A call to action for the appropriate use of antimicrobials and the control of antimicrobial resistance

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*This document is endorsed by the scientific societies listed in the appendix 1

ABSTRACT

The spread of antibiotic resistance is one of the leading problems in the public agenda worldwide. A group of experts belonging to the Italian Group of Antimicrobial Stewardship (GISA), actively working in the field, reviewed the available literature to provide a summary of 10 recommendations (the Decalogue). This document, intended for use by practicing physicians, aims to offer suggestions for more rational antimicrobial use. The goal of this document is to promote the culture of appropriateness in the treatment of infections and in the control of antimicrobial resistance, through the translation of theoretical knowledge into priority actions.

The Decalogue has been endorsed by several national scientific societies from Italy, and reflects the particular challenges that are faced in this country. Nevertheless we believe that the general principles and approaches that we discuss are relevant, in particular to other developed economies.

INTRODUCTION

Health professionals from all around the world are witnessing a significant increase in antimicrobial resistance (AMR) to which antibiotic overuse has contributed. Antibiotics are unique drugs with an “ecological” impact, and the prescription to a patient can influence the colonization/infection of many other patients. It is estimated that currently at least 700,000 people die of resistant infections every year globally, and by 2050, 10 million lives a year might be lost to AMR, exceeding the 8.2 million lives a year currently lost to cancer.[1] This is the reason why antibiotic prescription should be based on a rational and methodical process, by evaluating the available epidemiological, microbiological, clinical, and pharmacological information.

Within the European Union, some countries such as Greece and Italy face a worrisome epidemiological situation, with an endemic diffusion of multi-drug resistant organisms (MDRO), especially multidrug resistant (MDR) Gram-negative bacilli (GNB). The most recent (15 Nov 2017) European Centre for Disease Prevention and Control (ECDC) surveillance report confirms the spread of MDR strains, especially among *Klebsiella*, *Pseudomonas* and *Acinetobacter* spp, with alarming percentages of resistance (>50% in several countries) to antibiotic classes such as fluoroquinolones and third-generation cephalosporins, and an increasing detection of carbapenem-resistant Enterobacteriaceae (CRE).[2]

Italy is one of countries with the highest levels of AMR.[3-4] Several reasons may justify this situation: first, prescribers frequently lack expertise in infectious disease and antimicrobial therapy and have a poor perception of the negative effects of inappropriate antibiotic prescription; second, recommendations and guidelines for good practice are often not transferred into daily clinical practice. A further challenge is the disparity observed at a regional level: in Italy there are twenty-one different regional health authorities, with the highest levels of resistance recorded in specific regions. This document has been prepared in the context of the Italian health services and reflects the particular challenges that are faced in this country. Nevertheless we believe that the general principles and approaches that we discuss are relevant, in particular to other developed economies.

The goal of this guide is to promote the culture of appropriateness in the treatment of infections and in the control of antimicrobial resistance, through the translation of theoretical knowledge into priority actions. The present "guide" consists of 10 issues ("Decalogue"), described in **Figure 1.**

METHODOLOGY

This Decalogue has been drafted under the auspices of the recently established, multidisciplinary scientific society called GISA (Gruppo Italiano per la Stewardship Antimicrobica – Italian Group for Antimicrobial Stewardship). GISA consists of 140 members, distributed across various regions of Italy, belonging to different sub-specialties: the majority are Infectious Diseases (ID) specialists (40%), followed by intensivists (16%), internists (14%), and others (30% including microbiologists, haematologists, hospital pharmacists, pharmacologists, physicians in training).

