1 **Original Article**

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3 **Early Switch from Intravenous to Oral Antibiotics in Skin- and Soft-tissue Infections:**

4 **An Algorithm-based Prospective Multicentre Pilot Trial.**

5 Sandra Dellsperger,[1] Simea Kramer,[2] Michael Stoller,[2] Annika Burger,[1] Elio

6 Geissbühler,[1] Isabel Amsler,[1] Anna Hirsig,[1] Linda Weyer,[1] Ursula Hebeisen,[2] Philipp

7 Aebi,[1] Nicolas Burgherr,[1] Fabienne Brügger,[2] Edouard Chaix,[3] Jérôme Salamoni,[3] Sandra

8 Glauser,[1] Annina Elisabeth Büchi, [4,5] Charles Béguelin,[3] Gabriel Waldegg,[2] Bernhard

9 Kessler,[2] Martin, Egger,[1] Parham Sendi[6]

10 [1]Clinic of Internal Medicine, Emmental Hospital, Langnau, Switzerland

11 [2]Clinic of Internal Medicine, Emmental Hospital, Burgdorf, Switzerland

12 [3]Department of Internal Medicine, Spitalzentrum Biel, Biel/Bienne, Switzerland

13 [4]Department of General Internal Medicine, Inselspital, Bern University Hospital, University

14 of Bern, Bern, Switzerland

15 [5]Department of Emergency Medicine, Inselspital, Bern University Hospital, University of

16 Bern, Bern, Switzerland,

17 [6]Institute for Infectious Diseases, University of Bern, Bern, Switzerland.

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21 **Correspondence:**

22 Parham Sendi, MD, FIDSA

23 Institute for Infectious Diseases,

24 University of Bern, Friedbühlstrasse 51, 3010, Bern, Switzerland

25 Tel. +41 31 632 69 86; Fax. +41 31 632 86 67

26 Email: parham.sendi@ifik.unibe.ch

27 **Alternate Corresponding Author:**

28 Dr. med. Sandra Dellsperger

29 Institute for Infectious Diseases,

30 University of Bern, Friedbühlstrasse 51, 3010, Bern, Switzerland

31 Tel. +41 31 632 21 11; Fax. +41 31 632 86 67

32 Email: sandra.dell@gmx.ch

33

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.,

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86 bacteraemia with *S. aureus* or *Pseudomonas aeruginosa*, necrotizing fasciitis, skin abscess, a

87 septic shock or infection requiring intensive medical care, septic arthritis, osteomyelitis,

88 tendosynovitis, bursitis, foreign body infection). Other exclusion criteria included Gram-

89 negative bacteria as the causative organism for an SSTI or ecthyma gangrenosum. If these

90 latter criteria were fulfilled after enrollment, study participants were excluded after being

91 included in the first 48 hours of treatment.

92 Demographics, comorbidities, clinical characteristics, microbiology findings and laboratory

93 values (designated as 'lab1' to 'lab3') were prospectively collected. Variables specifically

94 obtained for SSTI included visual analogue scale (VAS) for pain, the anatomic body site of

95 the infection, and the size of the skin lesion in cm^2 over time. Erythema in each enrolled

96 patient was photographed.

97 Empiric IV antibiotics consisted of amoxicillin/clavulanate 2.2 g every 8 hours. In the case of

98 penicillin allergy, cefuroxime 1.5 g (every 8 hours in case of delayed type allergy) or

99 vancomycin (15 mg per kg body weight every 12 hours in case of immediate type allergy)

100 was administered. In case of renal function impairment, doses were adapted accordingly. Oral

101 antibiotics consisted of amoxicillin/clavulanate 1 g (3 times per day) or clindamycin (600 mg

102 3 times per day). The decision about total treatment duration was at the discretion of the

103 responsible physician.

