Aus dem Institut für Infektionskrankheiten (IFIK), Universität Bern

Direktor: Prof. Dr. Stephen Leib

Arbeit unter der Leitung von Prof. Dr. Parham Sendi

Oral antibiotics in skin and soft tissue infections: An algorithm-based prospective multicentre pilot trial

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Sandra Martina Dellsperger
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Abstract

Background:

Skin and soft tissue infections (SSTIs) are among the most common outpatient-acquired bacterial infections. In hospitalized patients, these infections are typically treated with intravenous antibiotics, which are switched to oral formulations during the course of treatment. The optimal time point for switching from intravenous to oral treatment is unknown and depends on numerous factors. In this study, we investigated an algorithm-based switch from intravenous to oral antibiotics within 48 hours after treatment initiation.

Methods:

Hospitalized patients with uncomplicated SSTIs were screened for eligibility at 3 study sites (Langnau, Burgdorf, Biel/Bienne) from July 2019 to September 2020. Eligible participants with SSTIs were older than 18 years, required hospitalization because of the severity of the disease, were able to understand the study information and provided written informed consent. Exclusion criteria included antibiotic treatment 14 days or less before study inclusion, surgical site infections, impetigo without erysipelas/cellulitis, mastitis, nonbacterial infection or sterile skin inflammation (e.g., sweet syndrome, hypersensitivity reaction) and criteria consistent with "complicated" SSTIs (i.e., bacteraemia with *Staphylococcus aureus* or *Pseudomonas aeruginosa*, necrotizing fasciitis, skin abscess, septic shock or infection requiring intensive medical care, septic arthritis, osteomyelitis, tenosynovitis, bursitis, foreign body infection). Patients with a diabetic foot infection, classed on perfusion, extent, depth, infection and sensation (PEDIS) classification 3, were excluded. Other exclusion criteria included gram-negative bacteria as the causative organism for the SSTI or an ecthyma gangrenosum.

After 48 hours of intravenous antibiotics, patients were assigned to either the intervention group or the non-intervention group. In the intervention group, intravenous antibiotics were switched to oral formulations. The switch was performed after 1 or more of the following predefined criteria were fulfilled: decreased pain, normalization of PEDIS grade 4 criteria, decreased or steady inflammation parameters, decreased localization and a temperature of ≤37.8°C for at least 24 hours. Patients in the non-intervention group were treated according the decision of the responsible physician. A total treatment duration of 5 to 10 days at the discretion of the treating physician was recommended. Follow-up phone calls were median conducted on day 39.

Results:

Of 128 screened patients, 90 were included (73 in the intervention group and 17 in the non-intervention group). Patients had a median age of 63 years, 64% were male, the majority had at least 1 comorbidity and the most affected site was the lower extremity (76.67%). In 7.8% of patients (7 cases) a microorganism was identified in blood cultures or swabs from skin blisters (5 in the intervention group and 2 in the non-intervention group). The most common isolated microorganism was group C or group G *Streptococcus*.

The median antibiotic treatment duration was 11 days in the intervention group and 15 days in the non-intervention group; the median intravenous treatment duration was 2 days in the intervention group and 4 days in the non-intervention group; and the median duration of hospitalization was 5 days in the intervention group and 7 days in the non-intervention group. Treatment failures were noted in 3 (4%) cases in the intervention group and in 1 case (6%) in the non-intervention group.

Conclusions:

In this prospective pilot trial on uncomplicated SSTIs in hospitalized patients, an algorithm-based switch from intravenous to oral antibiotic treatment after a maximum of 48 hours was successful in 96% of cases. A prospective non-inferiority multicentre trial is required to confirm these results on level 1 evidence.

1. Background

Skin and soft tissue infections (SSTIs) such as erysipelas rank among the most common outpatient-acquired bacterial infections. The infection manifests as swelling, redness and pain in the affected skin region.

The incidence of SSTIs is approximately 20 cases per 10'000 person-years[1,2]. The infection is typically caused by beta-haemolytic streptococci (approximately 75%)[3] and *Staphylococcus aureus*[1]. However, a causative pathogen is identified in only approximately 4% to 13% of cases[1,4–7]. Even when no microorganisms are identified, the clinical response to beta-lactam antibiotics is more than 95%[2]. Most frequently, the lower limb is affected[2,5,8,9].

In the geographic region of the study sites (Canton Bern), the prevalence of methicillin-resistant *S. aureus* is low. Beta-haemolytic streptococci are uniformly susceptible to penicillin[10]. The Swiss empiric treatment recommendations for SSTIs (i.e., erysipelas and cellulitis without abscess formation or necrosis) include amoxicillin/clavulanate without surgery. In the case of penicillin allergy, oral cephalosporins or clindamycin are possible alternatives[11].

In many Swiss institutions, the treatment procedures for SSTIs are as follows. Depending on the severity of the disease, a decision for hospitalization or outpatient treatment is made. In hospitalized patients, intravenous empiric antibiotic treatment is initiated. The antibiotic treatment should be switched to an oral therapy, provided that there is a clinical response. The best time point for switching from intravenous to oral antibiotic treatment is, however, unknown. The recommended total treatment duration for SSTIs ranges between 5 and 14 days[6,12].

An early switch from intravenous to oral antibiotic therapy may offer a substantial benefit to both the patient and the healthcare system, as shown in a recent study on bone and joint infections[13]. Nonetheless, no guidelines or uniformly accepted criteria are available on the duration of intravenous antibiotics prior to the switch to an oral formulation in SSTIs. Most clinicians use their clinical experience for decision making concerning this switch. However, criteria for switching to oral antibiotics for various other infectious diseases have previously been published [14–18] and have also been proposed by the Institute for Infectious Diseases at the University of Bern[19].

Although visible improvement of erythema may take longer, patients with an SSTI have symptomatic improvement within 24-48 hours after beginning antimicrobial therapy. A

recent study from Norway showed that concordance between the clinical and the biomedical response was strongest on days 2 and 3. Non-response at day 3 predicted treatment duration over 14 days, but not clinical failure[20]. This may indicate that clinical observations or biochemical variables show a delayed response in comparison to the dynamics of bacterial killing. A delayed clinical response is not (or is rarely) related to inappropriate therapy.

2. Study aim, objectives and hypothesis

We aimed to investigate the treatment outcome for uncomplicated SSTIs in hospitalized patients by using an algorithm-based switch from intravenous to oral antibiotics within 48 hours after treatment initiation.

The objective of the study was to estimate the efficacy of the antibiotic treatment concept in a pilot trial.

We hypothesized that patients receiving intravenous antibiotic therapy for a maximum of 48 hours followed by an oral formulation of antibiotic therapy (designated as the intervention group) would have the same clinical cure rate for SSTIs as patients not receiving such an intervention (designated as the non-intervention group: duration of intravenous therapy not restricted and decided at the discretion of treating team) and reported in the literature for SSTIs (85% to 90%)[21].

3. Methods

3.1. Study design

This was a prospective, non-randomized, multicentre pilot trial. It was designated as a pilot trial because the study aimed to test the proof of concept in clinical practice with a conceivable number of study subjects. The results will serve as data for a larger non-inferiority trial (see section 3.9, sample size calculation).

3.2. Study sites

The study was performed in 2 centres in the Canton Bern (Regionalspital Emmental AG and the Spitalzentrum Biel). Regionalspital Emmental AG included 2 study sites (Hospital Langnau and Hospital Burgdorf). Hence, 3 institutions participated overall.

The Regionalspital Emmental is within commuting range for more than 110'000 citizens and over 10'000 inpatients per year (2019)[22] with a bed capacity of 177.5 (2018)[23]. Biel is within commuting range for 150’000 citizens and over 13’000 inpatients patients per year with a bed capacity of 224 in 2019 [24].

3.3. Study period

The study was initiated at Regionalspital Emmental in July 2019 and in December 2019 at Spitalzentrum Biel. For this thesis, an analysis was performed prior to reaching the target sample size in September 2020. The study will, however, continue until the target sample size (at least 100 participants in the intervention group) is achieved.

3.4. Study participants

Eligible participants with SSTIs were older than 18 years, required hospitalization because of the severity of the disease, were able to understand the study information and provided written informed consent. Exclusion criteria included antibiotic treatment 14 days or less before study inclusion, surgical site infections, impetigo without erysipelas/cellulitis, mastitis, nonbacterial infection or sterile skin inflammation (e.g., sweet syndrome, hypersensitivity reaction), and criteria consistent with a “complicated” SSTI (i.e., bacteraemia with *S. aureus* or *Pseudomonas aeruginosa*, necrotizing fasciitis, skin abscess, a septic shock or infection requiring intensive medical care, septic arthritis, osteomyelitis, tenosynovitis, bursitis, foreign body infection). Patients with a diabetic foot infection, PEDIS

classification 3 (Appendix, page XIII), were excluded. Other exclusion criteria included gram-negative bacteria as the causative organism for an SSTI or ecthyma gangrenosum.

