that in cellulitis, discordant therapy or other pharmacological factors are not the major causes of early failure.

The relatively high frequency of treatment escalation in the present study is consistent with a recent report [35]. Antibiotic

treatment escalation was often initiated already by day 2 and was particularly associated with nonresponse at day 1. However, early treatment escalation among patients with nonresponse at day 1 was not associated with improved response at day 3, suggesting that nonresponse at day 1 is not a definite sign of suboptimal initial therapy. Furthermore, the great majority of the cases with early nonresponse and treatment escalation had received appropriate initial therapy. Thus, performing response assessments very early is of uncertain benefit and may contribute to the reported common use of broad-spectrum therapy [5, 6, 35].

In accordance with a retrospective study by Garau et al [24], we did not find nonresponse at day 3 to be clearly predictive of clinical failure posttreatment. This is in contrast to what is reported in some clinical trials [26, 28, 29]. Our findings can be related to a more individualized treatment, such as the longer duration of treatment in cases with early nonresponse.

We found that factors registered at admission had discriminatory power regarding risk of nonresponse at day 3, whereas these factors were not useful in prediction of failure posttreatment. This contrasts with statements postulating that nonpharmacological baseline factors are mainly responsible for differences in late outcomes and that early response is more treatment-specific [13, 23, 36].

Strengths of the study include prospective design and an optimized multivariable analysis, using lasso regression, a new statistical tool giving more reliable models. Another strength is the representative adult cellulitis population of all ages and with different comorbidities. However, except for 1 patient, the population was white and fair-skinned and therefore was not representative of all populations. Another limitation is the lack of blinding. Investigators registering clinical response data were not systematically prohibited from knowing the treatment ordered. Although the goal and anticipations of the study were not to demonstrate response differences between treatment regimens, this adds to the importance of including objective parameters such as CRP reduction. The criteria for early response were not directly comparable to the latest regulatory standards, which recommend $\geq 20\%$ reduction of lesion size as the main endpoint [13]. However, lesion area is rarely measured in everyday clinical work, and the criteria used are, in our opinion, more compliant with clinical practice. The inclusion of local inflammation intensity as part of the clinical response evaluation may have resulted in bias related to the subjective nature of the parameter. However, our combined response criterion may have given increased validity compared to lesion size reduction, as discussed above. Due to the observational nature of the study, the treatment duration was variable, and clinical cure and failure posttreatment were assessed at different times after the start of therapy. This variability might have obscured associations between early and late outcomes and between baseline factors and late outcomes. The use of telephone

consultation as the main tool in evaluating outcome posttreatment also has weaknesses [37]. Variations in the duration of the recall periods might represent bias related to outcomes posttreatment, but somewhat shorter recall time among cases with inflammation at end of treatment may simply be related to the fact that these patients were more worried, more immobile, and more easily reachable.

Overall, the study indicates that nonantibiotic factors with impact on early treatment response should be considered as an integrated part of the clinical management of cellulitis. This may improve individualization of treatment and reduce costs and unnecessary rescue therapy. The discriminative power of early response regarding drug-specific effects needs further investigation.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Author contributions. T. B. designed the study, included cases, collected data, performed the data analyses, and drafted the manuscript. O. O. participated in inclusion of cases, collection of data, and drafting the manuscript. N. L. participated in the design of the study and drafting the manuscript. K. O. H. participated in the statistical analyses and drafting the manuscript. S. S. participated in the design of the study, inclusion of cases, collection of data, and drafting the manuscript.

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