Original Article

Early Switch from Intravenous to Oral Antibiotics in Skin- and Soft-tissue Infections: An Algorithm-based Prospective Multicentre Pilot Trial.

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Abstract

Objectives: In hospitalized patients with skin and soft tissue infections (SSTIs), intravenous (IV) empiric antibiotic treatment is initiated. The best time point for switching from IV to oral treatment is unknown. We used an algorithm-based decision tree for the switch from IV to oral antibiotics within 48 hours and aimed to investigate the treatment outcome of this concept.

Methods: In a non-randomized trial, we prospectively enrolled 128 patients hospitalized with SSTI from July 2019 to May 2021 at three institutions. Clinical and biochemical response data during the first week and at follow-up after 30 days were analyzed. Patients fulfilling criteria for the switch from IV to oral antibiotics were assigned to the intervention group. The primary outcome was a composite definition consisting of the proportion of patients with clinical failure or death of any cause.

Results: Ninety-seven (75.8%) patients were assigned to the intervention group. All of them showed signs of clinical improvement (i.e.; absence of fever or reduction of pain) within 48 hours IV treatment, irrespective of erythema finding or biochemical response. The median total antibiotic treatment duration was 11 (IQR 9–13) days in the invention and 15 (IQR 11-24) days in the non-intervention group (p<0.001). The median duration of hospitalization was 5 (IQR 4-6) days in the intervention group and 8 (IQR 6-12) days in the non-intervention group (p<0.001). There were five (5.2%) failures in the intervention group and one (3.2%) in the non-intervention group after a median follow-up of 37 days.

Conclusions: In this pilot trial, the proposed decision-algorithm for early switch from IV to oral antibiotics for SSTI treatment was successful in 95% of cases.

Introduction

Skin and soft tissue infections (SSTIs, i.e. erysipelas and cellulitis without abscess formation or necrosis) rank among the most common community-acquired bacterial infections. The incidence of SSTIs in the United States is approximately 50 per 1000 patient years [1, 2]. The infection is typically caused by beta-hemolytic streptococci (approximately 75%) and *Staphylococcus aureus* [1-3]. A causative microorganism is identified in only 20%–30% of cases [1, 3]. Even when no microorganisms are identified, clinical response to beta-lactam antibiotics occurs in 95% of the cases [3]. The empiric treatment recommendations for SSTIs (i.e., erysipelas and cellulitis without abscess formation or necrosis) in our institutions include amoxicillin/clavulanate as the first choice. In the case of penicillin allergy, oral clindamycin is a possible alternative. Depending on the severity of the disease, a decision for hospitalization or outpatient treatment is made. In hospitalized patients, intravenous (IV) empiric antibiotic treatment is commonly initiated. The optimal time point for switching from IV to oral antibiotic treatment is unknown. In this study, we aimed to investigate the treatment outcome for uncomplicated SSTIs in hospitalized patients by using an algorithm-based decision tree for the switch from IV to oral antibiotics within a maximum of 48 hours after IV treatment initiation.

Methods

The prospective, non-randomized, multi-centre pilot trial was performed in three institutions (two primary care level centres and one secondary care level centre) in the Canton Bern, Switzerland. Eligible participants with SSTIs were 18 years or older, and required hospitalization because of the severity of the disease. Exclusion criteria were antibiotic treatment in the 14 days before enrolment, 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, tendosynovitis, bursitis, foreign body infection). Other exclusion criteria included Gram-negative bacteria as the causative organism for an SSTI or ecthyma gangrenosum. If these latter criteria were fulfilled after enrollment, study participants were excluded after being included in the first 48 hours of treatment.

Demographics, comorbidities, clinical characteristics, microbiology findings and laboratory values (designated as 'lab1' to 'lab3') were prospectively collected. Variables specifically obtained for SSTI included visual analogue scale (VAS) for pain, the anatomic body site of the infection, and the size of the skin lesion in cm^2 over time. Erythema in each enrolled patient was photographed.