3.5. Screening and recruitment

Eligible patients with SSTIs were consecutively screened in the emergency department or in the ward in the case of elective hospitalizations. Included patients had to provide 2 consent forms. The first form covered willingness to share their health-related data for study purposes, irrespective of antibiotic treatment concept. The second form asked for patients' consent to participate in the study and in the intervention, provided that they fulfilled the predefined criteria for an early switch from intravenous to oral antibiotic treatment. Both consent forms were required within 48 hours following hospitalization. Patients who refused to provide the first consent form were excluded from the study. Patients who denied the second consent form or who were pregnant or lactating women were assigned to the non-intervention group.

3.6. Antibiotic treatment and intervention

Empiric intravenous antibiotics consisted of amoxicillin/clavulanate 2.2 g every 8 hours. In the case of allergies, cefuroxime 1.5 g was administered every 8 hours or vancomycin 15 mg per kilogram of body weight every 12 hours. In the case of renal insufficiency, antibiotic doses were adapted accordingly. Oral antibiotics consists of amoxicillin/clavulanate 1 g 3 times per day or clindamycin 600 mg 3 times per day.

The criteria for the switch to oral treatment included at least 1 of the following: clinical response to intravenous treatment, improvement of pain, improvement of erythema, diminishment of PEDIS 4 criteria, biochemical response (laboratory values), ability to swallow pills, or evidence of gastrointestinal absorption *AND* a body temperature of ≤37.8°C for at least 24 hours. Study participants fulfilling these criteria were assigned to the intervention group.

Study participants who did not fulfill these criteria were assigned to the non-intervention group. In addition, prior to the switch to oral treatment, the local primary investigator evaluated clinical and laboratory values and was able to overrule the study intervention at his discretion. Study participants who remained on intravenous treatment because of the primary investigator's decision were assigned to the non-intervention group.

Figure 1 illustrates the study flow chart. The decision about total treatment duration was at the discretion of the responsible physician.

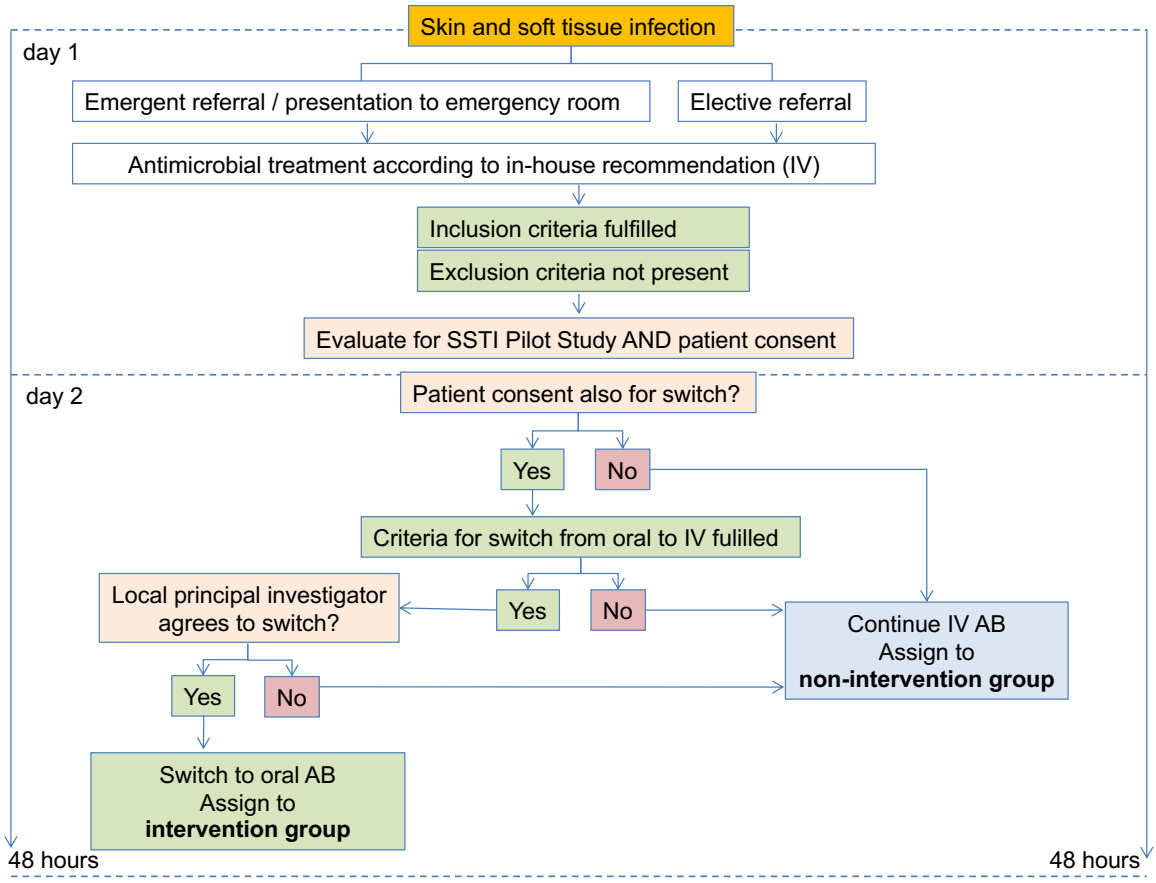

Figure 1 Study flow chart; IV: intravenous, SSTI: skin and soft tissue infection; AB: antibiotics

3.7. Assessment

Patient characteristics: The following patient characteristics were prospectively collected: age; gender; body mass index; cardiovascular comorbidities; renal function; presence of diabetes mellitus (and whether insulin dependent or not), allergies, immunosuppression, or cancer; alcohol consumption; and intravenous drug use.

Clinical characteristics: The clinical characteristics obtained included pain at the site of infection, the presence of chills, body temperature, blood pressure (diastolic and systolic), heart rate, and oxygen saturation with or without oxygen. The intensity of the pain was solicited through the visual analogue scale, which ranged from 0 (no pain) to 10 (subjectively maximum possible pain).

Skin and soft tissue infection: The anatomic body site of the infection was recorded, as well as the size of the skin lesion and, whenever possible, whether there was a portal of

entrance. The size of erythema (length × width) was registered 3 times during hospitalization (at day 1, prior to the start of oral antibiotic therapy and at discharge).

Laboratory values: C-reactive protein (CRP) levels and white blood cell (WBC) counts were used to monitor laboratory treatment response. Blood sampling was obtained at the discretion of the treating team. We consecutively numbered the laboratory values retrospectively and assigned the day of blood sampling according to the following definitions: Lab 1 was assigned to values obtained at day 1 of hospitalization; lab 2 to values at day 3 or 4; lab 3 to values at day 5, 6 or 7; and lab 4 to values closest to day 30 after initiation of antibiotic therapy. If multiple values for a laboratory number designation were available, the mean was calculated and used. We always calculated the progression of CRP and WBC count percentages (decrease and increase of values) in comparison with those in lab 1.

Microbiology: 4 blood cultures (2 aerobic and 2 anaerobic bottles) were obtained on the date of hospital admission. In patients with an obvious clinical portal of entrance or with blisters or bullae, a swab from the site of infection was obtained. The use of routine skin swabs was discouraged.

Clinical monitoring: Clinical examination, and hence, clinical and laboratory response to antibiotic treatment, was performed daily until discharge.

Use of antibiotics: The duration of intravenous and oral antibiotic treatment was measured as number of doses and days of treatment.

Follow-up: Patients were contacted via telephone on day 39 after initiation of antibiotic treatment and interviewed with a predefined questionnaire (Appendix, page XVI). If possible, clinical data were complemented with examination results performed by the general practitioner.

3.8. Outcome

The number and proportion of cured cases was calculated. The number of cured cases was measured as 'total number of treated cases' minus 'the number of failed cases'. Clinical failure was defined as a new increase in symptoms during antibiotic treatment or after the switch to oral therapy, a second course of antibiotic therapy after discontinuing the first course, readmission within 30 days because of SSTI, or death.

3.9. Data collection, data monitoring, sample size calculation and statistical analysis

Coded health-related data were entered by treating physicians in REDCap and stored at the server of the Clinical Trials Unit of the Faculty of Medicine of the University of Bern. All data were monitored for completeness by an independent physician who was not affiliated with the study centres.

Considering the null hypothesis outlined in the aim, we calculated that 902 patients (451 in each group, 2-sided alpha risk 5%, power 90%) would be necessary to confirm the non-inferiority hypothesis of oral treatment after 48 hours in a clinical trial. Because this is a pilot study, we aimed for 100 patients in the intervention group and did not define the patient numbers in the non-intervention group.

Categorical parameters were compared with Fisher's exact test, and continuous variables were compared with the Mann–Whitney *U* test. A p value of <0.05 was considered statistically significant. We dispensed with a comparative analysis of the intervention and the non-intervention groups because of the small size of the non-intervention group; in addition, members of this group were sicker than those in the intervention group based on their non-compliance with the switch criteria and frequently larger skin lesions. The analysis and graphs were made with Stata/IC15.1 and GraphPad Prism8.