The Decalogue was developed in several distinct stages, with the objective to propose some "priority actions" that translate the scientific evidence and knowledge gaps into practice solutions for clinicians. At the first stage, all GISA members received a questionnaire with a request to propose 3 topics of primary importance in the field of antimicrobial resistant infections; 80% of members responded to the invitation and sent their suggestions. The steering committee of GISA selected the 10 most frequently mentioned topics as the issues of the Decalogue (see **Figure 1**). After that, the GISA scientific board identified 10 top level specialists, belonging to different areas of expertise (infectious diseases specialists, hygienists, microbiologists, pharmacologists, pharmacists, veterinarians) and commissioned them to perform an updated review of the literature for each field and to summarize evidence in practical recommendations. The proposed priority actions are fully described in **Table 1**.

Finally, the document was critically revised by the scientific board of GISA, which approved the final version. The document was then submitted to several Italian scientific societies involved in the challenge of AMR for endorsement.

The Decalogue

1. Vaccination in adults and in the immunocompromised host

Vaccination plays a key role in infectious disease prevention and control, both for individuals and the community. An appropriate immunization coverage for selected diseases has a positive impact on antimicrobial use and, consequently, on AMR. Indeed, vaccination reduces the circulation of infectious agents, leading to a decrease in the use of antimicrobial agents and the opportunities to select resistant strains.[5-6]

However much can still be done in this field. Despite the implementation of vaccine programs, *S. pneumoniae* remains a leading cause of invasive bacterial disease (meningitis and sepsis) in several nations including Italy.[7-8] Moreover, influenza vaccine coverage in people with underlying conditions is very low, a phenomenon that favors inappropriate antimicrobial prescriptions during the winter season.[9] Thus, a multi-component vaccination strategy should be implemented in order to maximize the impact of vaccination on AMR. The introduction of new vaccines (already in the later stages of clinical development) to prevent infection with respiratory syncytial virus, *Clostridium difficile*, *Staphylococcus aureus* and group B *Streptococcus* could have a further significant impact on the inappropriate use of antibiotics.[5]

2. Appropriate use of antimicrobials in prophylaxis

Appropriate antibiotic prophylaxis can reduce the risk of infection in several situations, for example in patients undergoing surgical procedures or in immunocompromised patients. However, an indiscriminate use of antibiotic prophylaxis increases selective pressure and promotes the emergence of antimicrobial resistant strains.[10] Judicious use of antibiotics in the hospital environment is therefore essential.

The pillars of surgical antimicrobial prophylaxis are short-term administration (no more than 24 hours) and the use of narrow-spectrum antibiotics. The antibiotic infusion should be started within 60 minutes before the surgical incision and a second administration is not usually required (if surgical time does not exceed 2.5 half-lives of the antibiotic selected).[11] Importantly, antimicrobial prophylaxis should be selected and reviewed periodically according to the local epidemiology and resistance patterns. Specific patient populations, such as patients with splenectomy and functional asplenia, pregnant women, or subjects at high risk of endocarditis, could benefit from antimicrobial prophylaxis in specific circumstances. [12-14]

3. Infection control strategies

To reduce the risk of hospital-acquired infections (HAI), strategies of infection control (IC) must be implemented, aimed to prevent and control these infections in susceptible populations in both acute care hospitals and long-term care facilities.

IC procedures, a core part of patient safety programs, are central in order to contain AMR by directly limiting the cross transmission of MDR organisms in various health-care settings. In order to have an effective IC program, a high level of coordination between the national and local level is necessary: lack of coordination may contribute to an uncontrolled increase of AMR, as has been the case with the rapid spread of carbapenamase-producing Enterobacteriaceae (CPE) in Italy, where, over a three year period between 2009 and 2011, carbapenem-resistant *Klebsiella pneumoniae* increased from 1.2% to 26.7% and stabilized around 35% in 2014.[2,15]

Hand hygiene promotion campaigns, education programs in all specialties, focusing first on those at high risk of AMR (intensive care units, internal medicine, respiratory medicine, nephrology and dialysis, organ transplantation, general surgery), availability of national guidelines and local protocols, collection and dissemination of data on AMR and HAI (surveillance programs), and specific interventions for specific MDRO are all measures that should be implemented.[16]

Moreover, the availability of national guidelines and local protocols is a crucial part of any control program. Currently in Italy, national guidelines focusing on the main IC problems and some specific infections are already available. However, these measures should be organized both at national level (specific campaigns planned and organized by the Ministry of Health) and at local level (measures organized and adopted by each institution).