Empiric IV antibiotics consisted of amoxicillin/clavulanate 2.2 g every 8 hours. In the case of penicillin allergy, cefuroxime 1.5 g (every 8 hours in case of delayed type allergy) or vancomycin (15 mg per kg body weight every 12 hours in case of immediate type allergy) was administered. In case of renal function impairment, doses were adapted accordingly. Oral antibiotics consisted of amoxicillin/clavulanate 1 g (3 times per day) or clindamycin (600 mg 3 times per day). The decision about total treatment duration was at the discretion of the responsible physician.

The study protocol flow chart is illustrated in supplementary material (**Appendix, Fig. S1**). The criteria for the switch from IV (maximum 48 hours, irrespective of time point of study inclusion) to oral treatment are shown in **Appendix**, **Fig. S2**. Study participants who did not fulfill these criteria or refused to be included in the intervention-group were assigned to the non-intervention group. In addition, prior to the switch to oral treatment, the local principal investigator (PI) evaluated clinical and laboratory values and was allowed to overrule the study intervention at his discretion because of insufficient clinical response to treatment at

day two. Study participants who remained on IV treatment because of the PI's decision were assigned to the non-intervention group.

For follow-up examination, patients were contacted via telephone on day 30 after initiation of antibiotic treatment and interviewed with a predefined questionnaire (**Appendix, Fig. S3**). If available, clinical data were complemented with laboratory examination (designated as 'lab 4') results performed by the patient's general practitioner.

The primary outcome was the proportion of 'clinical failure', a composite outcome according to definition. Clinical failure was defined as (i) new increase in symptoms during antibiotic treatment *or* after switch to oral therapy, (ii) a second course of antibiotic therapy after discontinuing the first course, (iii) readmission within 30 days after making the diagnosis of then SSTI because of persistent SSTI, or (iv) death. Cure was defined as absence of clinical failure.

Because this was a pilot study, we aimed for 100 patients in the intervention group and did not define the patient numbers in the non-intervention group. The number in the intervention group was arbitrary chosen in the light of a previously reported study with a clinical response to beta-lactam antibiotics in 95% of the SSTI cases [3].

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. The analysis and graphs were made with Stata/IC15.1 (Copyright 1985-2017 StataCorp LLC, 4905 Lakeway, USA) and GraphPad Prism9 (Version 9.2.0, © 1994 - 2021 GraphPad Software, LLC).

The study was registered International Standard Randomised Controlled Trial Number (ISRCTN 15245496).

Patient Consent Statement: Written consent was obtained from all study participants. The design of the work has been approved by the ethics committee of the Canton Bern, Switzerland (KEK 2019-00558).

Results

We screened 166 eligible patients and recruited 128 participants across the three sites between July 2019 and May 2021. Thirty-one study (24.2%) participants were assigned to the non-intervention group and 97 (75.8%) to the intervention group (**Fig. 1**). Patient characteristics are shown in **Table 1**. The lower limb was the most commonly affected body site (79%), followed by the head (9%), upper limb (7%) and trunk/buttocks (5%) (**Table 2**). A causative microorganism was identified in 12 of 128 (9.4%) individuals; in 9 (7.0%) individuals blood cultures were positive, in 3 patients samples from a skin blister showed bacterial growth. *Streptococcus dysagalactiae* ssp. *equisimilis* was the most frequent microorganism (8 cases), followed by *Streptococcus agalactiae* (3 cases) and *Staphylococcus aureus* (2 cases). In both infections due to *S. aureus*, a second microorganism was co-isolated (one sample each with *Streptococcus dysagalactiae* ssp. *equisimilis* and *Enterococcus faecalis*).

All individuals in the intervention group showed clinical improvement as defined in the study protocol after 48 hours of IV antibiotic treatment, and hence, qualified for a switch to oral antibiotic treatment. In the non-intervention group, 77% (24/31) did not fulfill these switch criteria. Seven participants fulfilled these criteria but either refused to switch (one individual) or the switch decision was overruled by the local principal investigator (six individuals) (**Fig. 1**).

The proportions of the primary outcomes (failures) were 5.2% (n=5) in the intervention group and 3.2% (n=1) the non-intervention group. The five failures in the intervention group consisted of two individuals with increase in symptoms or findings (e.g.; abscess) after switch to oral therapy and 3 individuals with a second course of antibiotic therapy after discontinuing the first course and readmission within 30 days (i.e., relapse). In the non-intervention group, there was one relapse. There were no deaths in either group.