3.10. Missing data

As this was a prospective study and data monitoring was included, we aimed for a complete data set. Overall, the proportion of missing data was 5%. Analyses focused on variables with ≤10% missing data. The overall proportion of missing data in the intervention group *after* switching to oral antibiotics was 10%.

The variables with missing data are presented in Table 1. Compliance with consciously measuring the erythema size of the SSTIs was suboptimal (18% missing data).

Missing data	Intervention group (n=73)	Non-intervention group (n=17)
Localization 1		
Measurement 1	4	1
Measurement 2	7	1
Measurement 3	13	2
Localization 2		
Measurement 1	0	-
Measurement 2	1	-
Measurement 3	0	-
Pain		
Movement day 1	4	2
Movement day 2	4	1
Movement day 4	0	0
Movement day 6	1	0
Movement at date of discharge	4	1
Rest day 1	2	1
Rest day 2	0	1
Rest day 4	0	0
Rest day 6	1	0
Rest at date of discharge	4	0
Follow-up	1	0

Table 1 Overview of missing data during the clinical course

The erythema was also documented with a daily photograph in 97% (87/90) of the 90 patients.

3.11. Ethics and trial registration

The Ethics Committee of the Canton Bern, Switzerland, approved this study (KEK 2019-00558). This research project was conducted in accordance with the protocol of the Declaration of Helsinki[25], the principles of Good Clinical Practice, the Human Research Act and the Human Research Ordinance[26], as well as other locally relevant regulations.
The study was registered at KOFAM (SNCTP000003358) and the ISRCTN registry (ISRCTN 15245496; http://www.isrctn.com/ISRCTN15245496).

4. Results

4.1. Study participants

We screened 128 eligible patients and recruited 90 participants across 3 sites between July 2019 and September 2020. 17 study participants were assigned to the non-intervention group and 73 to the intervention group. Their enrolment and assignment to the intervention and non-intervention groups are illustrated in Figure 2.

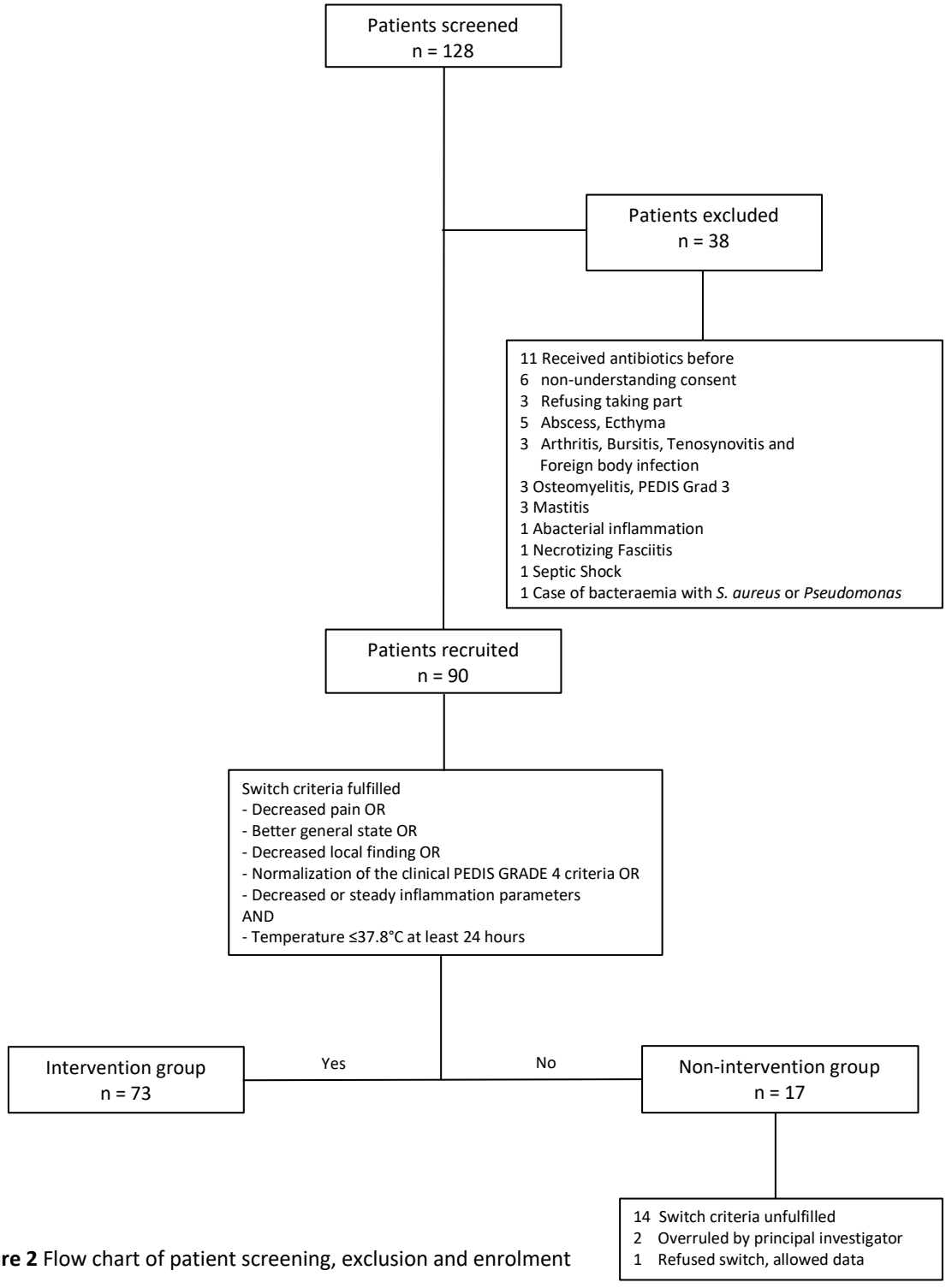

Figure 2 Flow chart of patient screening, exclusion and enrolment

4.2. Patient and clinical characteristics

In the intervention group, 64% were men, the median age was 63 years (range 20 to 94 years) and the median body mass index was 29.5 kg/m^2 (range 17.5 to 64.3 kg/m^2).

The majority of the study participants had at least 1 of the following comorbidities: diabetes mellitus, cardiovascular disease, or kidney insufficiency (Table 2). More than 90% of the study population had no obvious immunosuppression. 3% (2/73) in the intervention group and 6% (1/17) in the non-intervention group were alcoholics. Of those who reported at least 1 episode of SSTI in their patient history, 18% (13/73) were in the intervention group and 29% (5/17) in the non-intervention group. Patient characteristics are presented in Table 2.

Patient characteristics	Intervention group	Non-intervention group	Total
Number of patients	73	17	90
Male (%) Female (%)	47 (64.38) 26 (35.62)	13 (76.47) 4 (23.53)	60 (66.67) 30 (33.33)
Age, y, median (range)	63 (20 to 94)	60 (37 to 76)	63 (20 to 94)
BMI, kg/m^2, median (range)	29.5 (17.5 to 64.3)	35.2 (25.3 to 44.1)	30.5 (17.5 to 64.3)
Diabetes mellitus Type II (%) - With insulin therapy (%) Diabetes mellitus Type I	8 (10.96) 3 (37.50) 0 (0)	6 (35.29) 3 (50.00) 1 (5.88)	14 (15.56) 6 (42.86) 1 (1.11)
Kidney insufficiency (KI) - No KI, G1 (%) - G2 (%) - G3a (%) - G3b (%) - G4 and G5 (%) Total patients with KI	 41 (56.16) 24 (32.88) 2 (2.74) 6 (8.22) 0 (0) 32 (43.84)	 6 (41.18) 8 (47.06) 1 (5.88) 2 (11.76) 0 (0) 11 (64.71)	 47 (52.22) 32 (35.56) 3 (3.33) 8 (8.89) 0 (0) 43 (47.78)
Cardiovascular disease - PAOD - CHD - Hypertonia - 2 of them - all 3 Total (at least 1 of them)	 3 (4.11) 9 (12.33) 38 (52.05) 9 (12.33) 1 (1.37) 39 (53.42)	 4 (23.53) 5 (29. 41) 11 (64.71) 5 (29.41) 2 (11.76) 11 (64.71)	 7 (7.78) 14 (15.56) 49 (54.44) 14 (15.56) 3 (3.33) 50 (55.56)
Immunodeficiency (%) - Medical - Illness (not cancer) - Cancer - Immunocompetent	 2 (2.74) 1 (1.37) 1 (1.37) 69 (94.52)	 0 (0) 1* (5.88) 2* (11.76) 15 (88.24)	 2 (2.22) 2 (2.22) 3 (3.33) 84 (93.33)

Patient characteristics	Intervention group	Non-intervention group	Total
Local risk factors (%) - Status post-radiotherapy - Relapse - Local oedema before SSTI	 4 (5.48) 23 (31.51) 20 (27.40)	 1 (5.88) 6 (35.29) 7 (41.18)	 5 (5.56) 29 (32.22) 27 (30.00)

Table 2 Characteristics and comorbidities of the intervention and non-intervention group; * One patient with cancer and another with immunodeficiency; BMI: Body mass index; PAOD: peripheral artery occlusive disease; CHD: coronary heart disease; SSTI: skin and soft tissue infection

The clinical presentation varied considerably between study participants. The lower limb was the most commonly affected body site (77%), followed by the head (10%), upper limb (7%) and trunk/buttocks (7%). In 72% of the study subjects, a portal of entry (i.e., skin barrier break) was identified (Tables 3 and 4).

