

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 (REtrospective Study to Assess the Clinical Management of Patients with Moderate-to-severe cSSTI or CAP infections in the Hospital Setting [REACH] study)

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Background

- Complicated skin and soft tissue infections (cSSTI) are among the most common infections treated in the hospital setting, accounting for up to 10% of admissions to infection units, both in the USA,¹ and in the United Kingdom (UK).²
- cSSTI frequently require intravenous (IV) antibiotic therapy and surgical intervention, and may be further complicated by the presence of significant comorbidities.^{3,4}
- Data on the real life management of cSSTI and identification of factors predisposing for initial treatment modification and its impact are scarce.
- 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) study has systematically collected current (2010–2011) pan-European data on patients hospitalized for cSSTI (clinical trials.gov number NCT01293435).
- Data on the community-acquired pneumonia (CAP) analyses will be presented in oral presentations O174 and O175.

Objective

- To provide current, accurate real world data on the burden of cSSTI and its clinical management across Europe, by understanding patient and disease characteristics, current clinical practice and disease outcomes.

Methods

Study design

- REACH was a multinational, multicentre, retrospective, observational cohort study of patients hospitalized with cSSTI.
- Data were collected via an electronic Case Report Form from 129 sites in ten participating countries across Europe (Belgium, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Turkey and the UK) between March 2010 and February 2011.

Inclusion criteria

- The analysis population comprised adults ≥ 18 years of age, hospitalized with cSSTI and requiring IV treatment with antibiotics on admission.
- Patients were required to have:
 - an infection affecting deeper soft tissue and/or requiring significant surgical intervention
 - infection developing on a lower limb in subjects with diabetes mellitus or well-documented peripheral vascular disease, a major abscess, infected ulcer or deep and extensive cellulitis.
- In addition, patients were required to exhibit at least two local signs of cSSTI (purulent or seropurulent drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, swelling/induration) and at least one systemic sign (temperature of $> 38^\circ\text{C}$, white blood cell count of $> 10000/\text{mm}^3$ or $> 10\%$ immature neutrophils).

Exclusion criteria

- Patients with uncomplicated SSTI, such as simple abscesses, impetiginous lesions, superficial cellulitis, furunculosis, carbuncles or folliculitis were also excluded, as were patients with cSSTI with a high cure rate after surgical incision alone or after aggressive local skin care.