In the intervention group, the median size of the erythema was 486 (IQR 147-7380) cm2 on the day of hospital admission. During treatment, the size of the erythema diminished, and had

reduced to a median of 100 (IQR 9-531) cm2 on the day of discharge. On hospital admission, the mean reported VAS for pain was 3/10 and 2/10 when participants moved or rested, respectively, the extremity. During the course of hospitalization, these values improved to 1 and 0, respectively, in patients belonging to the intervention group (**Appendix, Fig. S4**).

In the non-intervention group, the median size on the day of admission was 924 (IQR 512-1750) cm^2, which had reduced to a median of 256 (IQR 42-910) cm^2 on the day of discharge. In the non-intervention group, higher VAS pain scores than ones in the intervention group were reported (**Appendix, Fig. S4**).

The dynamics of laboratory results obtained from study participants in the intervention group are illustrated in **Fig. 2**.

The median total antibiotic treatment duration in the entire study population was 11 (IQR 9–15) days, 11 (IQR 9–13) days in the intervention and 15 (IQR 11-24) days in the non-intervention group (P<0.001). The median duration of hospitalization in the study population was 5 (IQR 4-8) days, 5 (IQR 4-6) days in the intervention group and 8 (IQR 6-12) days in the non-intervention group (P=0.001).

The follow-up phone call of the study population was performed on day 37 (median, IQR 32-50). Four individuals (3.13%) were lost to follow-up. The results from the follow-up questionnaire in the cured cases are illustrated in **Fig. 3**.

Discussion

In this prospective pilot study, we aimed to investigate whether or not the switch from IV to oral antibiotic treatment within 48 hours is safe and effective for a selected group of hospitalized patients with uncomplicated SSTIs. We used predefined criteria to assess the clinical response to antibiotic treatment. A biochemical response was not a prerequisite for switching, if clinical criteria indicated a response. As an intended consequence of the selection process, the comparison groups are uneven with more severe SSTI cases (larger size of erythema, higher inflammation values) in the non-intervention group. We proposed an algorithm to identify patients who are too ill to be managed in an outpatient setting but still qualify for an early switch from IV to oral treatment. The proportion of cure was 95% in 97 patients with a median follow-up of 37 days. With our approach, we observed a median length of stay of 5 days in the intervention group and 8 days in the non-intervention group (P=0.001). This pilot trial demonstrates the potential save of hospitalization days for a frequent infectious diseases entity with a good prognosis.

In our experience, IV antibiotic treatment is continued in hospitalized patients despite qualifying for an early switch to oral treatment. The reasons for prolonged IV treatment in these patients have not been explored and may include inadvertence, fear of unfavorable outcomes or the reliance on erythema or laboratory values for decision making.

Variable criteria for switching from IV to oral antibiotic treatment have been previously published. Ahkee et al. [4] applied improvement in local signs and symptoms of an infection, guarantee of adequate gastrointestinal absorption, absence of fever (<37.8°C) for at least 8 hours and decreasing leukocytosis as decision arguments. The authors did not restrict this concept to SSTIs. They included respiratory and urinary tract infections as well as intra-abdominal infections in their study [4]. A study from the Netherlands deemed a switch after 48 to 72 hours from IV to oral therapy as possible if the patient was hemodynamically stable, showed a trend towards normalization of body temperature and improvement in leukocytosis

for several infection entities [5]. Mertz et al. [6] used similar switch criteria for different types of infections after 48 to 72 hours of IV treatment. In their switch criteria, a body temperature of <38.0°C for at least 24 hours was mandatory. A study form Norway defined switch criteria for cellulitis for day 1 and 3 [7]. 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 to days 1 or 2 [7]. An improvement in local findings, a body temperature of <37.8°C for at least 24 hours, and a reduction in the white blood cell (WBC) count and C-reactive protein (CRP) values were useful criteria for an early switch, provided that there was no impairment of gastrointestinal absorption. The strongest concordance between biomedical and clinical response occurred on days 2 and 3 [7]. In our study, nearly 35% of patients in the intervention group showed an increase in the CRP value while being on IV treatment but were still switched to an oral antibiotic compound. Similar to reports of others [7], our study indicates that CRP dynamics may be delayed. In our view, the CRP value is not a useful criterion for the switch decision. In addition, the local findings are frequently difficult to interpret and correlate poorly with the time point bacterial killing, as erythema may persist for a prolonged time. Thus, in retrospect, CRP and erythema were overestimated as predefined switch criteria, and may be removed from the algorithm in the future.

