# Current management of patients hospitalized with complicated skin and soft tissue infections across Europe (2010–2011): assessment of clinical practice patterns and real-life effectiveness of antibiotics from the REACH study

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## Abstract

Complicated skin and soft tissue infections (cSSTI) are common and frequently require treatment in hospital. Comprehensive current data on management practices in patients hospitalized with cSSTI are limited. REACH was a retrospective, observational cohort study designed to provide data on current clinical management of moderate to severe cSSTI in European hospitals. Data were collected via an electronic case report form from 129 sites in ten European countries. The study population comprised patients $\geq$ 18 years, hospitalized between March 2010 and February 2011 with cSSTI who received intravenous antibiotic treatment. Presented here is an analysis of the disease characteristics, treatment patterns during hospitalization and clinical outcomes identified by the study. The total population included 1995 patients (mean age 60.6 years; 57.7% male). Initial antibiotic treatment modification was reported in 39.6% ($n$ = 791) of patients; it was more common in patients with co-morbidities (42.6%), those requiring surgical intervention (43.4%), those with more severe infections such as bacteraemia (51.6%) or with fascia affected (49.0%), those admitted to the intensive care unit (56.2%) and those with lesions > 50 $cm^2$ (44.3%). A switch to narrower-spectrum antibiotic treatment (streamlining) occurred in 5.6% of patients. Mean length of hospital stay was 18.5 days ($\pm$19.9; median 12.0) and the total mortality rate was 3.4%. The data collected in REACH give a comprehensive and current view of real-life clinical management of cSSTI in European hospitals and provide evidence of a high rate of initial antibiotic treatment modification.

**Keywords:** Antibiotic, complicated skin and soft tissue infections, epidemiology, Europe, hospitalized, management, moderate-to-severe, observational, outcomes, treatment modification

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## Introduction

Complicated skin and soft tissue infections (cSSTI), also termed 'acute bacterial skin and soft tissue infections' by the US Food and Drug Administration, are among the most common infections treated in the hospital setting. They represent a heterogeneous range of diseases, from patients with severe infection who are otherwise healthy to patients with relatively minor infection but underlying co-morbidities [1]. Some of these infections involve deep layers of skin and supporting structures, leading to substantial morbidity and mortality that can be resource intensive and incur high healthcare costs [2, 3]. Patients frequently receive intravenous (IV) antibiotic therapy and surgical intervention [2, 4], and treatment may be further complicated by the presence of significant co-morbidities such as immunological disorders and diabetes mellitus [4–6].

Common examples of cSSTI include abscesses, cellulitis, fasciitis, diabetic foot infections and post-trauma and surgical site infections [7], as well as superficial infections or abscesses in an anatomical site where the risk of anaerobic or Gram-negative pathogen involvement is high, such as the rectal area [1, 8]. cSSTI may be polymicrobial and may involve both aerobic and anaerobic, and Gram-positive and Gram-negative, pathogens [9].

The predominant pathogens causing cSSTI are aerobic Gram-positive cocci, specifically *Staphylococcus aureus*, and streptococci [6]. *S. aureus* was isolated from 44.6% of North American patients with cSSTI over a 7-year period (1998–2004) [10]. A number of other pathogens are linked with cSSTI in specific epidemiological or clinical situations, most notably anaerobes and Gram-negative bacilli in patients with diabetes mellitus, and *Pseudomonas aeruginosa* in patients with neutropenia [6]. The emerging incidence of resistance to multiple antibiotics in bacteria makes cSSTI increasingly challenging to treat [11]. Furthermore, the choice of treatment is often complicated by the need to treat without a confirmed microbiological diagnosis.

cSSTI are reported to account for up to 10% of admissions to infection units in the USA [12] and in the United Kingdom [13]. However, cSSTI are complex to categorize as no clear definitions of severity are available, making it difficult to reach consistent decisions regarding which infections require hospitalization.

Information about real-life management of cSSTI, identification of risk factors for initial antibiotic treatment modification and its impact is limited. The REtrospective Study to Assess the Clinical Management of Patients with Moderate-to-Severe cSSTI or Community-Acquired Pneumonia (CAP) Infections in the Hospital Setting (REACH; NCT01293435) was a collaboration involving independent experts in cSSTI and CAP, a health economist and clinical investigators across Europe. The primary objective of the study was to systematically collect new, current (2010–2011) pan-European data on patients hospitalized with cSSTI or CAP to create a better understanding of patient and disease characteristics, and current clinical management in response to the real-world challenges of treating these infections.

## Methods

REACH was a multinational, multicentre, observational, retrospective cohort study of patients hospitalized with cSSTI and CAP. Only cSSTI patients are included in this analysis.

Data were collected from 129 sites in ten participating European countries (see Appendix S1 for full list of investigators). A variety of hospitals were included in the study, including university-affiliated, general, regional, public, private and large, medium and small hospitals.

The study was performed according to Good Clinical Practice and the Declaration of Helsinki. All local ethics committees approved the study protocol. Local legislation relating to written informed consent for non-interventional studies was followed in each country; in Germany and Portugal, where this information is mandatory, written informed consent was collected.