Clinical presentation	Intervention group	Non-intervention group	Total
Fever >38°C (%)	42 (57.53)	13 (76.47)	55 (61.11)
Number of localizations (%) - 1 - 2 - 3	 62 (84.93) 10 (13.70) 1 (1.37)	 16 (94.12) 0 (0) 1 (5.88)	 78 (86.67) 10 (11.11) 2 (2.22)
Localization 1/Affected site (%) - Lower limb right - Lower limb left - Buttocks - Trunk - Upper limb right - Upper limb left - Head	 29 (39.73) 26 (35.62) 3 (4.11) 2 (2.74) 4 (5.48) 2 (2.74) 7 (9.59)	 8 (47.06) 6 (35.29) 0 (0) 1 (5.88) 0 (0) 0 (0) 2 (11.76)	 37 (41.11) 32 (35.56) 3 (3.33) 3 (3.33) 4 (4.44) 2 (2.22) 9 (10.00)
Localization 2/Affected site (%) - Lower limb right - Lower limb left - Buttocks - Trunk - Upper limb right - Upper limb left - Head	 6 (50.00) 4 (33.33) 0 (0) 1 (8.33) 0 (0) 0 (0) 1 (8.33)	 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 1 (100) 0 (0)	 6 (46.15) 4 (30.77) 0 (0) 1 (7.69) 0 (0) 1 (7.69) 1 (7.69)
Localization 3/Affected site - Lower limb right - Lower limb left - Buttocks - Trunk - Upper limb right - Upper limb left - Head	 1 0 0 0 0 0 0	 0 0 0 0 1 0 0	 1 0 0 0 1 0 0

Table 3 Localizations and affected sites of the intervention and non-intervention group

	Intervention group	Non-intervention group	Total
No chronic skin problems (%)	54 (72.60)	11(64.71)	65 (72.22)
Portal of entry available (%)	52 (71.23)	13 (76.47)	65 (72.22)
Rhagade (%)	9 (12.33)	2 (11.76)	11 (12.22)
Tinea (%)	14 (19.78)	5 (29.41)	19 (21.11)
Ulcer (%)	42 (57.53)	9 (52.94)	51 (56.67)
Psoriasis (%)	4 (5.48)	0 (0)	4 (4.44)
Atopic dermatitis (%)	1 (1.37)	0 (0)	1 (1.11)
Toxic contact dermatitis (%)	0 (0)	0 (0)	0 (0)
Allergic contact dermatitis (%)	1 (1.37)	0 (0)	1 (1.11)
Other skin impairment (%)	18 (24.66)	7 (12.88)	25 (27.78)

Table 4 Skin barrier impairment

4.3. Microbiological results

A causative microorganism was identified in 7 of 90 (7.8%) individuals, 5 (6.8%) in the intervention group and 2 (11.8%) in the non-intervention group. The organisms were identified in blood cultures in 4 cases (3 in the intervention group, 1 in the non-intervention group) and in swabs from blisters in 3 cases (2 in the intervention group, 1 in the non-intervention group). All but 1 case with positive blood cultures revealed *Streptococcus dysgalactiae*, subspecies *equisimilis* (GCS or GGS). One case in the intervention group showed growth of *Streptococcus agalactiae* (GBS). The swabs from blisters revealed GCS or GGS in 2 cases (in 1 case, *S. aureus* was co-cultured) and *Bacillus* spp. in 1 case. Whether or not the latter organism was a contaminant belonging to skin flora could not be elucidated.

4.4. Clinical course during antibiotic treatment

4.4.1. Clinical assessment after 48 hours

Consistent with the study protocol, all individuals in the intervention group showed clinical improvement after 48 hours of intravenous antibiotic treatment, and hence, qualified for a switch to oral antibiotic treatment. These participants revealed at least 1 of the predefined criteria (Table 5). In the non-intervention group, 82% (14/17) did not fulfill these switch criteria. 3 participants fulfilled these criteria but either refused to switch (1 study participant) or the switch decision was overruled by the primary investigator (2 study participants) (Figure 2).

Switch criteria	Intervention group	Non-intervention group	Total
Fulfilled at least 1 of the following criteria only (%): - Better general state - Improvement of pain - Decreased local report - PEDIS grade 4 criteria not fulfilled - Lab inflammation parameters not increased	73 (100)	2 (11.76)	75 (83.33)
Fulfilled the following criterion only: temperature ≤37.8°C for at least 24 hours (%)	73 (100)	9 (52.94)	82 (91.11)
Fulfilled both criteria	73 (100)	3 (17.65)	76 (84.44))

Table 5 Switch criteria

4.4.2. Pain

On hospital admission, the mean reported visual analogue scale score was 3 when participants moved the body site/extremity, and 2 when they rested the body site/extremity. During the course of hospitalization, these values improved to 1 and 0, respectively, in most patients belonging to the intervention group. In the non-intervention group, higher values were reported (Figure 3).

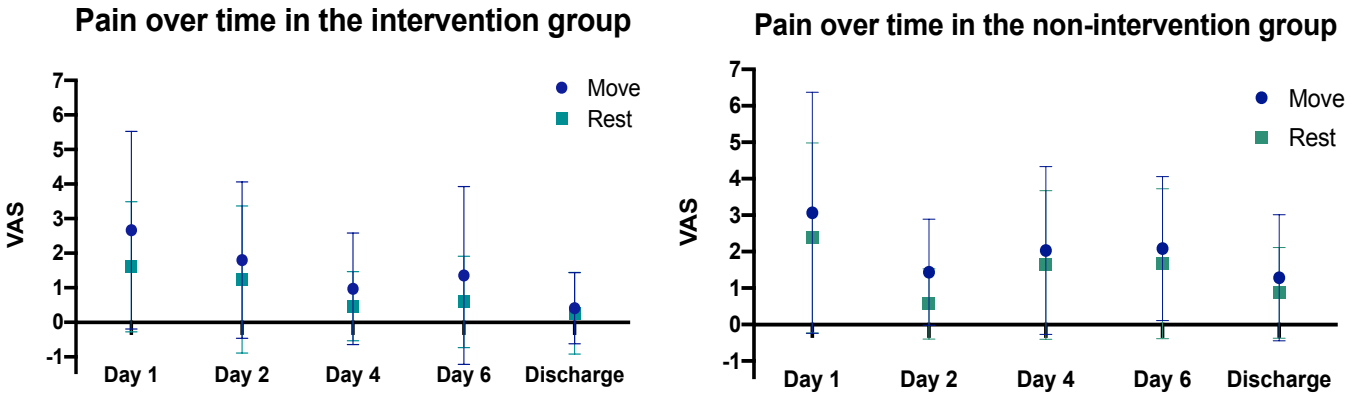

Figure 3: Mean and SD of pain measured on visual analogue scale (VAS) (0: no pain, 10: maximal pain)

4.4.3. Size of the erythema

In the intervention group, the SSTI affected 1 body site in 84% (61/73) of the patients. The median size of the erythema was 496 cm^2 (range 0 to 7'380 cm^2) on the day of hospital admission. In 15% (11/73) of the patients, 2 localizations were identified, and in 1 person (1%), 3 localizations were noted (Table 4). During treatment, the size of the erythema diminished. On the day of discharge, the median size had reduced to 100 cm^2 (range 0 to 2'480 cm^2) (Figure 4a/4b). In patients with 2 SSTI localizations, the median size of the second erythema was 96 cm^2 (range 0 to 968 cm^2) on the day of admission and 6 cm^2 (range 0 to 342 cm^2) on the day of discharge (Figure 5).

In the non-intervention group, the median size on the day of admission was 1'020 cm^2 (range 0 to 3'896 cm^2), which had reduced to a median of 550 cm^2 (range 0 to 1'953 cm^2) on the day of discharge (Figure 6).

Illustrative cases within the intervention group are presented in Appendix 2, page XIX.

