The Challenges of Antimicrobial Drug Resistance in Greece

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Antimicrobial drug resistance rates in Greece are among the highest in Europe. The prevalence of carbapenem-resistant Gram-negative species has increased considerably, including endemic strains in intensive care units. Pandrug-resistant *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* are sporadically reported. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus rates are also high in Greek hospitals. Multidrug resistance increases risk of mortality, hospitalization duration and costs, and undermines the medical system. Administrative responses initiated include action plans, monitoring systems, and guidelines. Common terminology among involved parties for defining and grading resistance is required. Multidrug-resistant microorganisms challenge clinical laboratories; uniform recommendations towards detection of resistance mechanisms need to be established. Prospective multicenter outcome studies comparing antibiotic regimens and containment methods are needed. Because new antimicrobials against Gram-negative pathogens are not foreseeable, judicious use of the existing and strict adherence to infection control best practice might restrain resistance spread. Awareness of resistance patterns and organisms prevailing locally by reporting laboratories and treating physicians is important.

Antibiotic use radically reduced morbidity and mortality associated with infectious diseases. The emergence of antimicrobial resistance threatens for bacterial revenge. The medical community is called into action by major infectious disease bodies [1]. Antibiotic use drives resistance; pathogens resistant to all available antimicrobials have appeared. Availability of new agents for the treatment of such infections is not foreseen in the near future [2].

Rates of bacteria resistant to wide-spectrum antibiotics recorded in Greek hospitals are among the highest in Europe [3] (Figure 1). Data from the Greek System for the Surveillance of Antimicrobial Resistance (GSSAR; http://www.mednet.gr/whonet) show remarkably increased rates (Figure 2) for almost all multidrug-resistant organisms (MROs) of outstanding interest (the ESKAPE pathogens) [2].

A REAL-WORLD SCENARIO

A 40-year-old accident victim with insignificant medical history was admitted to the intensive care unit (ICU) with pulmonary contusions and fractures. On the third day, his fever spiked (temperature, 38.5°C). He received empirical meropenem (2 g every 8 h) and vancomycin. Two days later, the patient was afebrile; urine culture revealed extended-spectrum β-lactamase (ESBL)–producing *Proteus mirabilis* resistant also to gentamicin and ciprofloxacin. Vancomycin was discontinued. Meropenem was stopped on day 10, but the patient was unable to be weaned off mechanical ventilation. Three days later, fever recurred, with a new-onset pulmonary infiltrate. Bronchoalveolar lavage fluid and blood cultures yielded *K. pneumoniae* susceptible to tigecycline (started 100 mg every 12 h) and colistin (started 3 m units—240 mg—colistimethate sodium every 8 h). A phenotypic test [4] suggested

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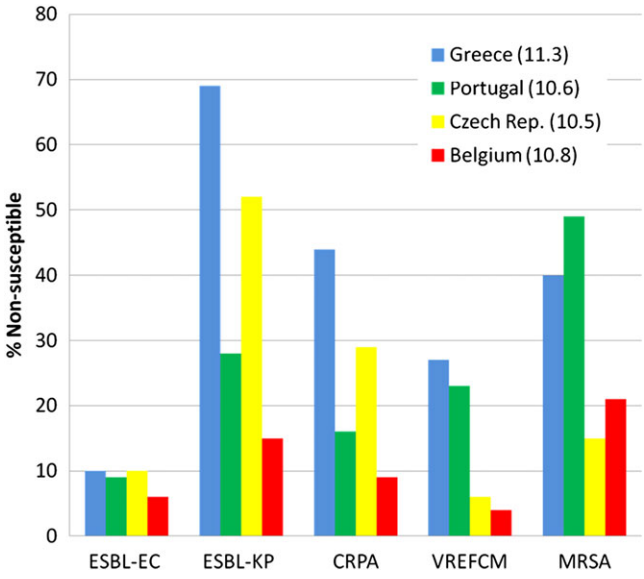

Figure 1. Prevalence of nonsusceptible invasive (blood and cerebrospinal fluid) isolates of five multiresistant bacterial pathogens monitored by the European Antimicrobial Resistance Surveillance System during 2009 [3]. Data from 4 European countries of similar population size (in million inhabitants, given in parentheses next to each country) are compared. EC: *Escherichia coli*; KP: *Klebsiella pneumoniae*; ESBL: Extended-spectrum beta lactamase (resistance to 3rd Generation Cephalosporins); CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; VREFCM: Vancomycin-resistant *Enterococcus faecium*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