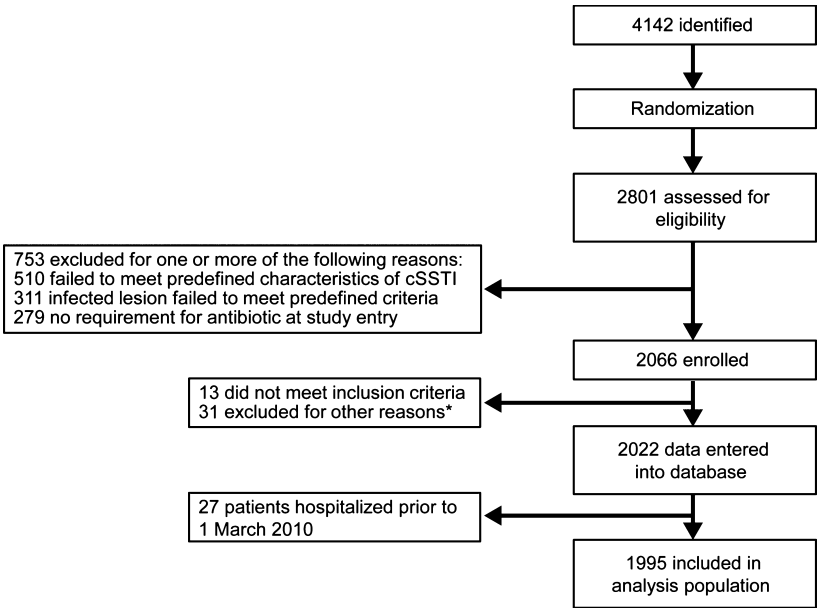


**FIG. 1.** Patient flow. *For example, patients assigned a patient number but eCRF not completed before database lock.

### Patients

The study population comprised patients diagnosed with cSSTI hospitalized between December 2010 and January 2011. The identification period was extended to include November 2010 and February 2011 and then extended backwards, month by month, until sufficient numbers of patients were obtained, or until March 2010, whichever was reached first.

*Inclusion and exclusion criteria.* Adults aged ≥18 years, hospitalized with cSSTI and receiving treatment with IV antimicrobials were included in the analysis population. Patients were selected from the total number of patients admitted to hospital within that time frame with cSSTI, as identified by World Health Organization ICD-10 diagnostic codes [14], using an automatic randomization tool. The selected patients were then assessed for eligibility by conducting a first review of the medical charts. Patients who did not meet the predefined criteria of cSSTI (detailed in Data S1) or who did not require IV antibiotics were excluded. The rest were enrolled (Fig. 1). Further inclusion and exclusion criteria are detailed in Data S1.

### Study variables

Variables collected and measured by completion of an electronic case report form are detailed in Data S1.

### Data analysis

This was a retrospective non-interventional study, using a descriptive analysis approach to assess clinical management and clinical outcomes. All calculations and summaries were produced using SAS Version 9.2.

'Initial antibiotic treatment modification' was defined as the need for a change in initial antibiotic treatment due to insufficient response, adverse reaction, interaction with other drugs, non-suitability of the initial antibiotic based on the results of microbiological tests, or changes to antibiotic therapy or addition of further agents, alone or in combination. Cases of 'streamlining', defined as change to narrower-spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis, were recorded separately. Cases of patient death while on initial antibiotic treatment were also recorded.

## Results

### Patient population

Patients ($N$ = 1995) were enrolled between March 2010 and February 2011 (the majority between October 2010 and February 2011; Fig. 1, Table S1, Data S1).

The mean age of patients was 60.6 years; 45.2% ($n$ = 902) of patients were ≥65 years old and 57.7% ($n$ = 1152) were male. There was a high degree of co-morbidity, with 78.0% ($n$ = 1556) of patients reporting one or more conditions, the most common being diabetes mellitus. The mean age of patients with co-morbidities was higher than for patients without (63.8 ± 16.0 vs. 49.3 ± 18.6 years, respectively; Table 1).

Disease characteristics, including types of infectious lesions, recurrences, nosocomial infections and pretreatment with antibiotics, are shown in Table 2. Bacteraemia was diagnosed in 6.3% ($n$ = 126) of the total number of patients. This represents 11.9% of the 1058 patients who had blood cultures performed.

*Diagnostic information.* All patients underwent a microbiological test; 53.0% ($n$ = 1058) had a blood culture and 48.6% ($n$ = 970) had a superficial swab and culture (Table S2). A microbiological diagnosis was obtained for 1001 (50.2%) patients (Table 3).

Of the patients with a microbiological diagnosis, 70.1% ($n$ = 702) were diagnosed with infection with Gram-positive cocci, with staphylococci accounting for 49.5% ($n$ = 495).