104 The study protocol flow chart is illustrated in supplementary material (**Appendix, Fig. S1**).

105 The criteria for the switch from IV (maximum 48 hours, irrespective of time point of study

106 inclusion) to oral treatment are shown in **Appendix**, **Fig. S2**. Study participants who did not

107 fulfill these criteria or refused to be included in the intervention-group were assigned to the

108 non-intervention group. In addition, prior to the switch to oral treatment, the local principal

109 investigator (PI) evaluated clinical and laboratory values and was allowed to overrule the

110 study intervention at his discretion because of insufficient clinical response to treatment at

111   day two. Study participants who remained on IV treatment because of the PI's decision were

112   assigned to the non-intervention group.

113   For follow-up examination, patients were contacted via telephone on day 30 after initiation of

114   antibiotic treatment and interviewed with a predefined questionnaire (**Appendix, Fig. S3**). If

115   available, clinical data were complemented with laboratory examination (designated as 'lab

116   4') results performed by the patient's general practitioner.

117   The primary outcome was the proportion of 'clinical failure', a composite outcome according

118   to definition. Clinical failure was defined as (i) new increase in symptoms during antibiotic

119   treatment *or* after switch to oral therapy, (ii) a second course of antibiotic therapy after

120   discontinuing the first course, (iii) readmission within 30 days after making the diagnosis of

121   then SSTI because of persistent SSTI, or (iv) death. Cure was defined as absence of clinical

122   failure.

123   Because this was a pilot study, we aimed for 100 patients in the intervention group and did

124   not define the patient numbers in the non-intervention group. The number in the intervention

125   group was arbitrary chosen in the light of a previously reported study with a clinical response

126   to beta-lactam antibiotics in 95% of the SSTI cases [3].

127   Categorical parameters were compared with Fisher's exact test, and continuous variables were

128   compared with the Mann–Whitney U test. A p value of <0.05 was considered statistically

129   significant. The analysis and graphs were made with Stata/IC15.1 (Copyright 1985-2017

130   StataCorp LLC, 4905 Lakeway, USA) and GraphPad Prism9 (Version 9.2.0, © 1994 - 2021

131   GraphPad Software, LLC).

132   The study was registered International Standard Randomised Controlled Trial Number

133   (ISRCTN 15245496).

134   *Patient Consent Statement:* Written consent was obtained from all study participants. The

135   design of the work has been approved by the ethics committee of the Canton Bern,

136   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

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163   reduced to a median of 100 (IQR 9-531) cm2 on the day of discharge. On hospital admission,

164   the mean reported VAS for pain was 3/10 and 2/10 when participants moved or rested,

165   respectively, the extremity. During the course of hospitalization, these values improved to 1

166   and 0, respectively, in patients belonging to the intervention group (**Appendix, Fig. S4**).

167   In the non-intervention group, the median size on the day of admission was 924 (IQR 512-

168   1750) cm^2, which had reduced to a median of 256 (IQR 42-910) cm^2 on the day of discharge.

169   In the non-intervention group, higher VAS pain scores than ones in the intervention group

170   were reported (**Appendix, Fig. S4**).

171   The dynamics of laboratory results obtained from study participants in the intervention group

172   are illustrated in **Fig. 2**.

173   The median total antibiotic treatment duration in the entire study population was 11 (IQR 9–

174   15) days, 11 (IQR 9–13) days in the intervention and 15 (IQR 11-24) days in the non-

175   intervention group ($P<0.001$). The median duration of hospitalization in the study population

176   was 5 (IQR 4-8) days, 5 (IQR 4-6) days in the intervention group and 8 (IQR 6-12) days in

177   the non-intervention group ($P=0.001$).

178   The follow-up phone call of the study population was performed on day 37 (median, IQR 32-

179   50). Four individuals (3.13%) were lost to follow-up. The results from the follow-up

180   questionnaire in the cured cases are illustrated in **Fig. 3**.