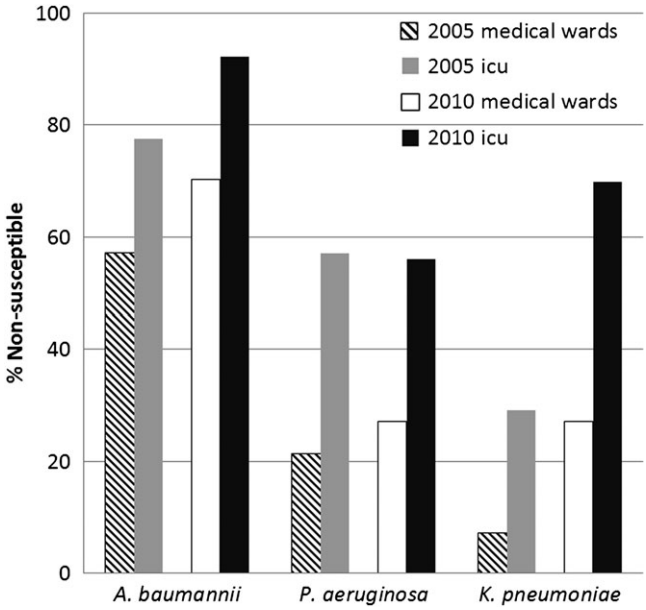

Figure 2. Increasing rates of nonsusceptibility to carbapenems among *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* clinical isolates in medical wards and ICUs of Greek Hospitals (comparative data from http://www.mednet.gr/whonet for the January-June period of 2005 and 2010).

K. pneumoniae carbapenemase (KPC) production. Pulmonary function and chest radiograph findings worsened; a new bronchoalveolar lavage fluid culture revealed *A. baumannii* resistant to all antibiotics except fosfomycin, which was added (4 g every 6 h intravenously). Fever continued, and blood cultures grew fosfomycin-resistant *A. baumannii*. The patient developed multiorgan failure and died on day 27.

This case illustrates a gloomy reality: Clinicians may confront bacterial infections without effective antibiotics in their hands. Such organisms are now endemic in Greek hospitals, including carbapenem-resistant *K. pneumoniae, P. aeruginosa,* and *A. baumannii*.

RESISTANCE ATTRIBUTES

β-Lactam resistance is common among *Enterobacteriaceae* in Greece. The prevalence of ceftriaxone resistance among *K. pneumoniae* bloodstream infections in Greek ICUs in 2010 reached 96.7%; the prevalence among *Enterobacter* species and *P. mirabilis* was 46.7% and 42.4%, respectively. ESBL–producing organisms frequently encountered in Greece belong to class A, functional group 2be (http://www.lahey.org/Studies/), including SHV-5 (particularly prevalent among *K. pneumoniae* strains) and CTX-M (with increasing prevalence among community *E. coli* strains). Plasmid transfer and/or clonal expansion of epidemic carrier strains account for the rapid spread of ESBLs among *Enterobacteriaceae* [5]. ESBL carriers are often resistant to other antibiotic classes; plasmids cotransfer aminoglycoside resistance genes, whereas up to 60% in Greece may also be resistant to quinolones [6]. AmpC β-lactamases are chromosomally encoded in *Enterobacteriaceae*; their derepression after exposure to β-lactams confers irreversible class resistance, except from cefepime and carbapenems. Of concern, plasmidic transfer of *ampC* has resulted in spread among *E. coli, K. pneumoniae,* and *Proteus* species [7].

Carbapenem resistance among *Enterobacteriaceae* is a major public health issue in Greece. *E. coli* and *K. pneumoniae*–producing VIM-type metallo-β-lactamases (MBLs) have been endemic in hospitals since the early 2000s. Many outbreaks of VIM-1–producing *K. pneumoniae*, even with community onset [8] and sporadic isolations of *Enterobacteriaceae* carrying VIM-type MBLs, have been described. Recently, KPC-type enzymes became prevalent, able to spread very rapidly [9]. Outbreaks of strains coproducing KPC and VIM have also occurred [10]. Of interest, the OXA-48 carbapenemase, although disseminated in neighboring countries, has not been detected in Greece.