**TABLE 1. Patient demographics, characteristics and medical history**

| Characteristics | *N* = 1995 |
|---|---|
| Male, *n* (%) | 1152 (57.7) |
| Age, years, mean (SD ±) [median] | 60.6 (17.6) [62.0] |
| ≥65 years, *n* (%) | 902 (45.2) |
| Ethnic origin, *n* (%) | |
| White | 1596 (80.0) |
| Non-white | 51 (2.6) |
| Unknown/missing | 136 (6.8) |
| Not applicable[a] | 212 (10.6) |
| Invasive surgical treatment in the 3 months prior to initial visit,[b] *n* (%) | 279 (14.0) |
| Hospitalization in the previous 3 months for any reason, *n* (%) | 418 (20.9) |
| Time since previous date of hospitalization (*n* = 377), days, mean (SD ±) [median] | 35.7 (26.9) [30.0] |
| Co-morbidities, any relevant condition,[c] *n* (%) | 1556 (78.0) |
| Diabetes | 676 (33.9) |
| Peripheral vascular disease | 422 (21.2) |
| Congestive heart disease | 244 (12.2) |
| Cancer/malignancy | 207 (10.4) |
| Renal disease | 196 (9.8) |
| Respiratory disease | 190 (9.5) |
| Liver disease | 113 (5.7) |
| Alcohol abuse | 80 (4.0) |
| Immune system impairment | 69 (3.5) |
| Injection drug use | 46 (2.3) |
| AIDS-HIV | 31 (1.6) |
| Infectious diseases | 20 (1.0) |
| Other relevant conditions[c] | 670 (33.6) |
| Unknown | 7 (0.4) |
| Medication in the 3 months prior to hospitalization, *n* (%) | 1284 (64.3) |
| Antibiotics/antivirals | 596 (29.9) |
| Anticoagulants | 383 (19.2) |
| Non-steroidal anti-inflammatory drugs | 179 (9.0) |
| Immunosuppressors/immunomodulators | 130 (6.5) |
| Any other relevant medication | 380 (19.0) |
| Unknown | 127 (6.4) |

SD ±, standard deviation.
[a]All patients in this category were from France, where this question is not permitted in clinical studies.
[b]Visit to hospital for current infection or date of diagnosis of infection for patients already hospitalized.
[c]As defined by the investigator.

**TABLE 2. Disease characteristics of full population**

| Characteristics | *n* (%) *N* = 1995 |
|---|---|
| Type of lesion[a] | |
| Cellulitis/fasciitis | 1179 (59.1) |
| Abscess | 461 (23.1) |
| Post-surgical wound | 252 (12.6) |
| Diabetic leg ulcer | 237 (11.9) |
| Peripheral vascular disease ulcer | 221 (11.1) |
| Post-traumatic wound | 178 (8.9) |
| Decubitus ulcer | 92 (4.6) |
| Bite | 27 (1.4) |
| Burn | 10 (0.5) |
| Unknown | 20 (1.0) |
| Systemic signs of cSSTI at diagnosis | |
| White blood cell count >10 000/mm$^3$ | 1466 (73.5) |
| Temperature >38°C | 1208 (60.5) |
| Immature neutrophils >10% | 205 (10.3) |
| Organ dysfunction | 129 (6.5) |
| Septic shock | 71 (3.6) |
| Unknown | 122 (6.1) |
| Recurrent skin infection episode[b] | 509 (25.5) |
| Nosocomial infection | 199 (10.0) |
| Treatment with antibiotics before initial visit[c] | 701 (35.1) |
| Penicillin/combined with $\beta$-lactamase inhibitor | 348 (17.4) |
| Fluoroquinolone | 156 (7.8) |
| Cephalosporin | 80 (4.0) |
| Macrolide | 40 (2.0) |
| Aminoglycoside | 26 (1.3) |
| Glycopeptide | 20 (1.0) |
| Carbapenem | 19 (1.0) |
| Sulphonamide | 8 (0.4) |
| Drug against mycobacteria | 1 (0.1) |
| Other | 118 (5.9) |
| Unknown | 51 (2.6) |
| Co-medications during treatment | 1334 (66.9) |
| Anticoagulants | 772 (38.7) |
| Non-steroidal anti-inflammatory drugs | 411 (20.6) |
| Immunosuppressors/immunomodulators | 113 (5.7) |
| Chemotherapeutic agents | 21 (1.1) |
| Any other medication | 470 (23.5) |
| Unknown | 38 (1.9) |

[a]Patients could be classified with more than one type of cSSTI lesion.
[b]Patients hospitalized again due to same cSSTI.
[c]Visit to hospital for current infection or date of diagnosis of infection for patients already hospitalized.

Polymicrobial infections were identified in 30.2% ($n$ = 302) of patients.

Staphylococci were identified in 53.2% ($n$ = 67) of patients with bacteraemia and a microbiological diagnosis ($n$ = 126).

### Clinical management

Hospital types and specialists treating patients are shown in Table S3.

Most patients (77.8%; $n$ = 1553) were treated with an IV antibiotic on the first day of hospitalization. Empirical therapy was received by 81.6% ($n$ = 1628) of patients and 17.3% ($n$ = 346) received specific therapy directed by microbiological diagnosis (Table S3). Surgery was required by 37% ($n$ = 739) of patients, 26.7% ($n$ = 197) of whom underwent more than one surgical intervention.

### Clinical outcomes

Clinical outcomes for the full analysis population are detailed in Table 4. Initial antibiotic treatment modification, for any reason, was reported in 39.6% ($n$ = 791) of patients. Streamlining of treatment occurred in 5.6% ($n$ = 111) of patients. A number of cases listed as 'Other', 'Unknown' and 'No reason reported' were reviewed case-by-case by the investigators and were not related to clinical improvement, the availability of a microbiological diagnosis or narrowing of antibiotic spectrum. The time to treatment modification was $< 4$ days in 31.3% ($n$ = 124) of patients, $\geq 4$ days in 68.4% ($n$ = 271) and unknown in 0.3% ($n$ = 1).

