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Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

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ABSTRACT

This retrospective observational medical chart review aimed to describe country-specific variations across Europe in real-world meticillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft-tissue infection (cSSTI) treatment patterns, antibiotic stewardship activity, and potential opportunities for early switch (ES) from intravenous (i.v.) to oral formulations and early discharge (ED) from hospital using standardised data collection and criteria and economic implications of these opportunities. Patients were randomly sampled from 12 countries (Austria, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Slovakia, Spain and the UK), aged ≥18 years, with documented MRSA cSSTI, hospitalised between 1 July 2010 and 30 June 2011, discharged alive by 31 July 2011. Of 1502 patients, 1468 received MRSA-targeted therapy. Intravenous-to-oral switch rates ranged from 2.0% to 20.2%, i.v. length of therapy from 10.1 to 18.6 days and hospital length of stay (LoS) from 15.2 to 25.0 days across Europe. Of 341 sites, 82.9% had antibiotic steering committees, 23.7% had i.v.-to-oral switch antibiotic protocols and 12.9% had ED protocols for MRSA cSSTI. ES and ED eligibility ranged from 12.0% (Slovakia) to 56.3% (Greece) and from 10% (Slovakia) to 48.2% (Portugal), respectively. Potential cost savings per ED-eligible patient ranged from €414 (Slovakia) to €2703 (France). MRSA cSSTI treatment patterns varied widely across countries, but further reductions in i.v. therapy, hospital LoS and associated costs could be realised. These data provide insight into clinical practice patterns across diverse European healthcare systems and identify potential opportunities for local clinicians and policy-makers to improve clinical care and cost-effectiveness of this therapeutic area.

1. Introduction

European healthcare systems are under increasing economic pressure, with greater demand to provide care despite stable or declining budgets [1]. The percentage of patients aged ≥80 years is projected to increase (4.4% in 2008, 8% in 2035, 12.1% in 2060),

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whilst the number of hospital facilities and beds in Europe will likely decrease [2]. This underscores the need for programmes that can enable hospitalised patients to continue treatment in outpatient settings with few negative impacts.

Outpatient parenteral antibiotic therapy (OPAT) programmes enable patients to receive intravenous (i.v.) antibiotics after hospital discharge but require additional resources and are not available to all patients in Europe [3–5]. Early switch (ES) programmes promote switching patients from i.v.-to-oral antibiotic therapies, and early discharge (ED) programmes enable patients to finish treatment after hospital discharge. ES and ED programmes are beneficial [6–10], require few additional resources and are considered relatively low cost and high impact antimicrobial stewardship strategies [11]. These programmes are regarded as having the greatest potential benefit for the management of meticillin-resistant *Staphylococcus aureus* (MRSA) infections, particularly complicated skin and skin-structure infections [7,12]. Clinical trial data in MRSA complicated skin and soft-tissue infection (cSSTI) have suggested longer length of stay (LoS) in Europe compared with other world regions owing to different healthcare systems and incentives [13].

Variations have been reported in ambulatory use of antibiotics and hospitalised respiratory infections [6,7]; however, little is known about variations in real-world MRSA cSSTI treatment patterns in hospitals across different European countries. Given limited pan-European data on real-world practice patterns for treatment of MRSA cSSTI as well as expected economic pressures to optimise available resource use, a retrospective observational study was conducted using consistent methodology across 12 European countries. The objectives were: (i) to illustrate cross-country variations in practice patterns for MRSA cSSTI treatment, including initiation of therapy, choice of drugs, treatment regimen changes, and duration of therapy and hospitalisation; (ii) to assess current availability and impact of hospital antibiotic drug use policies; (iii) to describe potential opportunities for ES and ED by application of standardised criteria across countries; and (iv) to demonstrate the potential economic impact of ES and ED programmes at the country level. These data may provide insight into clinical practice patterns across diverse European healthcare systems and may help identify opportunities to improve the efficiency of patient care.

2. Methods

A retrospective observational medical chart review was conducted including 12 European countries: Austria, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Slovakia, Spain, and the UK. The complete methods will be published in a forthcoming paper. Study investigators [hospital-based infectious diseases (ID) specialists, internists with an ID subspecialty and medical microbiologists] identified patients for data collection.