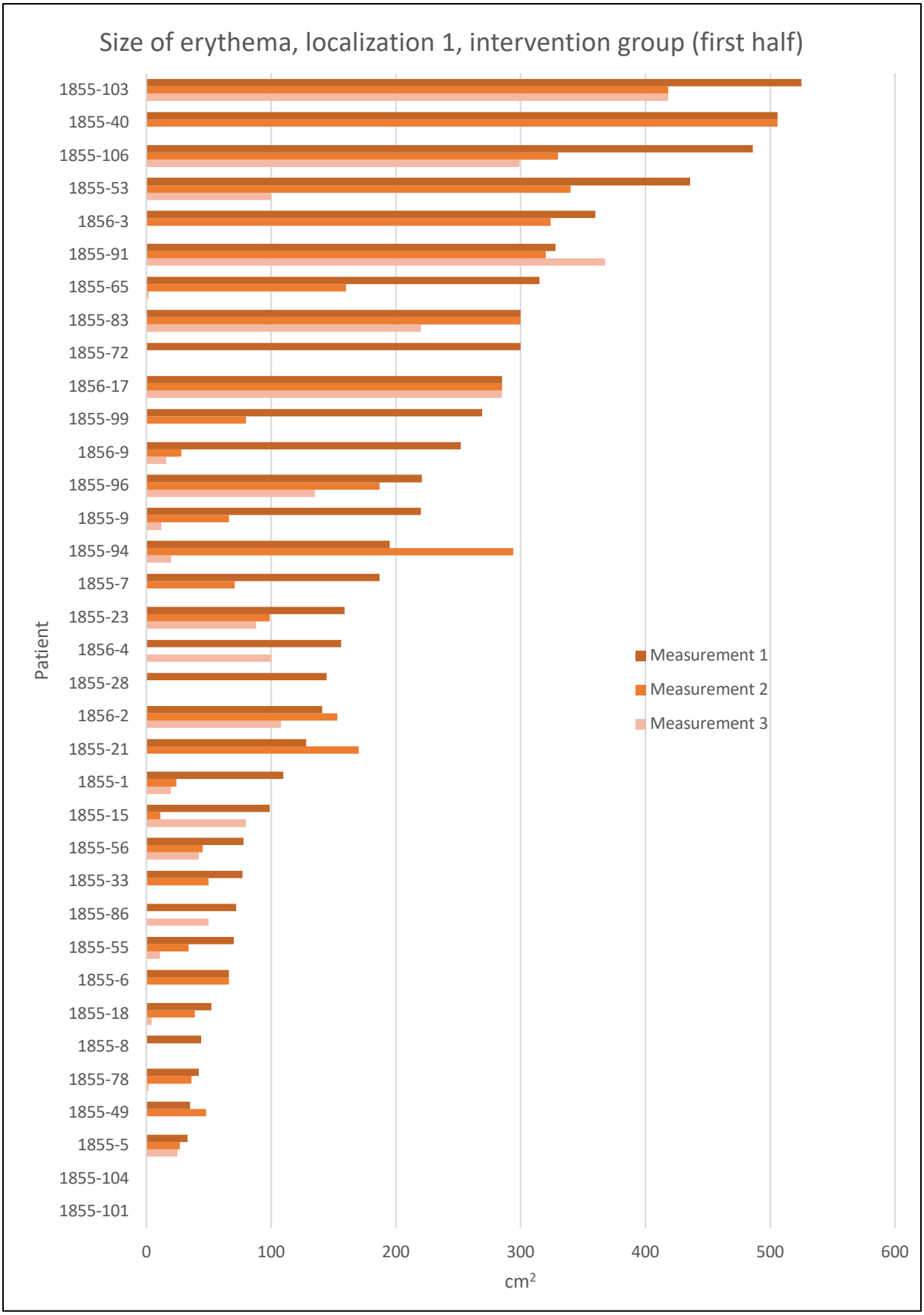

Figure 4a: Size of the erythema at hospital admission date, before the switch and on date of discharge in the intervention group; 2 patients had no redness to measure

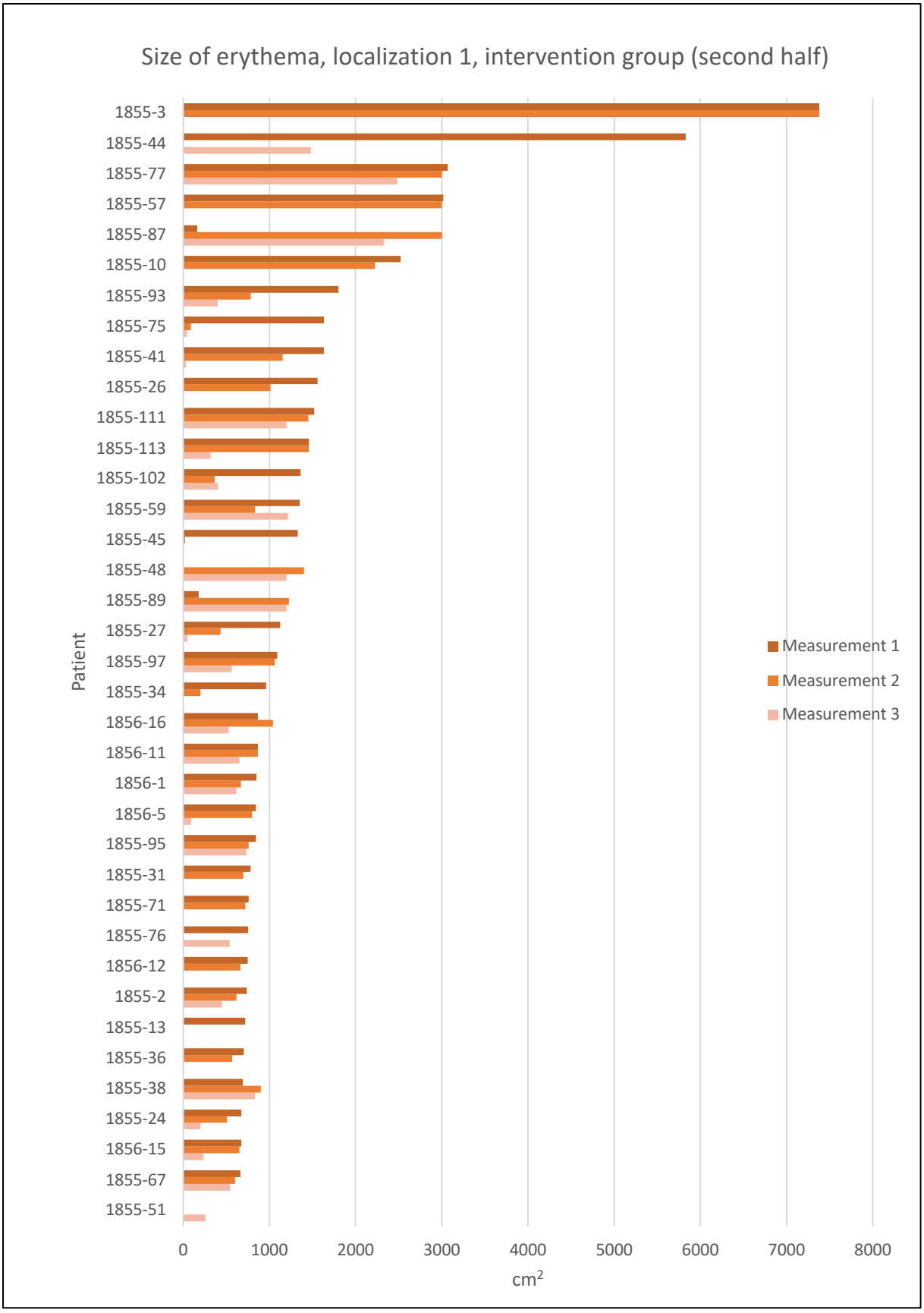

Figure 4b: Size of the erythema at hospital admission date, before the switch and on date of discharge in the intervention group;

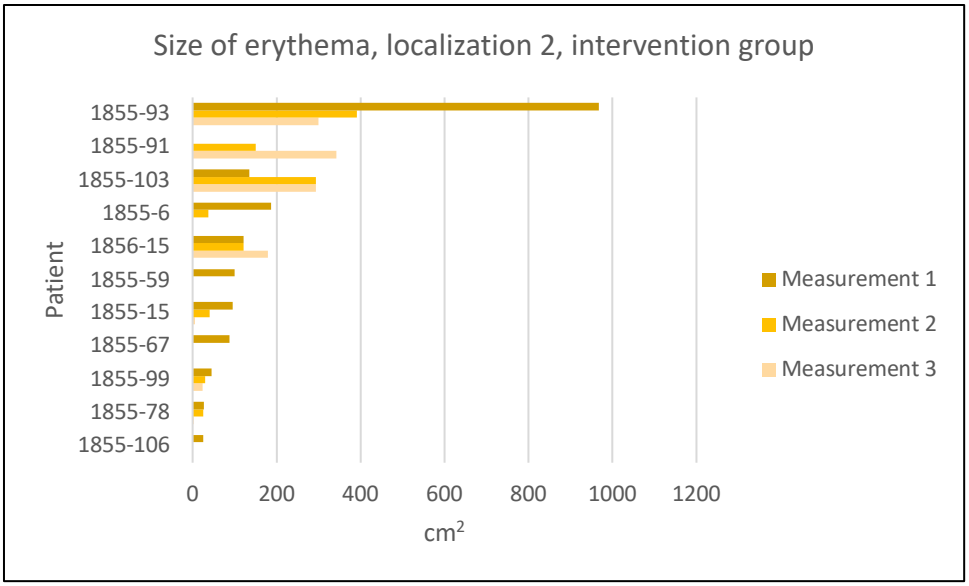

Figure 5: Size of the erythema on hospital admission date, before the switch and on date of discharge in the intervention group