Imipenem resistance among *K. pneumoniae* clinical isolates in 2010 reached 69.8% in Greek ICUs and 27.2% in medical wards, respectively; those rates have more than doubled within 5 years (Figure 2). Carbapenem resistance is lower among other *Enterobacteriaceae*. Carbapenemase-producing

strains hydrolyze efficiently all β-lactams, except that MBLs do not hydrolyze aztreonam. Similar to ESBL-producers, those strains are frequently coresistant to aminoglycosides and quinolones [11].

Pandrug-resistant *A. baumannii* and *P. aeruginosa* strains exist in Greek hospitals [12]. *A. baumannii* strains in Greek ICUs are typically (>90%) resistant to ciprofloxacin, cefepime, and amikacin (>80%). *P. aeruginosa* has been the initial resistance reservoir for bla_{VIM} genes, and outbreaks preceded those of *Enterobacteriaceae* [13]. Other carbapenemases harbored by *A. baumannii* include OXA-type (class D) and VIM-type enzymes [14]. Carbapenem resistance among *A. baumannii* clinical isolates in Greek hospitals exceeds 70% (90% in ICUs). For *P. aeruginosa,* carbapenem resistance rates exceed 25% and 55%, respectively (Figure 2).

Methicillin resistance among *S. aureus* in Greece is among the highest in Europe. More than 50% of methicillin-resistant *S. aureus* (MRSA) infections are community associated, mainly of the Panton-Valentine leukocidin (PVL)–positive European predominant clone (ST80-IV); the rare clone ST377-V has emerged in several areas [15]. The prevailing community-associated MRSA isolates are also resistant to fusidic acid, tetracycline, and, frequently, ciprofloxacin. Particularities of the MRSA issue in Greece include high percentage of community-associated MRSA and unusually frequent carriage of the PVL toxin among health care–associated isolates [16]. To our experience, incidence of hospital-acquired MRSA infection is relatively low in most Greek ICUs. Of note, rates of MRSA in Greece show a decreasing trend overall (from 48% in 2007 to <40% in 2010), mainly because of decreases in ICUs (63.4% vs 48.1%), rather than in medical wards (from 39% to 38.1%). Curiously, this occurred without any nationwide action plan having targeted MRSA. Similar to other countries, oxacillin-susceptible MRSA isolates have emerged in Greece [17].

Although percentages of vancomycin-resistant *Enterococcus faecium* in Greece decrease (37% in 2005; 26.9% in 2009), they remain only behind Ireland and, perhaps, Luxemburg in Europe [3]. Data from GSSAR show great variability between VRE rates among hospitals. Linezolid-resistant VRE strains have emerged [18]. Ampicillin remains active against almost all *E. faecalis* strains in Greece [18]; resistance among *E. faecium* reaches 90% [3]. High-level aminoglycoside resistance exceeds 60%. Such rates often preclude the use of combination regimens for invasive infections.

Resistance rates of *S. pneumoniae* in Greece are alarming. Strains that are not susceptible to penicillin minimum inhibitory concentration, [MIC]> 0.06 mg/L have been found in 35% of child carriers; 14.4% were highly resistant (MIC> 2 mg/L). Rates were higher among adult clinical isolates (48.3% and 25.8%, respectively) [19]. Fewer data with the new (revised upwards) Clinical Laboratory Standards Institute (CLSI) break points still suggest high resistance rates, which seem, however, reduced after the widespread implementation of heptavalent vaccination [20]. Macrolide resistance among pneumococci has increased from 7.4% to 53.7% within 20 years [21]. In contrast to most European countries, macrolide resistance in Greece is *mef* (efflux) mediated (M phenotype), similar to North America, and is usually associated with lower-level resistance (MIC, ≤ 32 mg/L), compared with the *erm* (MLS) phenotype [21].