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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

209   for several infection entities [5]. Mertz et al. [6] used similar switch criteria for different types

210   of infections after 48 to 72 hours of IV treatment. In their switch criteria, a body temperature

211   of <38.0°C for at least 24 hours was mandatory. A study form Norway defined switch criteria

212   for cellulitis for day 1 and 3 [7]. On day 1, there had to be an improvement in clinical

213   presentation (cessation of lesion spread and local inflammation defined by the intensity of

214   erythema, warmth and tenderness). On day 3, there had to be an improvement in clinical

215   presentation and a reduction of ≥20% in CRP levels compared to days 1 or 2 [7]. An

216   improvement in local findings, a body temperature of <37.8°C for at least 24 hours, and a

217   reduction in the white blood cell (WBC) count and C-reactive protein (CRP) values were

218   useful criteria for an early switch, provided that there was no impairment of gastrointestinal

219   absorption. The strongest concordance between biomedical and clinical response occurred on

220   days 2 and 3 [7]. In our study, nearly 35% of patients in the intervention group showed an

221   increase in the CRP value while being on IV treatment but were still switched to an oral

222   antibiotic compound. Similar to reports of others [7], our study indicates that CRP dynamics

223   may be delayed. In our view, the CRP value is not a useful criterion for the switch decision.

224   In addition, the local findings are frequently difficult to interpret and correlate poorly with the

225   time point bacterial killing, as erythema may persist for a prolonged time. Thus, in retrospect,

226   CRP and erythema were overestimated as predefined switch criteria, and may be removed

227   from the algorithm in the future.

228   All patients included in our study had a level of severity of infection (not of comorbidity) that

229   required hospitalization. The algorithm led to uneven distribution of the groups, with more

230   severe cases in the non-intervention group. Similarly, the median BMI and the frequency of

231   diabetes mellitus was significantly higher in this group (**Table 1**). Both comorbid conditions

232   are risk factors for SSTI and poor outcome [8, 9]. In addition, obesity is an independent risk

233   factor for recurrent skin infection, and failure of antibiotic treatment in patients with cellulitis

234   or cutaneous abscesses [10]. Thus, the proposed algorithm may also be helpful in identifying

235 patients who do not qualify for an early switch for IV to orals, and who are at risk for failure

236 if switched too early. However, this hypothesis was not the scope of the study. Our study

237 demonstrates that the proposed criteria can be applied to a large proportion of patients

238 hospitalized for SSTI, taken into account the regional epidemiology of comorbidities and low

239 rates of methicillin-resistant bacteria.

240 Patients were assessed by a senior infectious disease physician after 48 hours to confirm or

241 overrule the switch decision. Under these conditions, the cure rate for SSTIs was 95% in the

242 intervention group, and similar to reports of other studies [3]. However, the cure rate

243 according to oral or IV antibiotic treatment stratification is less known, because most studies

244 report the overall cure rate of SSTI. The cure rate in the non-intervention group was 97%. We

245 cannot exclude that a prolonged IV treatment would have led to an even higher cure rate in

246 the intervention group. However, IV antibiotics should be switched to orals when clinical

247 improvement is apparent [11]. In an antibiotic stewardship program, Gibbons et al. [12]

248 diminished median number of days of IV antibiotic therapy to oral conversion in SSTI

249 infections by two days (i.e., from 5 to 3 days). These data illustrate that the time point of

250 switch is reasonable between two and three days in most SSTI cases.

251 Our study has limitations. The enrollment of patient was delayed because of COVID-19. The

252 algorithm led to an intended uneven distribution of cases, with more severe cases in the non-

253 intervention group. As this was a pilot study, there was no randomization, and the non-

254 inferiority statement would clearly require a larger sample size. We enrolled 97 patients in the

255 intervention group. Both the targeted sample size of 100 patients in the intervention group and

256 the switch time point of 48 hours were scientifically arbitrary, but in our view clinical

257 reasonable. To demonstrate the number of hospital days saved on a larger scale, a further

258 study is necessary. The group – designated as intervention group in this study – must be

259 further randomized in an oral and IV treatment arm in a future trial. Considering a cure rate of

260 95% in this study, a sample size of 902 patients (451 in each group) would be necessary to

261 confirm the non-inferiority hypothesis. The measurement of the size of the erythema is

262 subject to an inter-examiner bias and the measurement of the pain intensity is subjective,

263 adding bias in an open study setting. However, these variables did not play a major role in the

264 decision-making process for the switch to orals. Similarly, the decision to overrule despite

265 fulfilling criteria for switch to orals is biased by the perspective of the treating physicians.