4. Control of the use of antimicrobials in farm animals

Antimicrobial agents are used for different purposes in the production of food of animal origin. This includes treatment of infections in clinically ill animals, preferably with a bacteriological diagnosis (therapeutic use), treatment of clinically healthy animals belonging to the same flock or pen as animals with clinical signs (metaphylactics), treatment of healthy animals in specific periods during farming when they are either stressed or in other ways more susceptible, in order to prevent disease (prophylactics), and continuous inclusion of antimicrobial agents in animal feed to improve their growth (growth promotion). The unnecessary use and abuse of antibiotics in animals and agriculture is a significant concern for human health because it promotes the development of antibiotic-resistant bacteria and resistance genes that can be transferred to people through environmental contamination.[17]

It has been demonstrated that the increasing use of antibiotics in agriculture over the past decade contributed to the emergence of a range of highly resistant bacteria in farm animals, such as methicillin-resistant *S. aureus* (MRSA), fluoroquinolone-resistant *Campylobacter*, extended-spectrum beta-lactamases (ESBL) *E. coli*, ESBL *Salmonella*, and others.[18]

Furthermore, the use of antibiotics in animals can result in the accumulation of antibiotic residues in food (meat, milk and eggs) intended for human consumption, leading to concern about the potential for direct toxicity and the colonization by resistant strains in humans.[19] In the European Union, antibiotics for growth promotion have been banned since 2006, and for all the other uses, a veterinary prescription is always required. However, most European countries, including Italy, still permit antibiotics to be used for routine disease prevention, a practice considered unwise in animals.

5. Use of biomarkers to guide antibiotic therapy

Biomarkers can be measured in the blood of infected patients and used either as an indicator of pathological pathways or as a response to therapy.[20] They have been evaluated as tools to help physicians to monitor the clinical course as well as the response to antibiotics. The most investigated biomarker is procalcitonin (PCT), which several studies have indicated as a useful parameter allowing a more rational administration of antibiotics in septic patients.[21-23] Further biomarkers such as presepsin and mid-regional pro-adrenomedullin are promising alternatives that can be used to evaluate the need for antibiotics and monitoring the response to therapy.[24] The most important value of these tools, when used together with clinical evaluation, is their usefulness in promoting an early discontinuation of antibiotic therapy, lowering not only drug-related adverse events but also exposure to antibiotics and playing an important role in antimicrobial stewardship programs (ASP).[25]

6. Early microbiological diagnosis and antimicrobial susceptibility testing

The clinical importance of microbiological diagnosis and antimicrobial susceptibility testing (AST) is increased in the current scenario of growing AMR.[26] In addition, cumulative AST data are important for the compilation of epidemiological surveillance reports, which are used as guidance for the selection of empirical antimicrobial regimens and to monitor the evolution of AMR over time [23].

The impact of microbiological diagnosis on ASPs is expected to be higher when the rapidity of data reporting is increased. Recent studies show that more rapid laboratory data reports result in shorter patients' hospitalization and lower antibiotic consumption, resulting in cost savings for the healthcare system and containment of the selective pressure.[27]

Some newly introduced technologies, such as PCR-based methods, *in situ* hybridization and Matrix Assisted Laser Desorption Time of Flight (MALDI-TOF) mass spectrometry, have expedited the time-to-identification of bacterial and fungal pathogens. The clinical usefulness and the positive impact on ASP of MALDI-TOF-based identification have been clearly documented.[28]

Regarding AST techniques there are several novel technologies that allow a reduction in the response time, such as the use of liquid cultures coupled with light scattering reading, time-lapse microscopy-based technologies, and the use of molecular methods for the rapid detection of the genetic determinants of AMR. [29] Some of these systems are designed to combine rapid identification and detection of resistance mechanism with a syndromic approach.[30]

7. Antibiotic Management Strategies (AMS)

AMS include all the strategies needed for the rational use of antibiotics, balancing the need of cure of the patient and the containment of AMR.