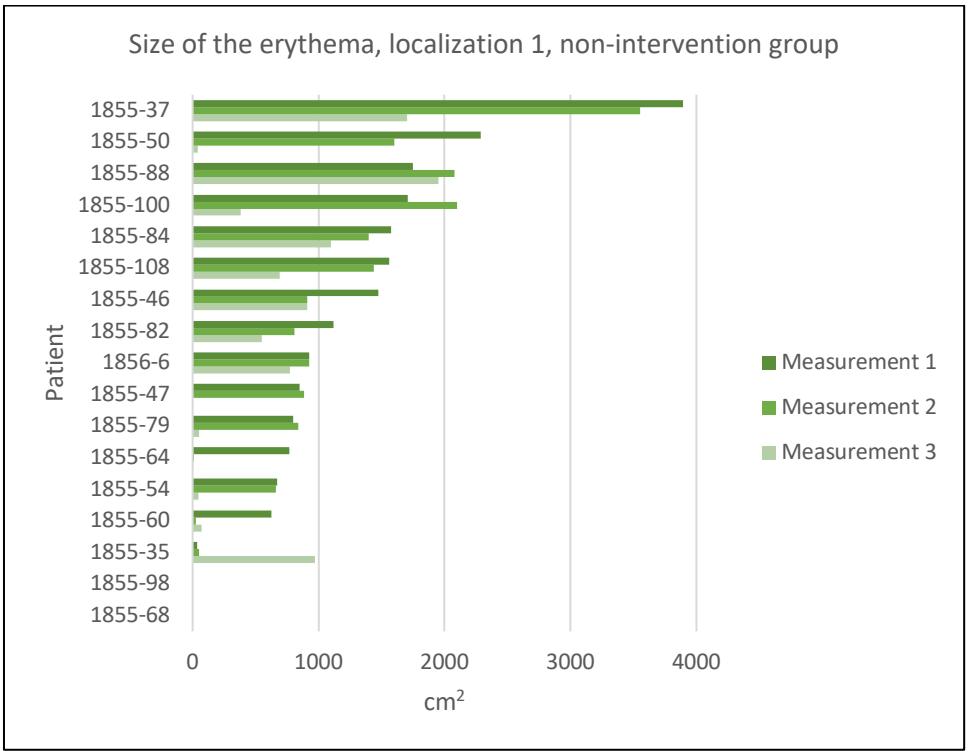

Figure 6 Size of the erythema on hospital admission date, before the switch and on date of discharge in the non-intervention group

4.5. Laboratory course during antibiotic treatment in the intervention group

The median CRP value of lab 1 was 99 mg/L (range 1 to 403 mg/L) and the median white blood cell (WBC) count was 10.95 G/L (range 4.43 to 38.30 G/L). Both parameters demonstrated decreasing dynamics. The values of lab 2 were median CRP level 85 mg/L (range 8 to 335 mg/L) and WBC count 7.49 G/L (range 3.15 to 15.20 G/L). At the last lab (preferably close to day 30, lab 4) the median CRP level was 6 mg/L (range 0 to 78 mg/L) and the median WBC count was 6.90 G/L (range 4.27 to 11.10 G/L).

2% of intervention group participants (1/57) had an increase in the WBC count and 39% (22/56) had an increase in the CRP level from the first to the second measurement (i.e., from lab 1 at day 1 to lab 2 at day 3 or 4).

All study subjects showed decreasing dynamics in lab values from lab 1 to lab 4 (Figure 7).

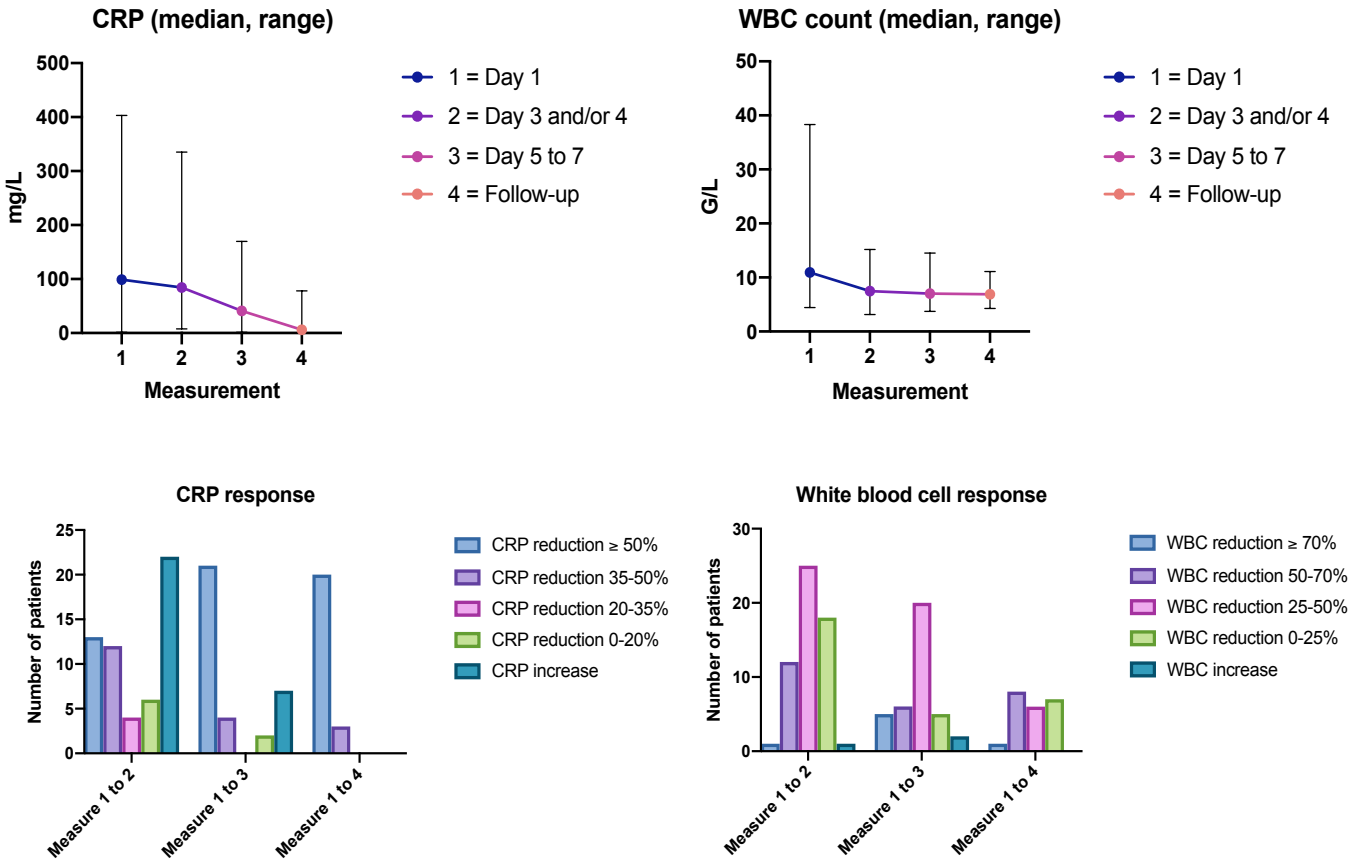

Figure 7: Biomedical response compared with the first measurement at hospital admission of the intervention group. Upper graphs: median and range; lower graphs: number of patients. CRP: C-reactive protein; WBC: white blood cell; Leuk: leukocyte

4.6. Antibiotic treatment

The median total antibiotic treatment duration in the study population was 11 days (range 6 to 40 days). In the intervention group, the median duration was 11 days (range 6 to 42 days) and in the non-intervention group, it was 15 days (range 6 to 38 days).

Consistent with the study protocol, the median and mean duration of the intravenous therapy in the intervention group was 2 days (range 1 to 9 days). Treatment of 1 patient assigned to the intervention group failed, and the patient was switched back from oral to intravenous treatment for 9 days. There was 1 documented protocol violation because physicians forgot to switch a patient from intravenous to oral treatment, resulting in the patient receiving 10 intravenous doses for 4 days, although an early switch was possible. The range of intravenous treatment duration without the treatment failure was 1 to 3 days in the intervention group.

The non-intervention group received a median of 4 days (range 3 to 11 days) of intravenous therapy. The duration of oral therapy in the intervention group was a median of 9 days (range 4 to 38 days) and in the non-intervention group it was a median of 10 days (range 3 to 27 days).