REASONS

Resistance risk factors are common for MROs: prolonged or numerous hospitalizations and transfer between hospitals, ICU stay, age, comorbidities, immunosuppression, presence of prosthetic devices (eg, indwelling catheters and central lines), and previous antibiotic administration (multiple courses and/or prolonged use) [22–24]. Organ transplant recipients and patients receiving hemodialysis or chemotherapy are particularly vulnerable to the acquisition of MROs. Antibiotic use has been identified as the strongest risk factor for colonization. Of importance, this can involve agents of different class than the antibiotic to which resistance emerged (eg, carbapenem-resistant *Enterobacteriaceae* [previous use of β-lactams and/or quinolones] or *P. aeruginosa* [colistin]and VRE [anti-anaerobic agents or quinolones]) [22–24].

Reasons for increased antimicrobial resistance are many fold. Greece has the highest antibiotic consumption rates in Europe, both in total and in outpatients (http://app.esac.ua.ac.be/public/). Population mobility (eg, immigration and tourism; because of the country's geographic position) can introduce resistant strains. Infrastructure and resources for infection control are insufficient (eg, absence of electronic alert systems, nursing shortage, and hospitals understaffed in terms of infectious diseases physicians and/or infection control nurses). This, along with reduced awareness for detection, increases the likelihood of in-hospital spread of MROs

IMPACT

Antibiotic resistance contributes to mortality because of untreatable pathogens or ineffective initial empirical antibiotic regimens [25]; the latter is particularly important for critically ill patients. Mortality from MRO infections in Greece is high; attributable rates of 18.8%–37.5% have been reported [12, 24, 26]. Limited prospective data concur that mortality is significantly higher among patients infected with carbapenem-resistant (than susceptible) organisms (42.9% vs 15.8%) [27]. Accurate estimations are difficult, because MRO hosts usually have high risk of all-cause mortality (ie, almost 50% among those at risk for systemic *A. baumannii* infections).

Resistance severely impacts antibiotic prescribing and vice-versa. Physicians use broad-spectrum antibiotics that have potential for adverse events and can only be given intravenously. The vicious circle of further resistance (conferred by selection pressure) is perpetuated, and effective options are exhausted: resistance to tigecycline [26, 28] and colistin [24] increases in Greece. Very disturbing is the increasing resistance among community strains; during 2010, 10.1% among *E. coli* isolated from outpatient urine cultures were resistant to ciprofloxacin, doubled since 2005 (5%). Spread of resistance to the community can compromise the successful selection of empirical treatment regimens.

Infections from MROs complicate admissions, increasing hospitalization duration and cost [29]. Associated morbidity has adverse economic impact on individuals and societies. To achieve maximum containment, endemicity of MROs requires stringent infection control measures [30]. Impact on the medical system may occur from implementation of measures, such as temporary closure of ICUs, operating rooms, and hemodialysis units, or from operation under conditions of endemic resistance. The effect of such situations on performance of Greek hospitals remains unknown. Of importance, antimicrobial resistance knows no borders: index cases of KPC outbreaks recently reported from other European countries have been linked to Greece [31].

DETECTION CHALLENGES

Spread of MROs harboring various resistance mechanisms impedes accurate diagnosis in routine laboratory settings. One important issue is the variable performance of ESBL detection tests (incorporated into automatic systems), compared with manually performed conventional phenotypic methods [32]. Sensitivity of the latter may be also reduced from coexistence of an AmpC-type or carbapenem-hydrolyzing enzyme (poor substrates for clavulanate, used in the combined-disk ESBL detection test). Modifications (using boronic acid) can increase ESBL detection among KPC or AmpC producers [33]. The CLSI previously recommended reporting ESBL producers as nonsusceptible to all penicillins, cephalosporins, and aztreonam, irrespective of individual MIC given by automatic methods. Lower cephalosporin breakpoints, recently issued by CLSI [34], aim to eliminate the need to perform ESBL confirmatory testing. Those changes might also result in more strains being classified as nonsusceptible in Greece.