Empiric antibiotics are essential in critical settings, especially in septic or immunocompromised patients. As suggested by the most recent Surviving Sepsis Campaign guidelines, the goal of therapy is the administration of broad-spectrum antibiotics within three hours from Emergency Department triage.[31-32] On one hand, broad spectrum empirical antibiotics maximize the chance of treating the causative organisms and minimize the chance of missing a treatable infection. On the other hand, overuse of broad-spectrum antibiotics may lead to increased selection pressure, promoting AMR. Therefore, a gradual decrease of antibiotics towards a narrower spectrum, as soon as the microbiological results are available, should be recommended, in order to minimize the emergence of MDRO, as well as to reduce costs.

De-escalation therapy is that strategy applied by switching from antimicrobials that provide good empiric coverage to alternatives based on laboratory susceptibility results, stopping unnecessary or redundant treatment, and switching from intravenous to oral therapy.[33-34] In this context, information provided by biomarkers (e.g. PCT) and the rapidity of microbiological diagnosis and AST are crucial.[35]

Another important field of application of AMS is the choice of therapy in patients who are known to be colonized by MDRO (MRSA, ESBL-producing Gram-negative bacteria, carbapenemase-producing Enterobacteriacae or complex antimicrobial resistance profiles produced by *P. aeruginosa* or *A. baumannii*). The choice of antibiotic therapy in these cases, which may be thought of as “targeted-empirical treatment”, is directed to bacteria that have already colonized the patient. This strategy, however, needs an intensive, time-consuming and expensive microbiological work-up involving multiple screening cultures, recognizing that the results do not have the same positive (or negative) predictive value in all patients. The screening cultures permit the early identification of patients with colonization due to MDRO after hospital admission, and this procedure allows the early application of contact precautions and hence a reduction in person-to-person spread. The implementation of evidence-based AMSs is complex and requires education programs, infection control protocols, and a multistep approach.[36]

8. Role of the pharmacology laboratory for antibiotic optimization

The inappropriate selection of an antimicrobial agent, inappropriate dosing, and an excessive duration of the therapy are three key pharmacological aspects contributing to the emergence of AMR. Thus, optimal regimens must be utilized not only to maximize effectiveness in a specific patient, but also to minimize the development of AMR.[37]

There are extensive data showing that the administration of antimicrobials according to pharmacokinetic/pharmacodynamic (PK/PD) parameters improves the likelihood of a positive clinical outcome, particularly in severely ill patients.[38-39] Evidence is growing that when PK/PD parameters are used to target not only clinical cure but also eradication, the spread of resistance will also be contained.[40] PK, when considered as part of a specific dosing regimen, can help determine the time course of drug concentrations in serum, tissues, body fluids, and site of infection. In general, for hydrophilic antibiotics only a fraction of the plasma concentration may diffuse into tissue, and the penetration may be further reduced in the presence of comorbidities such as diabetes. Consequently, in some clinical circumstances, the optimal treatment of bacterial infections might require a more aggressive dosing schedule: for time-dependent drugs, the application of prolonged or continuous infusion may be helpful, while for concentration-dependent antibiotics higher doses might be effective.[38,40] On the other hand, the penetration into the interstitial fluid of lipophilic agents at standard dosing is usually unaffected by the underlying pathophysiological status, and is successful in the majority of cases.