All patients included in our study had a level of severity of infection (not of comorbidity) that required hospitalization. The algorithm led to uneven distribution of the groups, with more severe cases in the non-intervention group. Similarly, the median BMI and the frequency of diabetes mellitus was significantly higher in this group (**Table 1**). Both comorbid conditions are risk factors for SSTI and poor outcome [8, 9]. In addition, obesity is an independent risk factor for recurrent skin infection, and failure of antibiotic treatment in patients with cellulitis or cutaneous abscesses [10]. Thus, the proposed algorithm may also be helpful in identifying

patients who do not qualify for an early switch for IV to orals, and who are at risk for failure if switched too early. However, this hypothesis was not the scope of the study. Our study demonstrates that the proposed criteria can be applied to a large proportion of patients hospitalized for SSTI, taken into account the regional epidemiology of comorbidities and low rates of methicillin-resistant bacteria.

Patients were assessed by a senior infectious disease physician after 48 hours to confirm or overrule the switch decision. Under these conditions, the cure rate for SSTIs was 95% in the intervention group, and similar to reports of other studies [3]. However, the cure rate according to oral or IV antibiotic treatment stratification is less known, because most studies report the overall cure rate of SSTI. The cure rate in the non-intervention group was 97%. We cannot exclude that a prolonged IV treatment would have led to an even higher cure rate in the intervention group. However, IV antibiotics should be switched to orals when clinical improvement is apparent [11]. In an antibiotic stewardship program, Gibbons et al. [12] diminished median number of days of IV antibiotic therapy to oral conversion in SSTI infections by two days (i.e., from 5 to 3 days). These data illustrate that the time point of switch is reasonable between two and three days in most SSTI cases.

Our study has limitations. The enrollment of patient was delayed because of COVID-19. The algorithm led to an intended uneven distribution of cases, with more severe cases in the non-intervention group. As this was a pilot study, there was no randomization, and the non-inferiority statement would clearly require a larger sample size. We enrolled 97 patients in the intervention group. Both the targeted sample size of 100 patients in the intervention group and the switch time point of 48 hours were scientifically arbitrary, but in our view clinical reasonable. To demonstrate the number of hospital days saved on a larger scale, a further study is necessary. The group – designated as intervention group in this study – must be further randomized in an oral and IV treatment arm in a future trial. Considering a cure rate of 95% in this study, a sample size of 902 patients (451 in each group) would be necessary to

confirm the non-inferiority hypothesis. The measurement of the size of the erythema is subject to an inter-examiner bias and the measurement of the pain intensity is subjective, adding bias in an open study setting. However, these variables did not play a major role in the decision-making process for the switch to orals. Similarly, the decision to overrule despite fulfilling criteria for switch to orals is biased by the perspective of the treating physicians. However, as this was a pilot study, and 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. However, the proportion of lost to follow-up was <5%. Finally, the high cure rate in both groups together with the small sample size in the non-intervention group did not allow any firm statistical conclusions.

In summary, in this prospective pilot trial on uncomplicated SSTIs in hospitalized patients, an algorithm-based switch from IV to oral antibiotic treatment after a maximum of 48 hours was successful in 95% of cases. Approximately 75% of the study population was switched from IV to oral treatment according to the algorithm. We observed a significantly shorter median duration hospitalization by 5 (IQR 4-6) days in the intervention group compared to the non-intervention group with 8 (IQR 6-12) days. This pilot study proposes a method to identify SSTI-patients who do not require a prolonged hospitalization for IV treatment. A prospective randomized non-inferiority multi-centre trial will be required to confirm these results on level IA evidence.

Acknowledgments

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***Potential Conflict of Interest*:** None.