Carbapenemase detection is particularly challenging. Genotypic methods confirm their presence; however, use is limited to reference or research settings. Carbapenemase-producing (either KPC or MBL) *Enterobacteriaceae* may have MIC in the susceptible range [4, 27]; the newly proposed criteria by CLSI [34] and EUCAST [35] can optimize screening. Furthermore, for all carbapenems, performance of automated systems may be subject to inoculum effect [36]. Until new breakpoints for carbapenems can be implemented, the CLSI recommends the clover leaf (modified Hodge) test for phenotypic detection [34]; disadvantages include low specificity, interpretation difficulties, and inability to differentiate between KPC and MBL [37]. Tests for detecting KPC or MBL are based on inhibition by boronic acid or EDTA, respectively, in various versions [37, 38]; no specific test has been recommended by EUCAST or the CLSI. Recently, a simple algorithm able to detect KPC, MBL, and their coproduction (based on combining discs of meropenem, phenylboronic acid, and EDTA) has been developed and validated against genetic gold standard tests in Greece [4].

Detection issues exist also with MRSA. PVL-positive strains with low-level oxacillin resistance (MIC 0.5–4 mg/L) can be misclassified as susceptible, unless PBP2a is phenotypically detected. Treatment-induced clindamycin resistance (*erm* phenotype of erythromycin-resistant community-associated MRSA strains) may be unrecognized, unless the D-zone test is performed. Often discrepant susceptibilities between tetracycline (resistant) and doxycycline (susceptible) may lead to therapeutic failure of the latter, following efflux induction [15].

Major resistance mechanisms (ie, a carbapenemase and an ESBL) often coexist in high-prevalence areas [9]. Knowledge of the basic susceptibility profiles conferred by each enzyme is important (ie, resistance to aztreonam by MBL carriers implies presence of an additional ESBL or plasmidic AmpC). Awareness of resistance patterns predominating at local or hospital level is essential. This is a dynamic process with ever-changing features: examples include changes in the carbapenemase type predominating in Greek hospitals during ongoing epidemics [26] or the decrease in MRSA and VRE prevalence. High-level aminoglycoside resistance among enterococci is not interchangeable; although high-level streptomycin resistance is more frequent in Greece, strains highly resistant to gentamicin may not be so to streptomycin [18], which then can be used synergistically for invasive infections.

TREATMENT CHALLENGES

The contemporary challenge is to cure bacterial diseases with minimal ecologic impact. Development of resistant flora can occur in many ways (eg, unnecessary antibiotic use, imbalance toward inadequate cover or excessive spectrum, ineffective dosing, and undue treatment prolongation). Empirical treatment regimens should be guided by local resistance epidemiology. Treatment de-escalation (with narrower spectrum antibiotics) after culture results is always recommended, if effectiveness is supported by evidence: examples include the use of high-dose sulbactam for treatment of *A. baumannii* infection (35% are still susceptible to ampicillin-sulbactam in Greek ICUs), use of ampicillin against *E. faecalis*, the combination

of rifampicin and fusidic acid for MRSA infection (although resistance rates to fusidic acid in Greece are high because of a predominant clone), and trimethoprim-sulfamethoxazole or clindamycin for localized community-associated MRSA infection [12, 15].

Use of some β-lactams (ie, piperacillin/tazobactam, cefipime, or aztreonam) is controversial when organisms (ie, CTX-M, AmpC-, or MBL-producers, respectively) test susceptible in vitro [39]. This policy theoretically entails less selection pressure, possibly avoiding resistance to other antibiotic classes. Successful outcomes have been reported without, however, adequate prospective data on outcome or resistance benefit. They can be used for less severe infections at sites where β-lactams attain high concentrations (ie, urinary infections) [40], but not for life-threatening sepsis.

Treatment of infection due to carbapenemase-producing organisms, susceptible with minimum inhibitory concentration criteria, is challenging. Limited prospective data concur that outcome is not different from infections by noncarbapenemase-producing organisms [27]. Randomized controlled trials are missing; however, for life-threatening infections, safe practice appears to be the combination of carbapenem with a second active agent, such as colistin or an aminoglycoside [30].

Limited prospective observational data on treatment of carbapenem-resistant *K. pneumoniae* in Greece show lower mortality among patients treated with the combination of 2 susceptible agents [26, 27]; those may include an aminoglycoside, colistin, tigecycline, or fosfomycin.

