structure infections. However, in Argentina, in the first month after launch, 61% of the tigecycline prescriptions were 'off label', especially for patients with ventilator-associated pneumonia (VAP) due to MDR Acinetobacter spp. (D. Curcio, F. Fernández and F. Duret, unpublished data). The high concentration in alveolar cells (77.5-fold higher than serum), the increase in carbapenem-resistant Acinetobacter spp. in Argentina (54%), the lack of medical evidence to use colistin in pulmonary infections and the association between inappropriate initial antibiotic therapy with mortality in patients with VAP (defined as the susceptibility of cultured organisms to the antibiotics used) seem to be the main reasons for using tigecycline in this indication.

Concerning tigecycline and Acinetobacter spp. several points should be taken into account: (i) definitive breakpoints of susceptibility are not available; (ii) results for Phase 3 clinical trials regarding clinical efficacy of tigecycline in nosocomial pneumonia and other infections produced by MDR microorganisms are not available; and (iii) we know that the overexpression of the intrinsic multidrug efflux pump (AdeABC) may decrease the susceptibility to tigecycline in Acinetobacter spp. However, at least in Argentina, some physicians consider this new antibiotic as a possibility to treat microbiologically documented severe infections caused by MDR A. baumannii, in order to improve the patient outcome when the therapeutic options are limited (i.e. isolates only susceptible to colistin).

Moreover, from a clinical point of view, until data on tigecycline clinical efficacy in severe Acinetobacter spp. infections become available, before treating a patient, physicians must consider the pharmacological and microbiological profile of tigecycline for each specific patient condition and carefully assess local susceptibility data to support its use.

Finally, we agree with the authors, that the high MICs for A. baumannii found by them is a worrisome local phenomenon and requires further investigation.

Transparency declarations

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Correspondence

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Rapid decrease in the prevalence of macrolide-resistant group A streptococci due to the appearance of two epidemic clones in Cantabria (Spain)

Maria A. Oliver1, Celia García-Delafuente2, María E. Cano2, Flora Pérez-Hernández3, Luis Martínez-Martínez3 and Sebastián Alberti1*

1Institut Universitari d’Investigacions en Ciències de la Salut (IUNICS), Universitat de les Illes Balears (UIB), Palma de Mallorca, Spain; 2Servicio de Microbiología, Hospital Universitario Marqués de Valdecilla, Santander, Spain; 3Servicio de Gestión Farmacéutica, Servicio Cantábrico de Salud, Santander, Spain

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*Corresponding author. Tel: +34-971-173353; Fax: +34-971-173184; E-mail: sebastian.alberti@uib.es

Sirs,

An increase in erythromycin resistance rates among group A streptococci (GAS) has been reported in some European countries, including Spain, where in some regions the level of resistance is very high (62.3%). Resistance to erythromycin is commonly caused by the presence of an active drug efflux pump (M phenotype) or due to target site modification by inducible or constitutive methylases (MLSb phenotype).

It was well established that the prevalence of resistance to antimicrobials depends on the use of their community. In the case of GAS, a nationwide study in Finland indicated that a reduction in macrolide use correlated with a decrease in macrolide resistance. In contrast with this idea, between 2002 and 2004 there were no relevant variations in the attended population or in the consumption of macrolides in Cantabria (Spain), however, we noted a marked decrease in macrolide-resistant GAS in January–April 2004. This study was undertaken to determine the reasons for this rapid decrease.

Antibiotic consumption data from January 2002 to April 2004 were obtained from SIFARCAN (Pharmaceutical Information System of Cantabria). All GAS collected from January 2002 to April 2004 at the Hospital Marques de Valdecilla of Cantabria (Spain) were identified by conventional methods. More than 95% of these isolates were from GAS, pharyngotonsillitis. Susceptibility of isolates to macrolides during this period was routinely tested by E-test. However, we noted a marked decrease in macrolide-resistant GAS in January–April 2004. This study was undertaken to determine the reasons for this rapid decrease.

The prevalence of GAS resistant to macrolides in Cantabria was high from the second quarter of 2002 until the third quarter of 2003, when the percentage of the resistant isolates varied between 27.4 and 38.6, respectively, reaching a maximum of 53.6 between July and December of 2002 (Figure 1). The prevalence decreased rapidly in the last quarter of 2003, reaching a percentage as low as 3.7 in the first quarter of 2004. In parallel, the total number of GAS isolated from January 2002...
did not show significant changes until the first quarter of 2004 when we detected a dramatic increase (Figure 1).

In this period, macrolide-resistant GAS exhibited two different phenotypes of resistance: the constitutive MLSB (cMLSB) phenotype and the M phenotype. The M phenotype was expressed by 70% and 68% of the isolates in 2002 and 2003, respectively. In contrast, only 48% of the macrolide-resistant GAS isolated in 2004 presented the M phenotype. In parallel, 30% and 32% of the isolates presented the cMLSB phenotype in 2002 and 2003, respectively, while in 2004 52% of the macrolide-resistant isolates expressed the cMLSB phenotype. This rapid inversion of macrolide resistance phenotypes has been described in other regions of Spain5 and in Portugal, where the MLSB phenotype dominated in 1998 whereas the M phenotype prevailed in 2003.6

During January 2002–March 2004, the pattern of macrolide consumption in Cantabria did not exhibit significant changes (Figure 1). However, a sudden decrease in the frequency of erythromycin-resistant strains was observed suggesting the emergence and dissemination of some susceptible strains.