Mean time to first treatment modification (including streamlining) was 7.7 days (±8.0; median 6.0) and the total mortality rate was 3.4% ($n$ = 68) for the full population (7.3% of patients with initial antibiotic treatment modification). Clinical stability, defined by the switch from IV to oral therapy or any other possible criteria, was reached in $< 4$ days by 382 (19.2%) patients (Fig. 2), although the largest number of patients ($n$ = 188) reached clinical stability on the fourth day of treatment, with a mean time to clinical stability of 9.7 days (±11.2; median 7.0 days).

The mean length of hospital stay was 18.5 days (±19.9; median 12.0). Patients admitted to an intensive care unit (ICU) (6.5%; $n$ = 130) had a mean length of ICU stay of 9.7 days (±13.5; median 4.5 days). Home-based care after discharge was required by 14.1% ($n$ = 281) of patients [mean duration 26.9 days (±27.2; median 15.0)].

Clinical failure (defined as acute haemodynamic deterioration or death, or any other criterion considered indicative of clinical failure) occurred in 12.5% ($n$ = 250) of patients. Of these, the failure was related to the cSSTI in 62.4% ($n$ = 156) of patients, unrelated in 22.4% ($n$ = 56) of cases and due to unknown reasons in 15.2% ($n$ = 38) of cases.

*Antibiotics used and outcomes.* During treatment, 54 different antibiotic agents were used as monotherapy or in combinations. The antibiotics most commonly used as monotherapy for initial and subsequent lines of treatment, and their modification rates, are shown in Table S4.

Analysing treatments by antibiotic classes, used as monotherapy or in combination with any other agent/s, revealed that, overall, 60.3% of patients received a penicillin or penicillin plus $\beta$-lactamase inhibitor combination as their initial antibiotic coverage. Analysis of anti-methicillin-resistant *S. aureus* (MRSA) agents used as initial monotherapy or in combination with other antibiotics revealed that 5.2% ($n$ = 103) of patients received vancomycin, 4.4% ($n$ = 87) received daptomycin and 1.9% ($n$ = 37) received linezolid. Teicoplanin and tigecycline were less commonly used. Patients receiving some anti-MRSA agents experienced high rates of initial treatment modification (Table S4).

*Clinical outcomes according to disease characteristics.* Clinical outcomes according to disease characteristics are detailed in

**TABLE 3. Microbiological diagnosis for patients with cSSTI and bacteraemia and for patients with initial antibiotic treatment modification**

| Microbiological diagnosis | Patients with a microbiological diagnosis *n* = 1001 *n* (%) | Patients with initial antibiotic treatment modification *n* = 493 *n* (%) | Patients with bacteraemia and a microbiological diagnosis *n* = 126 *n* (%) | Patients with bacteraemia and initial antibiotic treatment modification *n* = 64 *n* (%) |
|---|---|---|---|---|
| Gram-positive cocci[a] | 702 (70.1) | 351 (71.2) | 97 (77.0) | 51 (79.7) |
| Methicillin-sensitive *Staphylococcus aureus* | 279 (27.9) | 116 (23.5) | 32 (25.4) | 14 (21.9) |
| Methicillin-resistant *Staphylococcus aureus* | 102 (10.2) | 58 (11.8) | 17 (13.5) | 12 (18.8) |
| Coagulase-negative *Staphylococcus* | 112 (11.2) | 59 (12.0) | 17 (13.5) | 8 (12.5) |
| *Vancomycin-intermediate S. aureus (VISA)* | 2 (0.2) | 2 (0.4) | 1 (0.8) | 1 (1.6) |
| *Streptococcus pyogenes* (group A β-haemolytic streptococci) | 40 (4.0) | 21 (4.3) | 11 (8.7) | 7 (10.9) |
| *Streptococcus agalactiae* (group B β-haemolytic streptococci) | 32 (3.2) | 16 (3.2) | 7 (5.6) | 3 (4.7) |
| Other β-haemolytic streptococci[b] | 66 (6.6) | 34 (6.9) | 10 (7.9) | 6 (9.4) |
| *Streptococcus pneumoniae* | 4 (0.4) | 1 (0.2) | 4 (3.2) | 1 (1.6) |
| *Enterococcus faecalis* | 85 (8.5) | 58 (11.8) | 7 (5.6) | 5 (7.8) |
| *Enterococcus faecium* | 29 (2.9) | 18 (3.7) | 5 (4.0) | 4 (6.3) |
| Other Gram-positive bacteria[c] | 33 (3.3) | 21 (4.3) | 1 (0.8) | 1 (1.6) |
| *Enterobacteriaceae*[d] | 341 (34.1) | 193 (39.1) | 26 (20.6) | 15 (23.4) |
| Non-fermenting Gram-negative bacilli[e] | 112 (11.2) | 65 (13.2) | 9 (7.1) | 4 (6.3) |
| Other Gram-negative bacteria[f] | 4 (0.4) | 3 (0.6) | 0 | 0 |
| Strict anaerobic bacteria[g] | 34 (3.4) | 15 (3.0) | 4 (3.2) | 1 (1.6) |
| Yeasts | 14 (1.4) | 11 (2.2) | 1 (0.8) | 1 (1.6) |
| Other microorganisms | 34 (3.4) | 9 (1.8) | 1 (0.8) | 1 (1.6) |
| Unknown diagnosis | 999 (50.1) | 301 (38.1) | 0 | 0 |