4.6.1. Antibiotic compounds

Intervention group

Amoxicillin/clavulanate: 64 patients received a median of 6 doses (range 2 to 25 doses) of intravenous treatment for a median duration of 2 days (range 1 to 9 days). The median number of doses of oral formulation was 22 (range 8 to 74 doses) for a median duration of 8.5 days (range 4 to 38 days).

Cefuroxime: 5 patients received intravenous therapy because of an allergy (see section 4.6.2). The median number of doses of intravenous formulation was 5 (range 3 to 6 doses) for a median duration of 2 days (range 1 to 2 days).

Vancomycin: 1 patient received vancomycin (4 doses) over 2 days intravenously.

Non-intervention group

Amoxicillin/clavulanate: 15 of 17 patients received a median of 12 doses of intravenous therapy (range 7 to 42 doses) for a median duration of 4 days (range 3 to 11 days). Intravenous therapy was followed by a median of 26 doses (range 4 to 80 doses) of oral formulation over a median duration of 10 days (range 5 to 27 days).

Cefuroxime and clindamycin: 1 patient received 10 doses of cefuroxime intravenously over 3 days followed by oral clindamycin (7 doses over 3 days).
Vancomycin and clindamycin: 1 patient received intravenous vancomycin for 7 days, followed by 23 days of oral treatment with clindamycin.

4.6.2. Allergies

7 individuals (9.6%) in the intervention group and 2 (12%) in the non-intervention group reported an allergy against an antibiotic compound. In the intervention group, 6 patients reported an allergy against penicillin or amoxicillin/clavulanate with a type 1 hypersensitivity, 2 of them with a history of anaphylaxis. 1 patient reported an allergy against clindamycin. In the non-intervention group, 1 individual reported a history of anaphylaxis against penicillin. One study participant reported penicillin intolerance (diarrhoea).

4.7. Duration of hospitalization

The median duration of hospitalization was 5 days (range 1 to 37 days). Median hospitalization was 5 days (range 1 to 37 days) in the intervention group and 7 days (range 4 to 17 days) in the non-intervention group. Figure 8 shows the alignment of duration of intravenous treatment, oral treatment and hospitalization.

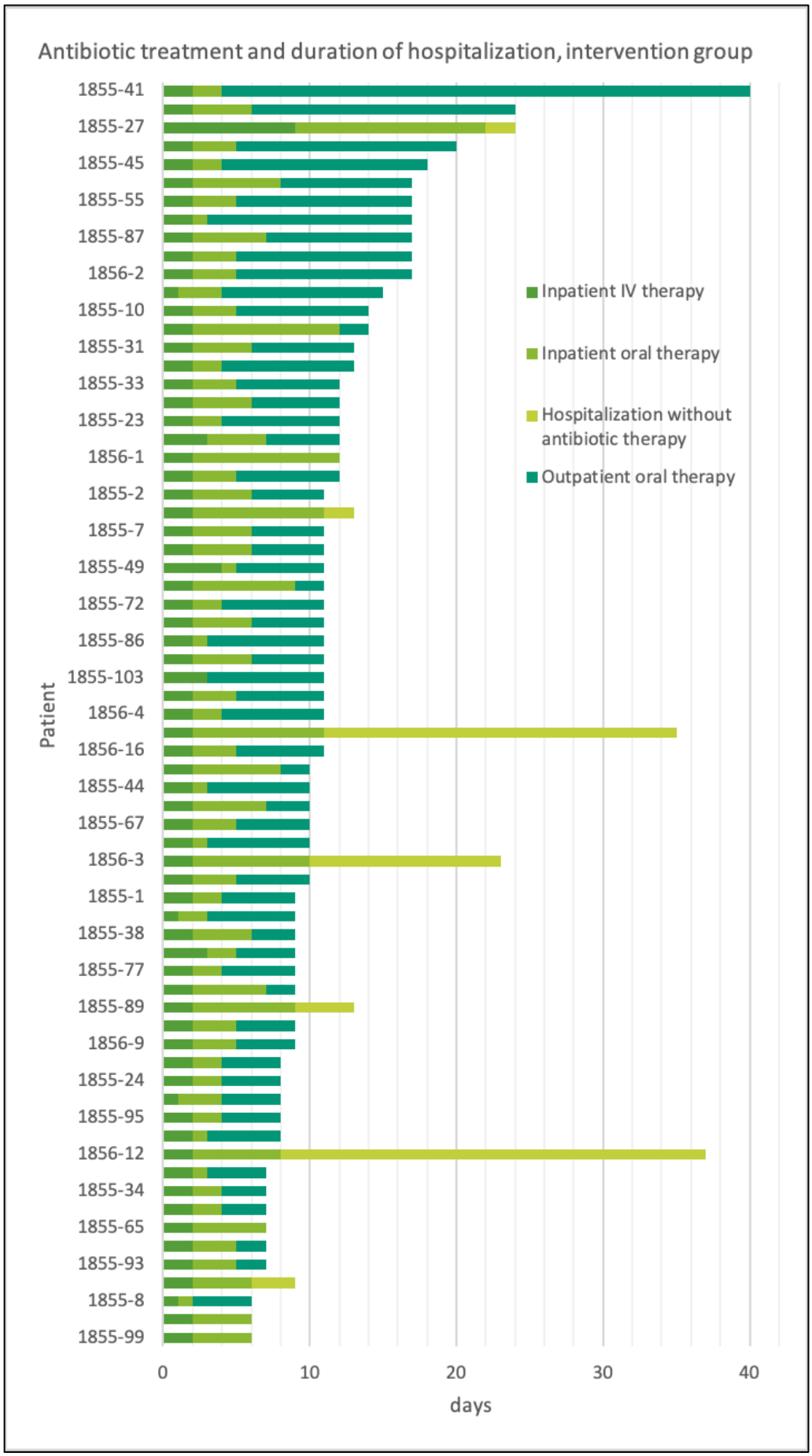

Figure 8 Duration of antibiotic treatment and hospitalization in days in intervention group. IV: intravenous

4.8. Follow-up

The follow-up phone call was performed on day 39 (median, range 28 to 90 days) in the intervention group and on day 39.5 (median, range 27 to 60 days) in the non-intervention group. There was 1 missing follow-up in the intervention group because the person was not available by phone.

In the intervention group, 69 of 73 study participants were available for follow-up examination, and in the non-intervention group, 17 patients were available (see Figure 9).

4.9. Outcome

There were 3 failures in the intervention group. One patient received 48 hours of intravenous antibiotic therapy with amoxicillin/clavulanate, and then 11 days of oral therapy. One day after cessation of the antimicrobial therapy, an abscess was detected. The abscess was incised, and intravenous antimicrobial treatment was restarted and continued for 8 days. Two patients receiving cephalosporins experienced a relapse within 30 days. Two patients in the intervention group received antibiotic treatment for other reasons (arthritis and otitis media) during the follow-up period. These 2 cases were not categorized as treatment failures. Thus, the cure proportion in the intervention group was 96% and the failure rate was 4%. In the non-intervention group, there was 1 relapse (6%).

In the follow-up interview, participants were asked about their subjective well-being in accordance with a predefined questionnaire (Appendix XVI). 86% (59/69) of the patients in the intervention group and 94% (16/17) in the non-intervention group reported a better general state in comparison to the date of hospital discharge.

In addition, patients were asked about their level of pain. In the intervention group, 84% (58/69) of patients reported reduced or no pain, and in the non-intervention group, 82% (14/17) reported the same.

Finally, patients were asked for their own judgment on the size of the erythema. Only 7% (5/69) in the intervention group and none (0/17) in the non-intervention group saw no considerable difference in size or redness of the erythema when comparing its size from the day of hospital discharge to the day of the telephone interview. However, 4 of the 5 patients in the intervention group reported a better general state and diminished pain. There were no adverse serious events, adverse events or rehospitalizations of the population during the study period.

The results of the follow-up examination are illustrated in the flow chart in Figure 9.