Author contributions: Study design, conceptualization, clinical responsibility, writing and critical revision (ME, BK, GW, CB, SD and PS). Conducting the study, clinical examination of patients and data entry (ME, BK, GW, CB, SD, AH, AB, EC, EG, FB, IA, JS, LW, MS, NB, PA, NB, SG, SK and UH). Follow-up and data entry (SD, SG and SK). Data monitoring AEB.

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Table 1: Patient characteristics and comorbidities of patients included in the study.

Patient characteristics	**Study population** **n = 128**	**Intervention** **n = 97**	**No Intervention** **n = 31**	***P* Value**
Gender				
- Male (%)	84 (65.6)	62 (63.9)	22 (70.9)	0.1331
- Female (%)	44 (34.4)	35 (36.1)	9 (29.0)	
Age (y), median (IQR)	62 (52-74.75)	62 (50-76)	60 (53-73)	0.7339
BMI (kg/m^2), median (IQR)	30.7 (26.3-36.2)	29.5 (25.5-34.1)	35.9 (29.1-43.3)	0.0010
Diabetes mellitus type II (%)	23 (17.9)	13 (13.4)	10 (32.3)	0.0292
- With insulin therapy (%)	9 (7.0)	4 (4.1)	5 (16.1)	
Diabetes mellitus type I	1 (0.8)	0 (0)	1 (3.2)	
Type not recorded	1 (0.8)	0 (0)	1 (3.2)	
Renal insufficiency				
- None or G1 (%)	63 (49.2)	53 (54.64)	10 (32.3)	0.1660
- G2 (%)	51 (39.8)	33 (34.02)	18 (58.1)	
- G3a (%)	5 (3.9)	4 (4.12)	1 (3.2)	
- G3b (%)	9 (7.0)	7 (7.22)	2 (6.5)	
- G4 and G5 (%)	0 (0)	0 (0)	0 (0)	
Total patients with RI	65 (50.8)	44 (45.4)	21 (67.7)	
Cardiovascular disease				
- PAOD	7 (5.5)	3 (3.1)	4 (12.9)	0.4026
- CHD	18 (14.1)	10 (10.3)	8 (25.8)	
- Hypertonia	70 (54.7)	48 (49.5)	22 (70.9)	
- 2 of them	18 (14.1)	10 (10.3)	8 (25.8)	
- all 3	3 (2.3)	1 (1.0)	2 (6.5)	
Total (≥ 1 of the listed)	60 (46.9)	38 (39.2)	22 (70.9)	
Immunodeficiency (%)				0.5286
- Exogenous (ie; drugs)	4 (3.1)	3 (3.1)	1 (3.2)	
- Endogenous (ie, disease)	3 (2.3)	2 (2.1)	1 (3.2)	
- Neoplasia	5 (3.9)	2 (2.1)	3 (9.7)	
Immunocompetent (%)	116 (90.6)	90 (92.8)	26 (83.8)	
Risk factors for SSTI (%)				0.2123
- Radiotherapy	10 (7.8)	5 (5.2)	5 (16.1)	
- Previous SSTI	38 (29.7)	26 (26.8)	12 (38.7)	
- Oedema	44 (34.5)	26 (26.8)	18 (58.2)	

IQR: interquartile range, BMI: Body mass index; PAOD: peripheral artery occlusive disease; CHD: coronary heart disease; SSTI: skin and soft tissue infection

Table 2. Localization and affected site of skin and soft-tissue infections.

Patient characteristics	**Study population** **n = 128**	**Intervention** **n = 97**	**No Intervention** **n = 31**	***P* Value**
Fever >38°C (%)	69 (53.91)	48 (49.48)	21 (67.74)	0.1145
Localization of SSTI (%)				0.0338
- Lower limb right	52 (40.6)	37 (38.1)	15 (48.4)	
- Lower limb left	49 (38.3)	36 (37.1)	13 (41.9)	
- Buttocks	4 (3.1)	4 (4.1)	0 (0)	
- Trunk	3 (2.3)	2 (2.1)	1 (3.2)	
- Upper limb right	5 (3.9)	5 (5.2)	0 (0)	
- Upper limb left	4 (3.1)	4 (4.1)	0 (0)	
- Head	11 (8.6)	9 (9.3)	2 (6.5)	

10 Patients (11.1%) had two localizations, and one patient three localizations of SSTI.

Figure legends:

Figure 1: Flow chart of patient screening, exclusion and enrolment.