[a]Includes *Staphylococcus warnerii, Staphylococcus lugdugensis, Staphylococcus haemolyticus, Staphylococcus epidermidis, Staphylococcus* spp. non-*aureus, Streptococcus mitis, Streptococcus constellatus,* viridans *Streptococcus,* Group G streptococci, *Streptococcus mitis, Enterococcus* spp., unspecified Gram-positive cocci.
[b]Includes *S. dysgalactiae*, Group C streptococci, microaerophilic streptococci, *S. mileri, S. intermedius, S. anginosus, S. bovis.*
[c]Includes *Bacillus anthracis, Corynebacterium* spp., diphtheroids, *Proprionibacterium* spp., *Lactobacillus* spp., *Clostridium* spp., Gram-positive bacilli non-specified.
[d]Includes *Proteus mirabilis, Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia marcescens, Providencia stuartii, Morganella morganii, Pantoea* spp.).
[e]Includes *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas maltophilia, Shewanella putrefaciens.*
[f]Includes *Neisseria* spp., *Aeromonas hydrophila, Pasteurella multocida.*
[g]Includes *Gemella morbillorum, Bacteroides fragilis, Peptostreptococcus* spp., *Prevotella melaninogenica, Porphyromonas* spp.

**TABLE 4. Clinical outcomes for the full analysis population**

| Clinical outcome | *N* = 1995 |
|---|---|
| Initial antibiotic treatment modification, streamlining removed,[a] *n* (%) | 791 (39.6) |
| Streamlining,[b] *n* (%) | 111 (5.6) |
| Primary reason for initial antibiotic treatment modification,[c] *n* (%) | |
| Insufficient response/treatment failure | 339 (17.0) |
| Adverse events | 55 (2.8) |
| Possible interaction with other treatment | 1 (0.1) |
| Other | 246 (12.3) |
| Unknown | 68 (3.4) |
| No reason reported | 82 (4.1) |
| Overall treatment duration (*n* = 1974), days, mean (SD ±) [median] | 14.6 (14.3) [11.0] |
| Treatment response, days, mean (SD ±) [median] | |
| Time to clinical stability (*n* = 1715) | 9.7 (11.2) [7.0] |
| Based on switch from IV to oral therapy (*n* = 1149) | 9.9 (11.6) [7.0] |
| Based on other criteria (*n* = 567) | 9.2 (10.4) [6.0] |
| Length of hospital stay (*n* = 1942), days, mean (SD ±) [median] | 18.5 (19.9) [12.0] |
| Discharged from hospital, *n* (%) | 1880 (94.2) |
| Reinfection or recurrence,[d] *n* (%) | 172 (8.6) |
| Home-based care after discharge, *n* (%) | 281 (14.1) |
| Length of home-based care (*n* = 138), days, mean (SD ±) [median] | 26.9 (27.2) [15.0] |
| Death while on initial therapy | 28 (1.4) |
| Total mortality rate, *n* (%) | 68 (3.4) |

IV, intravenous; SD ±, standard deviation.
[a]Several antibiotic treatment modifications in the same patient were counted as a single initial antibiotic treatment modification case. Changes in dose or frequency of an existing antibiotic (considered as dose escalation or adjustment) and removal of an antibiotic from a combination and adjustment of dose or frequency of the remaining antibiotic were not considered as initial antibiotic treatment modification.
[b]De-escalation of treatment to narrower-spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis.
[c]If multiple reasons are reported, the more clinically relevant reasons were selected first as the primary reason for change.
[d]Patients hospitalized again due to same cSSTI.

Table 5. Patients with co-morbidities experienced a numerically higher rate of initial antibiotic treatment modification than those without (42.6% vs. 29.2%), greater reinfection or recurrence (9.6% vs. 5.2%), a longer time to clinical stability (mean 10.4 days vs. 7.1 days), a longer hospital stay (mean 19.9 days vs. 13.3 days) and a higher mortality rate (4.0% vs. 1.1%).

Patients with a nosocomial infection (10.0%; *n* = 199) had a numerically longer hospital stay (mean 35.7 days vs. 16.4 days), a higher rate of initial antibiotic treatment modification (48.7% vs. 38.6%) a higher mortality rate (4.0% vs. 3.3%), and were more likely to be infected with a Gram-negative bacterium compared with those with a non-nosocomial infection (49.7% vs. 31.3%). Additionally, a higher percentage had MRSA (13.2% vs. 9.6%). Of the patients with a nosocomial *S. aureus* infection, nearly half (47.6%) had MRSA, compared with 24% of those with non-nosocomial *S. aureus* infection.

Of the 1995 patients hospitalized for cSSTI, 172 (8.6%) patients had recurrences after discharge. These patients presented with similar types of lesions to those patients without a recurrent infection, although a higher percentage had diabetic leg ulcer (22.1% vs. 10.5%) or peripheral vascular disease ulcer (20.3% vs. 8.9%).