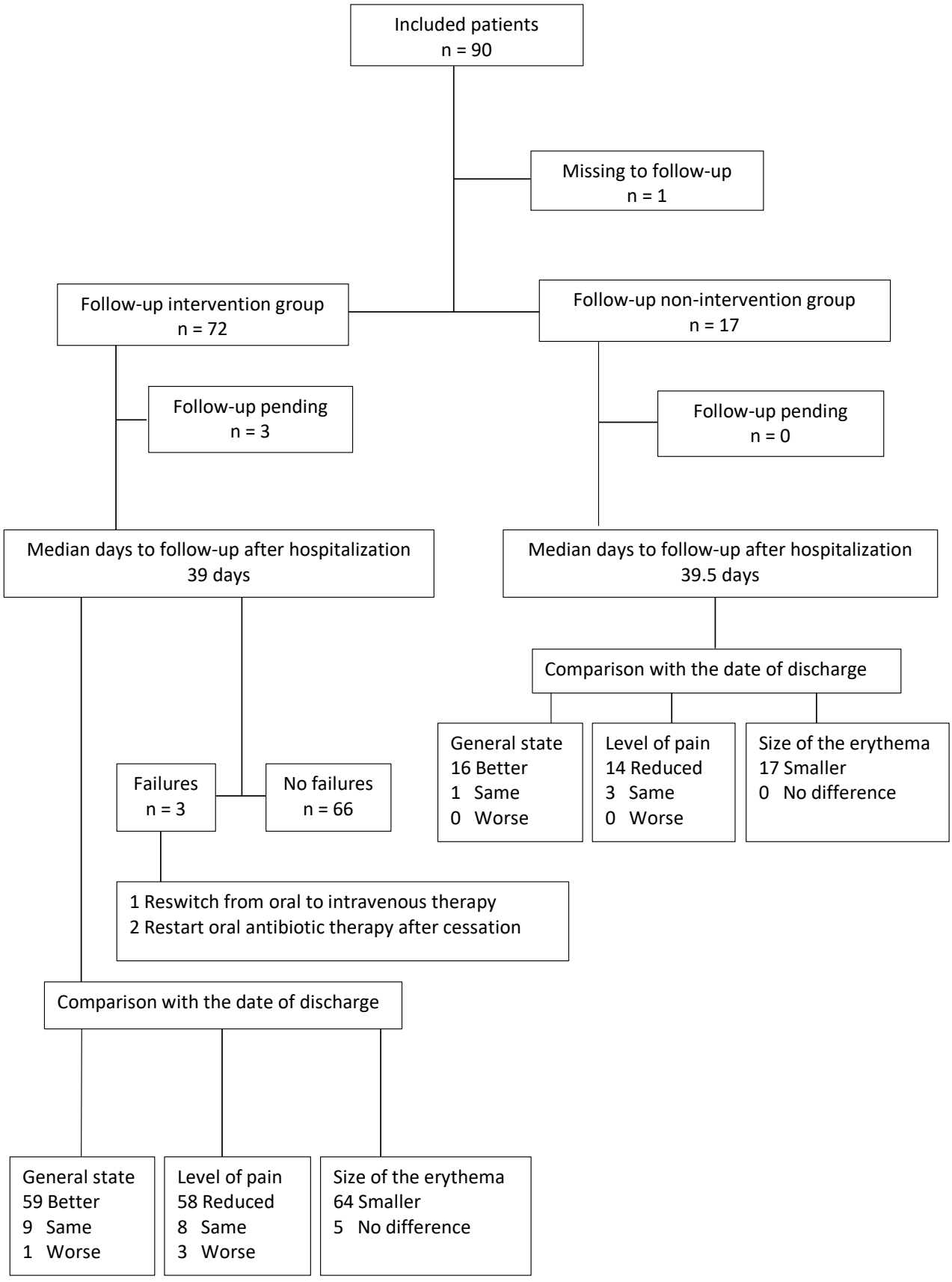

Figure 9 Results of follow-up

5. Discussion

In this prospective pilot study on uncomplicated SSTIs, we aimed to investigate whether or not the switch from intravenous to oral antibiotic treatment within 48 hours is safe and effective.

The recommended duration of antibiotic treatment for SSTIs is 5 to 14 days, depending on the clinical presentation. Clinical success is assessed as being when the SSTI improves during the treatment period[6,12]. In our study, the median duration of antibiotic treatment was 11 days (11 days in the intervention group and 15 days in the non-intervention group). The median duration of hospitalization was 5 days in the intervention group and 7 days in the non-intervention group.

A non-purulent, moderate SSTI, defined as the presence of systemic signs, should be initially treated with intravenous therapy[6]. This mode of therapy is recommended when the infection involves facial skin or when the peripheral circulation is impaired[12]. In this study, intravenous treatment was initiated in all patients because we included only those who required hospitalization because of the severity of infection. This severity is frequently classified as a moderate infection.

Concerning the criteria for switching from intravenous to oral antibiotic treatment, there appear to be different viewpoints in the literature. Ahkee et al.[15] used the following criteria: improvement in local signs and symptoms of an infection, guarantee of adequate gastrointestinal absorption, patient afebrile (>37.8°C) for at least 8 hours and leukocytosis decreased. The authors did not restrict this concept to SSTIs, however, as they included respiratory or urinary tract infections and intra-abdominal infection in their study[15]. A study from the Netherlands defined a switch after 48 to 72 hours from intravenous to oral therapy as being possible when the patient was hemodynamically stable with a trend towards normalization of body temperature and improvement in leukocytosis. They also included a broad range of infections in their study population (SSTIs and respiratory, urinary, abdominal and other infections)[14]. Mertz et al.[18] used similar switch criteria for different types of infections (lower respiratory, urinary tract, intra-abdominal, systemic inflammatory response syndrome/fever of unknown focus, SSTIs, fever in neutropenia, bone or joint, endocarditis, central nervous system and other infections) after 48-72 hours of intravenous therapy. In their switch criteria, a body temperature of <38.0°C (tympanic) for at least 24 hours was mandatory. In the case of bacteraemia with *S. aureus,* an early switch was not allowed[18].

All studies and recommendations agree, however, on the following criteria: Oral antibiotic therapy should be avoided in cases of severe infection during chemotherapy-related neutropenia. Moreover, enteral resorption must be present[14].

A study form Norway[27] defined switch criteria for cellulitis for day 1 and day 3. On day 1, there had to be an improvement in clinical presentation (cessation of lesion spread and local inflammation defined by the intensity of erythema, warmth and tenderness). On day 3, there had to be an improvement in clinical presentation and a reduction of ≥20% in CRP levels compared with those on days 1 or 2[27]. The results showed that, similar to the results of earlier studies, an improvement in local findings, a body temperature of >37.8°C for at least 24 hours, and a reduction in the WBC count and CRP values were useful criteria for an early switch, when gastrointestinal absorption was assumed. The strongest concordance between biomedical and clinical response occurred at days 2 and 3[27].

The assessment in our study after 48 hours was intended to identify severe infections that required prolonged therapy and prolonged hospitalization. We used predefined criteria to assess the clinical (not the biomedical) response to antibiotic treatment. For decision making, we used predefined criteria for the term 'uncomplicated' and included them in the exclusion criteria. However, all patients had a level of severity that required hospitalization. All patients were also assessed by a senior physician after 48 hours to confirm or overrule the switch decision. Under these preconditions, the cure rate for SSTIs was 96%. Our study indicates that CRP dynamics may be delayed; thus, the CRP value may be not a useful criterion for the switch decision. We valued the clinical response. Most patients reported improvement in symptoms and fulfilled the predefined clinical criteria within 48 hours (84% of patients: 100% in the intervention group, 18% in the non-intervention group), irrespective of laboratory values. Nearly 40% of patients in the intervention group showed an increase in the CRP value but were switched to an oral formulation. Our pilot study also shows that the algorithm was applicable to over 80% of included patients.

In other studies, a causative microorganism has been identified in only approximately 4% to 13% of SSTI cases[1,4–7]. The causative microorganism for SSTIs was identified in 7% of cases in our study, similar to that reported in previous studies. The most frequent microorganisms in SSTIs are beta-haemolytic streptococci (73%)[3,5,21] and *S. aureus*[1,21]. In recent years, GCS or GGS seems to be more prevalent than group A *Streptococcus* (GAS) (36 vs. 22 cases)[21]. In a Swedish study, GCS or GGS was the most commonly isolated microorganism (48%), followed

by GAS (26%), group B *Streptococcus* (GBS) (10%) and *S. aureus* (8%)[5]. In our study, GCS or GGS was found in 5 cases (2 in swabs and 3 in blood cultures) and GBS in 1 case.
Our study has limitations. The measurement of the size of the erythema has an inter-examiner bias and the measurement of the pain intensity is subjective, adding on an additional bias. As this was a pilot study, there was no randomization. We did not investigate whether there was an examiner bias when the switch criteria were assessed. In the follow-up phone call, there is potential recall bias, in particular when considering the telephone interviews. Finally, the small sample size in the non-intervention group did not allow any statistical conclusions. None of the statistical tests were significant.

Conclusions

In this prospective pilot trial on uncomplicated SSTIs in hospitalized patients, an algorithm-based switch from intravenous to oral antibiotic treatment after a maximum of 48 hours was successful in 96% of cases. The switch from intravenous to oral treatment could be performed in over 80% of the study population. We observed a shorter duration of hospitalization (median 2 days) in the intervention group than in the non-intervention group. The 2 study groups are, however, not comparable, because an algorithm with predefined criteria was applied to all study participants, leading to an uneven group distribution. A prospective non-inferiority multicentre trial is required to confirm these results on level 1 evidence.

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Potential conflicts of interest

There are no reported conflicts of interest.

Permission to conduct this study was granted by the ethical review committee of Canton Bern, Switzerland (KEK 2019-00558).

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Appendix