266 However, as this was a pilot study, and we did not investigate whether there was an examiner

267 bias when the switch criteria were assessed. In the follow-up phone call, there is potential

268 recall bias. However, the proportion of lost to follow-up was <5%. Finally, the high cure rate

269 in both groups together with the small sample size in the non-intervention group did not allow

270 any firm statistical conclusions.

271 In summary, in this prospective pilot trial on uncomplicated SSTIs in hospitalized patients, an

272 algorithm-based switch from IV to oral antibiotic treatment after a maximum of 48 hours was

273 successful in 95% of cases. Approximately 75% of the study population was switched from

274 IV to oral treatment according to the algorithm. We observed a significantly shorter median

275 duration hospitalization by 5 (IQR 4-6) days in the intervention group compared to the non-

276 intervention group with 8 (IQR 6-12) days. This pilot study proposes a method to identify

277 SSTI-patients who do not require a prolonged hospitalization for IV treatment. A prospective

278 randomized non-inferiority multi-centre trial will be required to confirm these results on level

279 IA evidence.

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338 **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)	

339 IQR: interquartile range, BMI: Body mass index; PAOD: peripheral artery occlusive disease; CHD: coronary
340 heart disease; SSTI: skin and soft tissue infection
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348 **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 (%) - Lower limb right - Lower limb left - Buttocks - Trunk - Upper limb right - Upper limb left - Head	52 (40.6) 49 (38.3) 4 (3.1) 3 (2.3) 5 (3.9) 4 (3.1) 11 (8.6)	37 (38.1) 36 (37.1) 4 (4.1) 2 (2.1) 5 (5.2) 4 (4.1) 9 (9.3)	15 (48.4) 13 (41.9) 0 (0) 1 (3.2) 0 (0) 0 (0) 2 (6.5)	0.0338

349 10 Patients (11.1%) had two localizations, and one patient three localizations of SSTI.

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Patients screened
n = 166

Patients excluded
n = 38

11 Received antibiotics before
6 non-understanding consent
3 Refusing taking part
5 Abscess, Ecthyma
3 Arthritis, Bursitis, Tenosynovitis, Foreign body infection
3 Osteomyelitis, PEDIS Grad 3
3 Mastitis
1 Abacterial inflammation
1 Necrotizing Fasciitis
1 Septic Shock
1 Case of bacteraemia with S. aureus

Patients recruited
n = 128

Switch criteria (≥ 1 of the following)
- Decreased pain OR
- Better general state OR
- Decreased local finding OR
- Normalization of the clinical PEDIS GRADE 4 criteria OR
- Decreased or steady inflammation parameters
AND (manditory)
- Temperature ≤37.8°C at least 24 hours

Intervention group
n = 97

Yes

No

Non-intervention group
n = 31

24 Switch criteria unfulfilled
6 Overruled by principal investigator
1 Refused switch

CRP (median, range)

WBC count (median, range)

CRP response

White blood cell response

Included patients
n = 128

Lost to follow-up
n = 4

Follow-up intervention group
n = 93

Follow-up non-intervention group
n = 31

Median days to follow-up after hospitalization
37 days

Median days to follow-up after hospitalization
37 days

1 Failure

Comparison with the date of discharge
n = 30

General state	Level of pain	Size of the erythema
25 Better	25 Reduced	30 Smaller
5 Same	5 Same	
0 Worse	0 Worse	

Failures
n = 5

No failures
n = 88

2 Reswitch from oral to intravenous therapy
3 Restart oral antibiotic therapy after cessation

Comparison with the date of discharge

General state	Level of pain	Size of the erythema
80 Better	82 Reduced	87 Smaller
12 Same	8 Same	6 No difference
1 Worse	3 Worse	