For this purpose, we monitored by \textit{emm} gene typing, following the protocol previously described,4 the diversity of all GAS isolated during April 2004 at the same hospital (94 isolates; 11 from adult patients and 83 from paediatric patients). All were susceptible to macrolides and caused acute pharyngotonsillitis. It was proved that, \textit{emm} type 1 and \textit{emm} type 3 were the most prevalent \textit{emm} types among GAS isolates susceptible to erythromycin. Besides these \textit{emm} types, all the other \textit{emm} types were represented by few isolates. \textit{emm} type 1 and \textit{emm} type 3 are the most frequent in Spain, however, the frequency of these \textit{emm} types was very high (43% \textit{emm} type 1 and 34% \textit{emm} type 3) when compared with a previous study (12.4% and 11.4%, respectively).4 For this reason, we investigated whether these \textit{emm} type 1 and \textit{emm} type 3 isolates represented only few clones.

Genotypic characterization of the 94 GAS isolates obtained during April 2004 was carried out by genomic DNA macrorestriction with SfiI and PFGE following the protocol described previously. All \textit{emm} type 1 and \textit{emm} type 3 isolates exhibited the same PFGE patterns, respectively. These results suggest that all \textit{emm} type 1 and \textit{emm} type 3 isolates collected from different patients in April 2004 in Cantabria represented only two different clones. Furthermore, it is likely that the rapid decrease in the frequency of the macrolide-resistant GAS isolates was caused by the emergence and successful dissemination of these GAS isolates susceptible to erythromycin.

In summary, we have shown that, without changes in the consumption of macrolides, the frequency of macrolide-resistant GAS in a particular geographical area may be significantly altered by the emergence of successful epidemic clones susceptible to these antimicrobial agents. This indicates that additional studies, including molecular analysis of genes involved in resistance and of clonal relationship of isolates, are required to establish a cause-effect between consumption and resistance.

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Transparency declarations

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Identification and determination of antimicrobial susceptibilities were performed in CHC using MicroScan WalkAway (Dade Behring) and CLSI (formerly NCCLS) breakpoints. Isolates with intermediate susceptibility were considered resistant in order to match better treatment decisions in clinical settings.

A multidrug-resistant (MDR) P. aeruginosa was defined as an isolate that was resistant to three or four of the following: piperacillin, ceftazidime, imipenem and ciprofloxacin.

During collection, a total of 1099 P. aeruginosa isolates were obtained in CHC, from nosocomial and community-acquired infections from different clinical specimens, including urine (17.1% and 35.5%, respectively), sputum (46.3% and 30.9%, respectively), exudates (15.6% and 13.5%, respectively), blood (4.5% and 4.6%, respectively) and other sources (16.5% and 15.5%, respectively).

Overall, susceptibility to the most commonly used anti-pseudomonal drugs was as follows: meropenem, 90.0%; piperacillin plus tazobactam, 89.0%; piperacillin, 86.2%; amikacin, 85.6%; ceftazidime, 85.0%; imipenem, 82.4%; aztreonam, 81.7%; ciprofloxacin, 69.2% and gentamicin, 65.9%.

Among hospital isolates, piperacillin plus tazobactam was the most potent agent (85.1% susceptible), followed by meropenem (84.8%), piperacillin (81.5%), ceftazidime (79.4%) and aztreonam (75%), and the least potent β-lactam was imipenem (74.7%). Amikacin demonstrated good activity (81.3%), but gentamicin showed poor activity (58.1%). Ciprofloxacin was only moderately active (64.2%). Community isolates were ≥90% susceptible to most antibiotics except for ciprofloxacin (77.3%) and gentamicin (78.7%). Meropenem was the most potent agent (98.6%) followed by piperacillin plus tazobactam (95.4%), imipenem (95.2%), ceftazidime (94.2%), piperacillin (94.0%), aztreonam and amikacin (92.8%) (Figure 1).

MDR was recognized in 100 isolates (9.1%). Twenty isolates (20%) were resistant to all antibiotics tested. All these were from nosocomial infections from the principal wards and 70% were from respiratory sources. Among isolates resistant to piperacillin, ceftazidime and imipenem, ciprofloxacin demonstrated some activity (32.9%, 33.8% and 31.8%, respectively). Some ciprofloxacin-resistant isolates (27.4%) were susceptible to ceftazidime (Table 1).

Studies of susceptibility held in Europe by MYSTIC and SENTRY demonstrated superior activity of meropenem and piperacillin plus tazobactam.

In our work, among nosocomial isolates, piperacillin plus tazobactam showed the best activity followed by meropenem. In CHC, imipenem was the worst among the β-lactams, with decreased activity over the 3 years of this study (10.9% decrease in susceptibility).

A study by European Surveillance of Antimicrobial Consumption demonstrated that Portugal (with Spain and Italy) was the European country with the highest fluoroquinolone use. Misuse of fluoroquinolones may, therefore, explain the low susceptibility of our isolates, whether they were from community (77.2% susceptible) or from hospital (64.2%). MYSTIC and SENTRY studies also revealed low susceptibility to these agents.

Incidence of MDR isolates was high, but within the results observed in Europe.

Choices of antimicrobial agents for empirical therapy for possible pseudomonal infections must be influenced by regional information as well as by changing local patterns of resistance. Since none of the antibiotics tested among nosocomial isolates reached 90% susceptibility, recommendations for empirical