Colistin has been used successfully as monotherapy [41], but should be preferred in combination schemes, to avoid emergence of resistance. Colistimethate doses 9 million IU (720 mg) daily are used for organisms resistant to other antibiotics (Table 1). Colistin appears to be safer than was previously thought. Its combination with tigecycline is active against KPC-producing *Enterobacteriaceae* in vitro [42]. Together with intravenous, colistin can be used aerosolized for ventilator-associated pneumonia and intraventricularly for nosocomial meningitis (ie, multidrug-resistant *A. baumannii*), respectively [41]. Recent pharmacokinetic data suggest that administration of a loading dose might optimize colistin use [43].

Table 1. Recommendations Included in the "Procrustes" Greek Nationwide Action Plan for Containment of Carbapenem-Resistant Gram-Negative Pathogens (http://www.keelpno.gr/)

Detection
–Phenotypic test [4] (using combined-disc of meropenem alone and with 400 mg of phenylboronic acid, 10 μl 0.1 M EDTA) for detection of KPC and/or MBL in *Enterobacteriaceae* strains with MIC > 1 μg/ml for any Carbapenem.
–Carriage screening using MacConkey agar containing meropenem 1 μg/ml (alternatively with MacConkey agar and meropenem discs) on:
A. Rectal or pharyngeal swabs or bronchial secretions in all ICU patients.
B. Rectal or pharyngeal swabs in ward patients with history of:
previous colonization with MRO, and/or
carbapenem use or ICU hospitalization during the previous 6 months.
Treatment
1. *Acinetobacter* spp.
–Ampicillin/Sulbactam 18–24 g/d in divided doses[a]
–Colistin 6.000.000 IU loading dose (over 2 hours) followed by 4.500.000 IU q12h (or 3.000.000 IU q8h)[b]
–Tigecyclin (for intra-abdominal and complicated skin and soft tissue infections) 100 mg loading dose followed by 50 mg q12h
2. *Pseudomonas* spp.
–Aztreonam 2 g q8h[a]
–Colistin (as above)
–Amikacin (7.5 mg/kg/q12h or 15 mg/kg/q24h) or Tobramycin i.v. (5.1–7 mg/kg/q24h or loading dose 2 mg/kg followed by 1.7 mg/kg/q8h)[b]
3. *Klebsiella* spp.
–Gentamicin 5.1 mg/kg/q24h or loading dose 2 mg/kg followed by 1.7 mg/kg/q8h[b]
– Colistin (as above)
– Tigecyclin (as above)
–For life-threatening infections, combination of 2 agents is recommended.
–Carbapenem MIC determination (using E-test) is recommended.
If MIC > 4 μg/ml carbapenem use is not recommended.
If MIC < 4 μg/ml, meropenem (6–8 g/d) can be used, always in combination with an aminoglycoside or colistin (to which the strain should be susceptible in vitro).

NOTE. These recommendations are based on expert opinion; their application started in November 2010.

[a] 4-h infusion is recommended.

[b] Doses are for patients with normal renal function.

Tigecycline offers a therapeutic option for otherwise resistant organisms [44]. Its urinary secretion is minimal. Activity is inconsistent against *Acinetobacter* or *Proteus* and absent against *Pseudomonas*. Of concern, most recent *Acinetobacter* isolates in Greece have MIC $\geq$1 μg/mL [45]. Because of bacteriostatic activity, tigecycline is not an attractive monotherapy for life-threatening infections. The Food and Drug Administration recently issued a warning (http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm) on increased death rates with tigecycline, especially for ventilator-associated pneumonia. Reports of fatalities due to breakthrough bacteremia [28] underscore the relatively low concentrations achieved in plasma. Higher dosages (ie, 100 mg twice daily) are often used off-label, and clinical trials are underway.

Fosfomycin orally (1 dose of 3 g) achieves >90% cure rates of uncomplicated urinary tract infections due to ESBL-producing *E. coli* [40]. Its minimal toxicity, ability to quickly reach high levels in serum and tissues, and activity in vitro against pathogens resistant to carbapenems, colistin, and/or tigecycline offer an attractive candidate for treating severe infections [46]. Experience increases in Greece with fosfomycin disodium used intravenously at doses 3–4 g every 6–8 hours, always in combination with a second active antibiotic (monotherapy leads rapidly to resistance).

Unfortunately, effectiveness of treatments for carbapenemase producers is largely supported by retrospective or observational data, small or suboptimally controlled studies, and personal experience. Such strategies are to be used only in the absence of agents with proven efficacy.