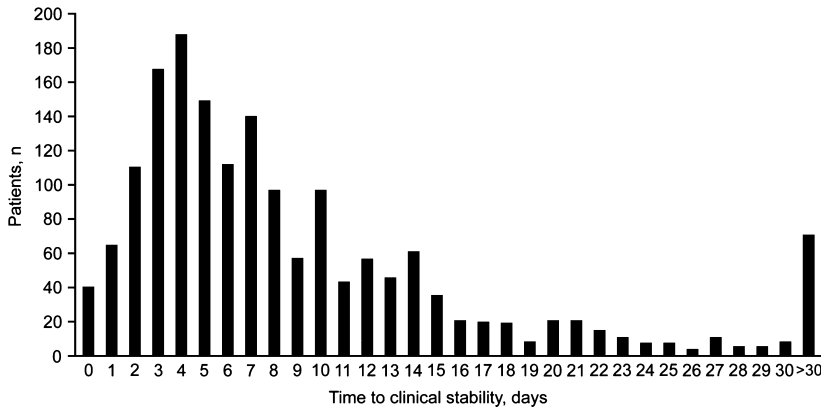


**FIG. 2.** Distribution of patients according to time to clinical stability.

**TABLE 5. Clinical outcome according to disease characteristics, in specific cSSTI patient groups and by site of infection**

| | Initial antibiotic treatment modification, *n* (%) | Streamlining, *n* (%) | Reinfection or recurrence,[a] *n* (%) | Length of hospital stay,[b] days, mean (SD ±) [median] | Time to clinical stability,[c] days, mean (SD ±) [median] | Total mortality rate, *n* (%) |
|---|---|---|---|---|---|---|
| Full analysis population, *N* = 1995 | 791 (39.6) | 111 (5.6) | 172 (8.6) | 18.5 (19.9) [12.0] (*n* = 1942) | 9.7 (11.2) [7.0] (*n* = 1715) | 68 (3.4) |
| With co-morbidities, *n* = 1556 | 663 (42.6) | 78 (5.0) | 149 (9.6) | 19.9 (20.4) [14.0] (*n* = 1514) | 10.4 (11.7) [7.0] (*n* = 1340) | 63 (4.0) |
| Without co-morbidities, *n* = 439 | 128 (29.2) | 33 (7.5) | 23 (5.2) | 13.3 (16.9) [8.0] (*n* = 428) | 7.1 (8.8) [5.0] (*n* = 375) | 5 (1.1) |
| Nosocomial cSSTI, *n* = 199 | 97 (48.7) | 8 (4.3) | 13 (6.5) | 24.0 (23.3) [16.0] (*n* = 193) | 11.2 (11.2) [8.0] (*n* = 153) | 8 (4.0) |
| Non-nosocomial cSSTI, *n* = 1796 | 694 (38.6) | 103 (5.8) | 159 (8.8) | 16.4 (17.5) [11.0] (*n* = 1749) | 9.5 (11.2) [7.0] (*n* = 1562) | 60 (3.3) |
| With recurrence,[a] *n* = 172 | 70 (40.7) | 11 (6.4) | 172 (100.0) | 35.7 (27.5) [29.0] (*n* = 172) | 12.3 (14.2) [7.0] (*n* = 145) | 0 (0.0) |
| Without recurrence,[a] *n* = 1563 | 611 (39.1) | 91 (5.8) | 0 | 16.4 (17.5) [11.0] (*n* = 1562) | 9.2 (10.9) [6.0] (*n* = 1404) | 1 (0.1) |
| With NSAIDs, *n* = 411 | 186 (45.3) | 31 (7.5) | 50 (12.2) | 18.9 (17.7) [13.0] (*n* = 407) | 10.0 (11.16) [7.0] (*n* = 355) | 8 (1.9) |
| Without NSAIDs, *n* = 1584 | 605 (38.2) | 80 (5.0) | 122 (7.7) | 18.3 (20.4) [12.0] (*n* = 1535) | 9.6 (11.3) [7.0] (*n* = 1360) | 60 (3.8) |
| With surgical intervention, *n* = 739 | 321 (43.4) | 54 (7.3) | 91 (12.3) | 24.4 (26.0) [16.0] (*n* = 713) | 12.8 (15.5) [8.0] (*n* = 631) | 31 (4.2) |
| Without surgical intervention, *n* = 1238 | 467 (37.7) | 57 (4.6) | 81 (6.5) | 15.0 (14.2) [11.0] (*n* = 1221) | 7.8 (7.1) [6.0] (*n* = 1082) | 37 (3.0) |
| Patients with bacteraemia, *n* = 126 | 65 (51.6) | 14 (11.1) | 13 (10.3) | 26.6 (26.4) [16.0] (*n* = 118) | 13.0 (14.8) [10.0] (*n* = 110) | 5 (4.0) |
| Patients with fascia affected, *n* = 431 | 211 (49.0) | 22 (5.1) | 59 (13.7) | 26.8 (26.3) [18] (*n* = 416) | 15.7 (17.6) [11.0] (*n* = 355) | 30 (7.0) |
| Lesion extension 10–50 $cm^2$, *n* = 504 | 220 (43.7) | 22 (4.4) | 48 (9.5) | 17.8 (20.5) [12.0] (*n* = 488) | 9.1 (8.9) [6.0] (*n* = 450) | 14 (2.8) |
| Lesion extension >50 $cm^2$, *n* = 318 | 141 (44.3) | 29 (9.2) | 22 (6.9) | 18.3 (21.6) [11.0] (*n* = 314) | 8.3 (8.4) [6.0] (*n* = 286) | 17 (5.3) |
| Patients admitted to ICU, *n* = 130 | 73 (56.2) | 10 (7.7) | 16 (12.3) | 37.1 (35.5) [25.0] (*n* = 123) | 16.8 (15.2) [14.0] (*n* = 92) | 22 (16.9) |
| Patients not admitted to ICU, *n* = 1844 | 715 (38.8) | 101 (5.5) | 156 (8.5) | 15.8 (15.6) [11.0] (*n* = 1810) | 9.3 (10.8) [7.0] (*n* = 1619) | 46 (2.5) |