Included patients were: hospitalised between 1 July 2010 and 30 June 2011 inclusive and were discharged alive by 31 July 2011; were aged ≥18 years; had a confirmed MRSA cSSTI (e.g. deep/extensive cellulitis, infected wound or ulcer, major abscess or other soft-tissue infection requiring substantial surgical intervention); and received ≥3 days of i.v. anti-MRSA antibiotics. Patients were excluded if they: were treated for the same SSTI ≤3 months from hospitalisation; had suspected or proven diabetic foot infection, osteomyelitis, infective endocarditis, meningitis, joint infection, necrotising fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection; were pregnant or lactating; had significant concomitant infection at other sites (e.g. bacteraemia, pneumonia); were immunosuppressed (e.g. diagnosed with haematological malignancy or rheumatoid arthritis, neutropenic, undergoing cancer chemotherapy, receiving chronic steroids); or were enrolled in another cSSTI-related clinical trial.

2.1. Study populations

The main study population included patients whose medical charts were randomly selected by study investigators so that the population accurately reflected practice patterns of each country. A limited number of patients received treatment with questionable or suboptimal coverage for MRSA. Thus, a subgroup was identified who received a confirmed MRSA-active antibiotic with a labelled or guideline indication for MRSA cSSTI or with anti-MRSA activity confirmed by susceptibility tests [e.g. i.v. chloramphenicol, i.v./oral clindamycin, i.v. daptomycin, i.v./oral doxycycline, i.v. fosfomycin, i.v./oral fusidic acid, i.v. lincomycin, i.v./oral linezolid, oral minocycline, i.v. netilmicin, i.v. norfloxacin, i.v. quinupristin/dalfopristin, i.v./oral rifampicin, i.v./oral trimethoprim/sulfamethoxazole, i.v. teicoplanin, i.v. tigecycline, oral trimethoprim and i.v. vancomycin]. The following antibiotics were considered MRSA-active after reviewing wound cultures for MRSA sensitivity: i.v./oral ciprofloxacin; i.v. ertapenem; i.v. imipenem; i.v./oral levofloxacin; i.v. meropenem; i.v./oral moxifloxacin; and oral ofloxacin. Owing to limited recruitment, patients from Ireland contributed to the overall cohort but their results are not presented separately.

2.2. Key outcomes

2.2.1. Hospital-level organisation and protocols for antibiotic use and early discharge

A separate hospital-level information form collected site data on the presence of antibiotic subcommittees and drug use policies for i.v.-to-oral antibiotic switching or ED. These data were summarised by country to understand existing country-level systems at the time of the study to address i.v.-to-oral antibiotic switching and ED.

2.2.2. Meticillin-resistant S. aureus-active antibiotic treatment patterns

Patient-level first and last MRSA-active therapies administered in hospital as well as MRSA-active therapies prescribed at discharge (including drug and administration pattern) were determined overall and by country. Administration patterns evaluated included i.v. only, i.v.-to-oral antibiotic switch and discharge on antibiotics (i.v./intramuscular or oral).

2.2.2.1. Actual length of intravenous therapy and hospital length of stay. Length of i.v. therapy and LoS were determined overall and for each country. Length of i.v. therapy was defined as the time between start of MRSA-active i.v. treatment and last date of inpatient i.v. antibiotic use. LoS was measured from hospital admission for patients admitted for treatment of MRSA cSSTI, from the date of cSSTI diagnosis (cSSTI index date).

2.2.2.2. Early switch and early discharge opportunities. To explore possible resource utilisation reductions, potential for ES (sooner than patients actually discontinued their MRSA-active i.v. antibiotics) and for ED (earlier than actual discharge date on oral antibiotics or through an OPAT programme) were evaluated. ES and ED criteria were developed through literature review [3–10] and expert consensus opinion. ES eligibility required patients to meet all of the following criteria before i.v. discontinuation: stable clinical infection; afebrile/temperature <38 °C for 24 h; white blood cell count normalised or not $<4 \times 10^9$/L or $>12 \times 10^9$/L; no unexplained tachycardia; systolic blood pressure ≥100 mmHg (for OPAT); and oral fluids/medications/diet tolerated with no gastrointestinal absorption problems. ED eligibility required meeting all of the above criteria for ES before discharge and having no reason to remain hospital except for infection management.

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