INFECTION CONTROL AND ANTIBIOTIC CONSUMPTION

After MROs become endemic, success of any containment effort is very difficult. Measures required are exigent, multifaceted, centrally coordinated, and resource-demanding [30]. Infection control policies need a sensitive and rapid screening method (tailored to the local epidemiology), accurate phenotypic tests for detection of resistance mechanisms, strict implementation of isolation precautions (often patient cohorting with dedicated staff in settings of endemicity), effective environmental decontamination, and an integrated recording system (with readmission alerts of carriers and inter-hospital communication) [30]. Antibiotic use to decolonize asymptomatic carriers or routine surveillance of health care workers are not recommended [47].

Firm adherence to hand hygiene and rationalizing empirical antibiotic prescription according to local resistance epidemiology are important. Hand hygiene compliance rates <50% are usually attained and necessitate intensification of educational campaigns, monitoring, and feedback [47].

Hospital antibiotic stewardship decreases resistance [48]; restriction strategies have been successfully implemented in Greek settings [22], but data on sustainment are required. Antibiotic use in the community has also been linked with resistance [49]. High rates of macrolide-resistant *S. pneumoniae* in Greece are coupled with excessive outpatient use [21]. Community resistance reservoirs include intrafamilial community-associated MRSA transmission, long-term care facilities, and rehabilitation centers.

FUTURE CHALLENGES

Research interest in antimicrobial resistance in Greece is reflected by the increasing number of publications (Figure 3). In contrast, limited data exist on the actual prevalence of infection due to MROs, with only scarce reports on hospital outbreaks due to organisms, such as MRSA or *C. difficile*. In addition, minimal data from prospective multicenter outcome studies compare available antibiotic regimens or infection control measures. Performing this kind of research on complex patients is difficult. Absence of common terminology for defining and grading resistance can cause confusion [50]; an initiative by the European Centre for Disease Prevention and Control is underway. Consensus guidelines from relevant bodies (ie, EUCAST and the CLSI) on detection methods and break point harmonization are expected to optimize examination in routine laboratory settings.

Ongoing organizational response includes the GSSAR network for resistance monitoring, guidelines for infection treatment by the Hellenic Centre for Diseases Control and Prevention, and the recently launched "Procrustes" nationwide

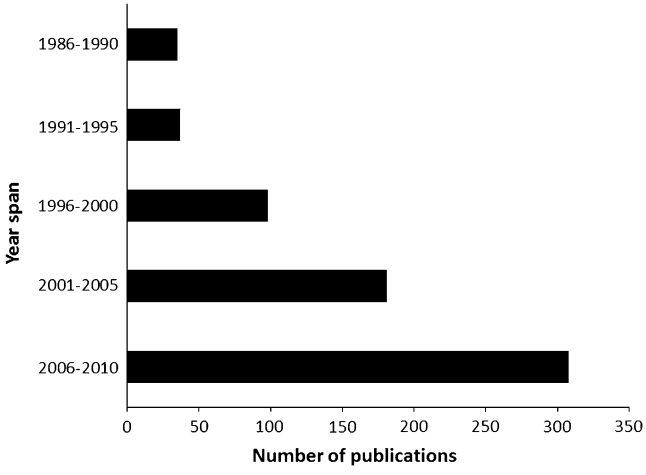

Figure 3. Articles published on antimicrobial-drug resistance in Greece during the last 25 years. A Pubmed search with the terms ("anti-bacterial agents"[MeSH Terms] OR "antibiotic"[All Fields]) AND "resistance"[All Fields] AND "Greece"[All Fields] retrieved 630 articles up until 31 July 2010, half of them during the last 5 years.

action plan (Table 1) for containment of carbapenem-resistant Gram-negative pathogens (http://www.keelpno.gr/). Despite increasing awareness, governmental efforts, and research initiatives, substantial containment of those organisms has not yet been possible; resistance rates and outbreak reports increase. Monitoring of the implementation of guidelines and policies into daily practice is needed. Resources must be allocated to infection control and antibiotic stewardship. Coordinated efforts of all involved parties (administrators, laboratories, and clinicians) are indispensable during the ever-lasting war with the MROs that threaten public health.

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