NSAIDs, non-steroidal anti-inflammatory drugs; SD ±, standard deviation.
[a]Patient hospitalized again due to same cSSTI.
[b]Includes duration of all hospitalizations for patients with recurrences. In cases of nosocomial infection, length of hospital stay was calculated starting on the date of cSSTI diagnosis.
[c]Based on switch from IV to oral therapy or any other possible criteria.

Clinical outcomes in some specific cSSTI patient groups and by site of infection are shown in Table 5. Initial antibiotic treatment modification rate was numerically higher, compared with the total population, in patients with more severe infections, such as patients with bacteraemia (51.6%), patients admitted to the ICU (56.2%), patients with lesions > 50 $cm^2$ (44.3%) and patients with fascia affected (49.0%). Of the patients with fascia affected, 65.9% (*n* = 284) required surgery and 73.5% (*n* = 317) had a microbiological diagnosis, 40.4% (*n* = 128) of which were mixed infections with two or more microorganisms identified. Patients with fascia affected and patients admitted to the ICU had longer hospital stays (mean 26.8 and 37.1 days, respectively), longer time to clinical stability (mean 15.7 and 16.8 days, respectively) and a higher rate of mortality (7.0% and 16.9%, respectively). Patients ≥65 years old had a numerically higher mortality rate than younger patients (5.5%; *n* = 50 vs. 1.6%; *n* = 18). Patients with a confirmed diagnosis of MRSA had a high requirement for

initial treatment modification (56.9%; $n = 58$), while that for patients with methicillin-sensitive *S. aureus* (MSSA) was 41.4% ($n = 116$). The characteristics of patients requiring initial antibiotic treatment modification and their disease characteristics are presented in Tables S5 and S6.

## Discussion

The real-world evidence collected in the REACH study revealed unexpectedly high first-line treatment modification rates in hospitalized cSSTI patients throughout Europe.

The patient population described in this study was similar to that of previous studies [15, 16], being composed of older adults (45.2% $\geq$65 years of age), with a high degree of co-morbidity and concurrent treatment with medications, including antibiotics and antivirals. However, the patients in this study may have had more severe infections, as a high percentage had fever, leukocytosis and bacteraemia, which may be due to the enrollment criteria selected. The impact of co-morbidities on clinical outcomes for patients was considerable, increasing the risk of initial antibiotic treatment modification, reinfection or recurrence, length of hospital stay and death. The types of infection encountered were similar to those seen in other studies, including abscesses, cellulitis/fasciitis, infected ulcers in patients with diabetes or peripheral vascular disease, and postoperative and traumatic wound infections [15, 17].

Diagnosis of a cSSTI is generally based on clinical criteria and treatment is usually initiated before a microbiological diagnosis is available. Therefore, the antibiotic choice initially depends on the type and severity of infection and the suspected pathogens. Hence, although all patients in this study underwent a microbiological test, only half had a microbiological diagnosis. Swabs, notoriously unreliable diagnostic tools, were used in almost half of all tests. Thus, the majority was treated empirically. The fact that swabs are used so often indicates that there is considerable room for improvement in the way microbiological diagnosis is carried out in routine practice in cSSTI; real-life studies are useful to unveil this type of information. Conversely, the number of blood cultures performed and the percentage of positive cultures was higher than reported by others [18, 19]. Bacteraemia is uncommon in cellulitis: among 272 patients, initial blood cultures were positive in 4% of patients [19]. Blood cultures produce a low yield, with less than 5% of cases being positive [18]. The incidence of bacteraemia in our study was high, at 6.3%, and mortality in this group of patients was also high at 4%. The incidence of bacteraemia in controlled trials for new antibiotic agents for the treatment of cSSTI has been reported to range from 1–5% and mortality in these patients ranged from 0–1.5% [20–22]. This indicates that patients in the real-life REACH study had more severe illness than the populations recruited into controlled trials. The decision-making process in cSSTI across European hospitals requires consideration of a broad range of potential pathogens and often the need to treat without a confirmed microbiological diagnosis. The lack of recent European treatment guidelines in cSSTI, together with a choice from a large generic pool of treatment options, may partly account for the high percentage of initial treatment modifications recorded in all countries. Thus, improved antimicrobial stewardship may be necessary, as well as initiatives to improve empirical treatment strategies and develop clear guidelines.

Recently, the US Food and Drug Administration explored the use of 'early clinical response' to antimicrobial therapy on Day 3 (for cSSTI) as an efficacy endpoint in clinical trials [23]. This endpoint was based on historical data, which indicated that the greatest antimicrobial treatment effect in controlled studies was after approximately 48–72 hours of antibiotic therapy. Data obtained from REACH (Fig. 2) indicate high levels of early response, with the peak number of patients reported achieving clinical stability at Day 4.