Figure 2: 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.

Figure 3: Responses of study participants to follow-up questionnaire.

Figure

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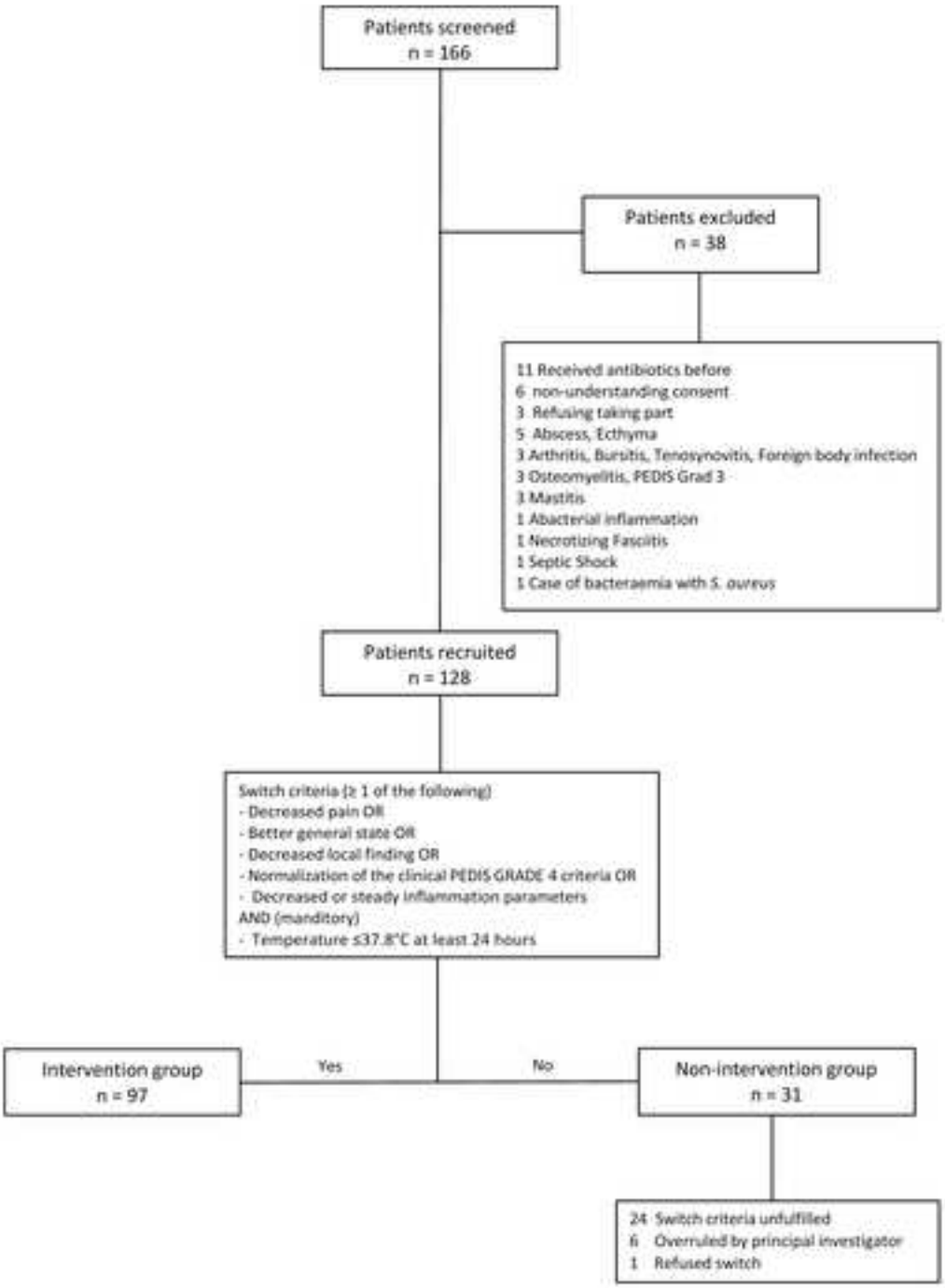