In some cases, mainly in intensive care patients, therapeutic drug monitoring (TDM) may be extremely useful to evaluate the antimicrobial concentration, in order to optimize the therapeutic approach.[41-42] It is important to be aware that minimum inhibitory concentrations (MICs) can also vary according to the infection site and type of patient (co-morbidities, immune status, organ function and so on), since the MIC can greatly influence the possibility of reaching and maintaining the optimal PK/PD goal, which can vary in itself. Evidence is currently being gathered (both from trials and clinical practice) that the application of PK/PD principles can also help control of AMR, by avoiding the exposure of microorganisms to antimicrobial doses that exert a selective pressure, instead of eradicating them.[43-44]

9. Antimicrobial Stewardship Programs

ASPs are necessary and useful to manage the complex issues related to antimicrobial resistant infections, and are mandatory to optimize the management of both old and new antibiotics.[45-46] The goals of ASP are the improvement of patient outcomes, the reduction of the inappropriate use of antimicrobials and their side effects and the control of AMR.[47]

An ASP should involve various specialists (infectious disease consultants, microbiologists, pharmacologists, pharmacists, hygienists) and prescribers (ICUs, internists, surgeons, transplant surgeons, onco-hematologists etc.), through the sharing of “ad hoc” programs, therapeutic recommendations, and application of microbiological and pharmacology laboratory methods. A multidisciplinary approach is more likely to generate consensus and permanent results, while the apparently simpler hierarchical approach produces instead a less consistent and durable outcome.

Two different organizational models could be used to apply the ASPs:

1. “Front-end” ASP model: based on pre-prescription authorization (PPA), restricted antibiotic list, and need for mandatory ID consultation;

2. “Back-end” ASP model: based on post-prescription review with feedback (PPRF) strategies. This approach provides free use of all antimicrobials for 48-72 hours by each physician, and a secondary intervention of the ID consultant to validate in a peer review-process the adequacy of previous prescription. Process indicators (antibiotic consumption, duration of therapy) and outcome

indicators (length of hospitalization, mortality) are necessary for properly assessing the impact of ASPs.

Tamma and coworkers compared these two different approaches to identify the most effective intervention. In a quasi-experimental, crossover trial they found that the PPRF strategy was more effective in reducing the days of antibiotic therapy compared to PPA[48] . Hence, we believe that a “back-end” ASP may be more efficient and useful to optimize antibiotic consumption in the hospital setting.

10. Infrastructure and Education

Adequate administrative support, including economic and human resources, is essential for successful ASPs. The most interesting example in this sense was the containment of a KPC-*K. pneumoniae* national outbreak in Israel. The authors applied a multifaceted approach including contact isolation measures and placement of patients in self-contained nursing units staffed by dedicated nurses, mandatory isolation of known carriers at the hospital level, monitoring of compliance with IC by a central authority, and creation of a task force (directly reporting to the Ministry of Health) with the statutory authority to intervene as needed to contain the outbreak.[49] Specific funding support was necessary to sustain infrastructures and dedicated staff in order to obtain a satisfactory outcome. Similarly, a recent survey from the USA about implementation of ASPs revealed that 60% of US hospitals reported hospital leadership commitment to ASPs through dedicated human, financial, and information technology resources.[50] In the final multivariate model, teaching hospital status, written support, and salary support were each independently predictive of reported achievement of successful ASPs, and the strongest predictor was written support from the facility administration (adjusted RR 7.2 [95% CI, 6.2–8.4]; $P < .0001$).[50]

Equally important, education is a key core component to reduce the transmission of MDRO in endemic or epidemic settings. Educational hospital meetings are core elements for any ASP.[16,50] Educational meetings should be performed periodically, including physicians, nurses, physical therapists, students, and other professionals working in affected areas. The main objective of these activities is to ensure that healthcare workers understand why MDRO are important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread should be adopted.[16] A last objective is to perform informative campaigns among family practitioners and the general population about the risk of the unnecessary prescription or of the self-use of antibiotics.

CONCLUSIONS

The containment and management of AMR is a subject of global concern. This paper was developed in the context of the Italian health service, in recognition of the fact that the national response to this challenge was suboptimal and the local implementation fragmented. The enthusiasm and willingness both of the national bodies, and the many specialist scientific societies to join together and agree an action plan to address this problem is in itself a significant outcome from this exercise.