The most common organisms identified in cSSTI infections in this study were Gram-positive cocci (70.1%), the majority of which were *S. aureus*, which is in concordance with the findings of other studies [10, 15]. MRSA incidence in cSSTI is known to vary considerably between countries, although the 10.2% of all microbiological diagnoses in this study appears low and at odds with other published studies reporting ranges from 22.8% in Europe to 59% in the USA [10, 15, 24, 25]. This variation may be partly explained by the majority of patients in REACH having community-onset infections where MRSA is rarely found in Europe, compared with nosocomial infections where MRSA is more frequently involved.

The rate of initial antibiotic treatment modification was high, particularly in certain groups of patients, such as those with co-morbidities, those with a recurrent or nosocomial infection, patients requiring surgical intervention, those taking non-steroidal anti-inflammatory drugs or patients with more severe infections. It is difficult to make comparisons across studies as definitions of treatment modification may differ; however, this initial antibiotic treatment modification rate is higher than has been reported previously (22–23%) [17, 26], but reflects current treatment and outcomes. Recommended treatment guidelines for cSSTI provide very little consensus on initial antibiotic choice and include a wide variety of antibiotic therapies dependent on the type and site of infection, its severity and local knowledge concerning possible antibiotic resistance [6, 7, 9]. The large variability in antibiotic treatments and high rate of antibiotic treatment modifications

in REACH, frequently within 4 days (before any reasonable time frame to assess the response to treatment has elapsed), suggests that the antibiotic treatment was modified in some cases on transfer of the patient from the emergency department to the general ward, with no reason specified. However, 17% of patients had initial treatment modification due to confirmed insufficient response, agreeing with previous reports for similar patients [15], as well as with a recent study reporting inappropriate initial antibiotic therapy in 18.5% of patients with a microbiological diagnosis [25] and an association with significantly worse clinical and economic outcomes [17]. A health economic analysis of our study showed an association between initial antibiotic treatment modification and higher use of resources (H. Ostermann, personal communication). If these results are to be taken as a true picture of the need for initial antibiotic treatment modification in cSSTI in Europe, then a reassessment of the current approaches to antibiotic prescribing is recommended to increase the success of initial antibiotic use, especially in the more vulnerable patient groups.

A possible limitation of the study was the notable differences in patient recruitment processes in the different countries, mostly due to differences in ethical committee requirements, which led to differences in the numbers of patients recruited from each country. Because of its retrospective design, there may have been variability in the assessment of outcomes by investigators. However, incomplete information in patient records resulting in missing data for some variables was not an important issue, as it was rather low ($\leq 7\%$) in all cases except one (tests used for diagnosis: 13.7% unknown). A further potential limitation is the possibility of different treatment approaches between hospitals, which may have an impact on the generalization of the study results.

This large Europe-wide study provides important current data to characterize the population of patients with cSSTI. The findings reveal the heterogeneity that exists in patients with cSSTI and in clinical management patterns, providing evidence of a high requirement for initial antibiotic treatment modification with some commonly used initial antibiotic regimens and suggesting reassessment of optimal management regimens of hospitalized cSSTI patients. For example, patients with comorbidities, compared with those without, are associated with a higher incidence of initial treatment modification, poorer clinical outcomes and significantly increased use of resources, such as longer time to clinical stability and longer hospital stay. These data highlight the potential need for reassessment of treatment regimens for this vulnerable patient group and the potential need for new cSSTI treatments. Data from REACH are likely to provide the foundations for such a reassessment.

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## Authorship Contribution

The chief investigators (JG, FB and HO) designed the trial, with input from the sponsor. The chief investigators, together with KM, initiated the analysis presented here, with the other investigators, JM and MA, contributing to the analysis and interpretation. The decision to submit the report for publication was made by the lead contributors and chief investigators, who drafted and finalized the report with the help of a medical writer. The sponsor funded editorial assistance and reviewed the draft before submission.

## Transparency Declarations

JG has received research grants, speaking invitations and conference invitations from Astellas, AstraZeneca, Bayer, GSK, Novartis, Pfizer and Vifor Pharma, and has recent or ongoing consultancies with Astellas, AstraZeneca, Bayer, Durata, GSK, Janssen Cilag, Novartis, Pfizer, Theravance and Vifor Pharma.

HO is a member of an advisory board for AstraZeneca.

JM and MA are employees of AstraZeneca.

KMB has received consultancy fees from ACT Oncology, AstraZeneca, BioSoteria, Celgene Corporation, Cypress Pharmaceuticals, Integrium LLC, Outcomes Research (now owned by Quintiles), MedImmune, Multiple Myeloma Research Foundation, Sigma-Tau Pharmaceuticals and Worldwide Clinical Trials.

FB has received research grants from Chiesi, GSK, Pfizer and Zambon, has received congress lecture fees from Abbott, Chiesi, GSK and Pfizer and has received consultancy fees from AstraZeneca, GSK and Pfizer.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Supplementary Appendix.

**Table S1.** Analysis population by country.

**Table S2.** Microbiological and diagnostic tests performed.

**Table S3.** Clinical management of hospitalized cSSTI.

**Table S4.** Most common antibiotics used and outcomes by initial antibiotic treatment.

**Table S5.** Characteristics of patients with initial antibiotic treatment modification.

**Table S6.** Disease characteristics of patients with initial antibiotic treatment modification.

**Appendix S1.** REACH study investigators.

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