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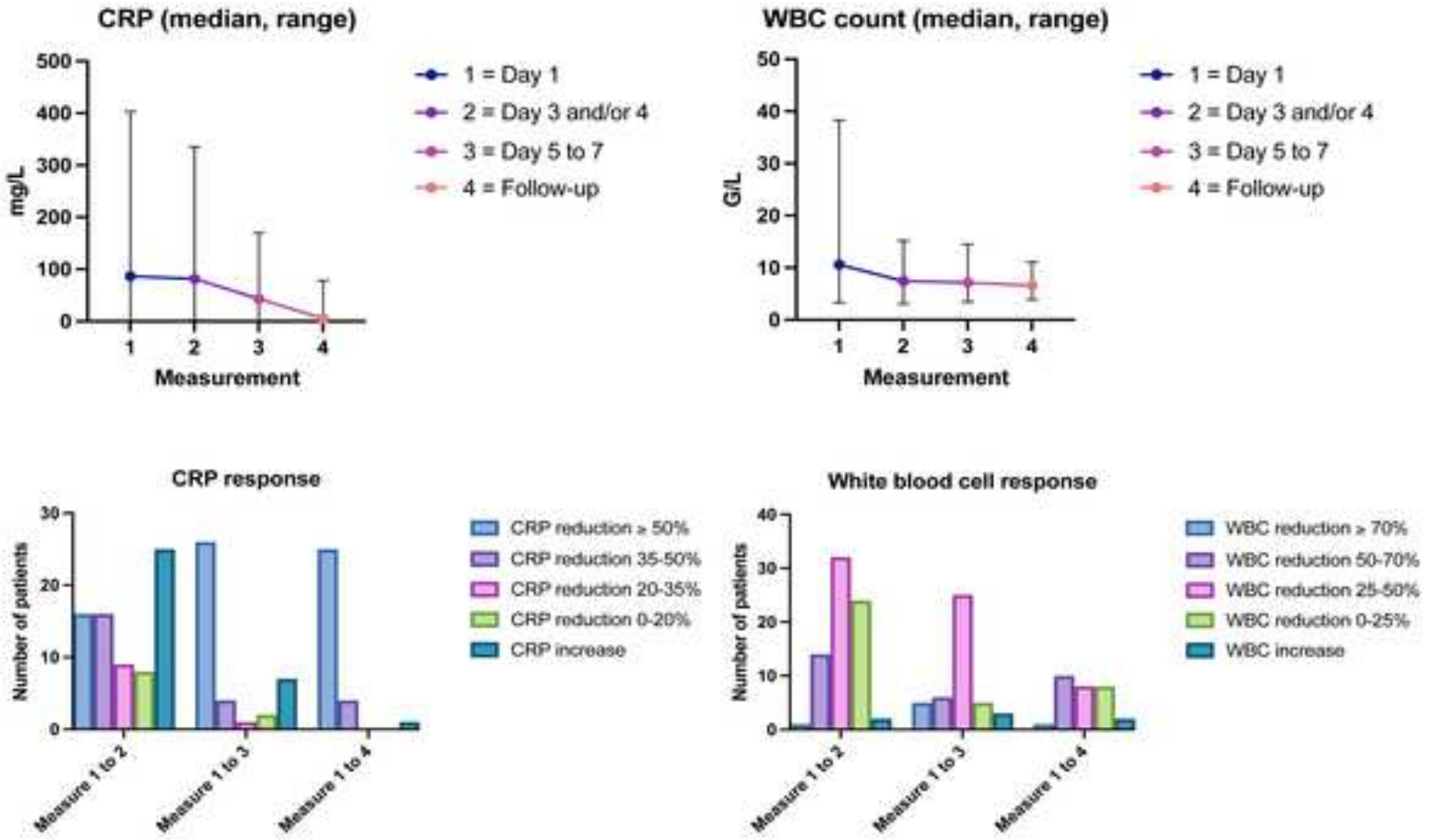

Figure

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