Data analysis

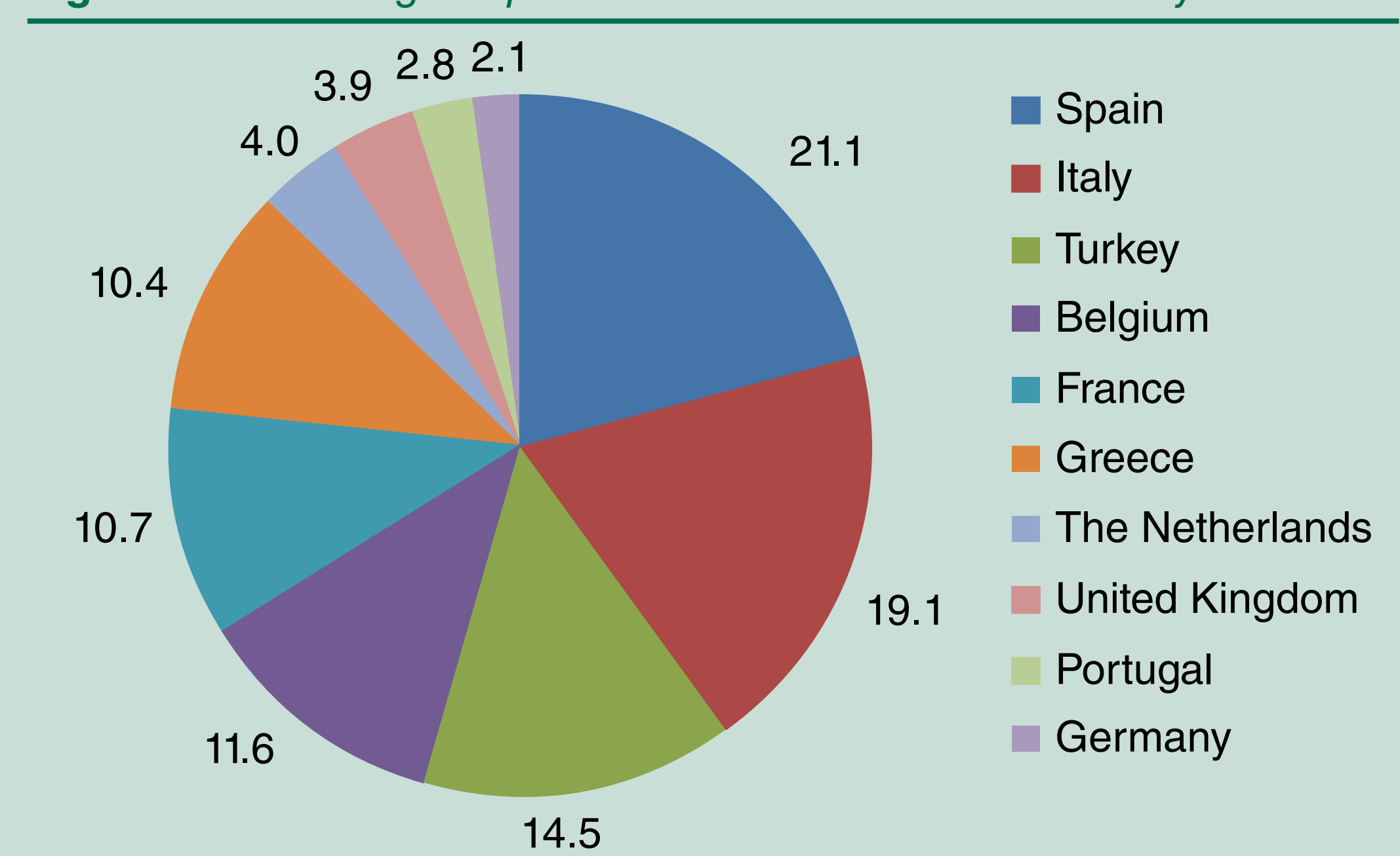
- This was a retrospective non-interventional study, using a descriptive analysis approach to assess clinical management, clinical outcomes and healthcare resource use. All calculations and summaries were produced using SAS Version 9.2.
- In REACH, 'initial treatment modification' was defined as the need for a change in first-line 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, changes to, or additions of, new agents in a subsequent line (alone or in combination), patient death, or streamlining (de-escalation of treatment to narrower spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis; this represents good clinical practice).

Results

Patient population

- A total of 1996 patients were included in the analysis population, with Spain, Italy and Turkey contributing the largest numbers of patients (Figure 1).
- Patient demographics, characteristics and relevant medical history are shown in Table 1.

Figure 1: Percentage of patients enrolled from each country



Disease characteristics

- The most common types of lesion were cellulitis or fasciitis and abscess (Table 2).
- A total of 701 patients (35.1%) had been treated with antibiotics within 1 week before the index visit or prior to development of cSSTI if already hospitalized.
- Bacteraemia was documented in 302 patients (15.1%).
- A total of 279 (14.0%) patients had undergone invasive surgical treatment in the 3 months prior to the index visit.

Table 1. Patient demographics, characteristics and medical history

	N = 1996
Male, n (%)	1153 (57.8)
Age, years, mean (SD) [median]	60.6 (17.6) [62.0]
≥ 65 years, n (%)	902 (45.2)
Invasive surgical treatment in the 3 months prior to index visit, n (%)	279 (14.0)
Hospitalization in the previous 3 months,* n (%)	418 (20.9)
Time since previous date of hospitalization (n = 377), days, mean (SD) [median]	35.7 (26.9) [30.0]
Comorbidities, n (%)	1557 (78.0)
Medications 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)

* For any reason; SD = standard deviation

Table 2: Disease characteristics

	n (%)
N = 1996	
Type of lesion	
Cellulitis/fasciitis	1180 (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)
Recurrent skin infection episode	510 (25.6)
Nosocomial infection	199 (10.0)

Clinical management

Study sites

- Half of the hospitals were university hospitals and in the majority of centres (76.0%), patients were treated by an infectious disease specialist or internist.
- Of the total number of patients, 1154 were treated in a university hospital and 842 in a non-university hospital.
- The majority (77.5%) of the hospitals were large (> 500 beds) and 122 (94.6%) were publicly funded hospitals.

Treatment during hospitalization

- Once hospitalized, 1553 (77.8%) patients were treated with an IV antibiotic on the first day, 1629 (81.6%) empirically and 346 (17.3%) with a pathogen-directed therapy.
- Surgery was required by 739 (37%) patients.
- A total of 54 different antibiotic agents were used either as monotherapy or in combinations.
- The most frequently chosen initial antibiotic treatments were amoxicillin-clavulanate (n = 366; 18.3%), ampicillin-sulbactam or sulbactam (n = 155; 7.8%) and piperacillin-tazobactam (n = 141; 7.1%).

Microbiological diagnosis

- All patients underwent a microbiological test; 1059 (53.1%) had a blood culture and 970 (48.6%) had a superficial swab and culture. A microbiological diagnosis was obtained for 1001 (50.2%) patients (Table 3).

Table 3: Microbiological diagnosis

Microbiological diagnosis	Full population n (%) n = 1001	Patients with bacteraemia n (%) n = 124
Gram-positive cocci	702 (70.1)	97 (78.2)
Methicillin-sensitive <i>S. aureus</i>	279 (27.9)	32 (25.8)
Methicillin-resistant <i>S. aureus</i>	102 (10.2)	17 (13.7)
Coagulase-negative <i>Staphylococcus</i>	112 (11.2)	17 (13.7)
Vancomycin-intermediate <i>S. aureus</i>	2 (0.2)	1 (0.8)
<i>Streptococcus pyogenes</i> (group A β -haemolytic streptococci)	40 (4.0)	11 (8.9)
<i>Streptococcus agalactiae</i> (group B β -haemolytic streptococci)	32 (3.2)	7 (5.6)
Other β -haemolytic streptococci*	66 (6.6)	10 (8.1)
<i>Streptococcus pneumoniae</i>	4 (0.4)	4 (3.2)
<i>Enterococcus faecalis</i>	85 (8.5)	7 (5.6)
<i>Enterococcus faecium</i>	29 (2.9)	5 (4.0)
Other Gram-positive bacteria†	33 (3.3)	1 (0.8)
Gram-negative bacteria‡	457 (45.7)	35 (28.2)
Other strict anaerobic bacteria§	34 (3.4)	4 (3.2)
Yeasts (including <i>Candida</i> spp.)	14 (1.4)	1 (0.8)
Other microorganisms	34 (3.4)	1 (0.8)

* *S. dysgalactiae*, group C streptococci, microaerophilic streptococci, *S. milleri*, *S. intermedius*, *S. anginosus*, *S. bovis*

† Includes *B. anthracis*, *Corynebacterium* spp., diphtheroids, *Propionibacterium* spp., *Lactobacillus* spp., *Clostridium* spp., non-specified Gram-positive bacilli

‡ Includes *Enterobacteriaceae* (eg. *P. mirabilis*, *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *S. marcescens*, *Providencia stuartii*, *Morganella morganii*), *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Shewanella putrefaciens*, *Neisseria* spp., *Aeromonas hydrophila*, *P. multocida*

§ Includes *Gemella morbillorum*, *Bacteroides fragilis*, *Peptostreptococcus* spp., *Prevotella melaninogenica*, *Porphyromonas* spp.

Clinical outcomes

- Clinical outcomes for the full analysis population are detailed in Table 4.
- A high proportion of patients required initial antibiotic treatment modification (46.6%). This included streamlining in 5.6% (n = 112) of the overall study population. Reasons for treatment modification are presented in Table 5.

Table 4: Clinical outcomes for the full analysis population

	N = 1996
Initial antibiotic treatment modification, n (%)	930 (46.6)
Time to first treatment modification (n = 947), days, mean (SD) [median]	7.7 (8.0) [6.0]
Overall treatment duration (n = 1975), days, mean (SD) [median]	14.6 (14.3) [11.0]
Time to clinical stability* (n = 1716), days, mean (SD) [median]	9.7 (11.2) [7.0]
Length of hospital stay (n = 1944), days, mean (SD) [median]	18.0 (20.6) [12.0]
Discharged from hospital, n (%)	1881 (94.2)
Reinfection or recurrence,† n (%)	172 (8.6)
Home-based care after discharge, n (%)	282 (14.1)
Length of home-based care (n = 138), days, mean (SD) [median]	26.8 (27.1) [15.0]
Mortality, n (%)	68 (3.4)

SD = standard deviation

* Based on the switch from IV to oral therapy

† Patients hospitalized again due to same cSSTI

- Patients with comorbidities (n = 1557), eg. diabetes (33.9%), peripheral vascular disease (21.2%), congestive heart disease (12.2%), cancer or malignancy (10.4%), experienced a higher rate of initial treatment modification than those without (49.3% versus 37.1%) and a longer duration of hospital stay (mean 19.4 days versus 13.2 days).
- Patients with a nosocomial infection (n = 199; 10.0%) had a longer time to clinical stability compared with those with a non-nosocomial infection (mean 11.2 days versus 9.5 days), a longer length of hospital stay (mean 30.4 days versus 16.6 days), a higher rate of initial treatment modification (53.3% versus 45.9%) and a higher rate of mortality (4.0% versus 3.3%).
- Patients with a recurrent infection (n = 172; 8.6%) had a longer time to clinical stability than patients without a recurrent infection (mean 12.3 days versus 9.2 days), had a higher rate of initial treatment modification (47.1% versus 44.9%) and required a longer hospital stay (mean 21.9 days versus 17.3 days) than patients with no recurrent initial infection.
- Initial treatment modification rate was higher, compared with the total population, in patients with more severe infections, such as patients with bacteraemia (51.0%), with fascia affected (57.3%), patients admitted to ICU (70.0%) and in patients with lesions $> 50\text{ cm}^2$ (55.7%).

Table 5: Reasons for initial antibiotic treatment modification

	n (% of full analysis population) n = 930 (46.6)
Adverse events	55 (2.8)
Insufficient response/treatment failure	339 (17.0)
Possible interaction with other treatment	1 (0.1)
Streamlining*	111 (5.6)
Other	246 (12.3)
Unknown	68 (3.4)
No reason reported	82 (4.1)
Death	28 (1.4)

If multiple reasons were reported, the more clinically relevant reasons were selected first as the primary reason for change. The ordering of reasons from most relevant to least relevant are: Adverse event, Insufficient response/treatment failure, Possible interaction with other treatment, Other, Unknown
* De-escalation of treatment to narrower spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis

Intercountry differences in clinical outcomes

- A comparison of the clinical outcomes variables in each participating country shows a wide range of initial treatment modification rates (from 33.8% in the Netherlands to 55.6% in Italy), duration of hospital stay (mean of 10.0 days in the Netherlands to 24.1 days in Germany) and percentage of patients admitted to ICU (1.3% in the United Kingdom to 22.0% in Germany).

Conclusions

- This large pan-European study provides important current data characterizing the population of patients with cSSTI in this region. The findings reveal the heterogeneity of patients with cSSTI and in clinical management patterns, and provides evidence of a high rate of initial treatment modification.
- The data presented here, and further analysis of the wealth of data accumulated in the REACH study, can be used as part of the evidence to reassess and to help refine current clinical practice in order to improve patient outcomes.

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