It is for this reason that we believe that the approach taken here might have general relevance for other developed countries. It is relatively easy to set out the general principles of the Decalogue, which are generally well known and agreed by most people. However, the most important challenge is then developing a plan to implement these recommendations. The approach we have taken is to identify “priority actions” which represent the most important elements that can be readily translated into daily clinical practice. Key to evaluating the impact of these priority actions is the identification of outcome measures. These measures have been well identified by the PNCAR (National Plan for the Containment of Antimicrobial Resistance) recently published by the Italian Ministry of Health.[51] We believe that any ASP or IC program that is introduced should be carefully and regularly monitored to assess changes in these outcome measures, both to reassure the institution that the program is effective and also to provide positive reinforcement of the benefit of the measures that have been implemented. These objective data will also provide a means of working with an institution (or an individual in an institution) in the event that they fail to follow the appropriate guidelines. A reinforced educational response should be used in the first instance; ultimately, sanctions can be considered if an individual or an organization does not follow these recommendations.

Finally, it is clear that the two key elements in a program such as this are commitment from the leadership both at national and local level, and the availability of resources to allow the "priority actions" to be introduced. The challenge of AMR should therefore be dealt with by the combined and coordinated efforts of the Ministry of Health (central level), Regional Health Services (peripheral level) and with the pivotal support of the scientific societies. We hope that this document will provide a helpful framework for others struggling with this challenge, and with appropriate local modifications, that it can be used as a road map to guide the implementation of national IC programs.

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TABLE 1. Proposed priority actions for each item of the Decalogue.

ISSUE	PRIORITY ACTIONS

1. Vaccination in adults and in the immunocompromised host	1) Implementation of childhood routine vaccination programs, designed to obtain coverage level against *Haemophilus influenzae* type b, *S. pneumoniae*, and meningo serotypes B and C. This goal could be achieved with the hexavalent vaccin pneumococcal conjugate vaccines. 2) Vaccination of risk groups. Appropriate vaccination should be offered to every with underlying conditions when accessing health care services, including general ho In these cases, the need for vaccination could be easily identified during hospitalizatio the vaccine could be administered before hospital discharge, without any major imp the hospital organization. 3) Vaccination of the elderly. Vaccine coverage for influenza and pneumococcal v among people aged 65 and over must be improved, through a strong collaboration be general practitioners, vaccination services, hospitals, and long-term care settings. 4) Vaccination of healthcare workers (HCWs). HCWs should be strongly encourage vaccinated against influenza, in order to reduce the risk to spread the disease healthcare environment during the influenza season. 5) Communication to fight skepticism towards vaccination. This problem is spr among the population and is reaching worryingly high levels. Fighting vaccine hesit important, in order to plan and implement new strategies needed for improvi aforementioned vaccine programs.
2. Appropriate use of antimicrobials in prophylaxis	1) Definition and implementation of an effective intervention strategy, in order to redu use of antimicrobials in surgical prophylaxis. Control by the health authorities of adh to national guidelines. 2) Active surveillance of the use of antimicrobials in surgery departments and of the of antimicrobial resistance in these units. 3) Active surveillance of adverse events to antibiotic prophylaxis including the incid *Clostridium difficile* colitis. 4) Development of communication and education programs to increase awaren adverse events due to an inappropriate use of antibiotics for surgical prophylaxis.
3. Infection control strategies	1) Define IC as a key priority of the healthcare system and identify specific fund 2018. 2) Implementation of a national campaign on hand hygiene in all healthcare institut the National Health Care system, both in acute and long term care facilities. 3) Reinforcement of basic infection control precautions (e.g. contact precautions, is rooms, environmental cleaning) in both epidemic and endemic settings. 4) Increase the availability and use of surveillance programs, both nationally and l and include surveillance for adverse effects from antimicrobial use.
4. Control of the use of antimicrobials in farming animals	1) Definition and implementation of an effective intervention strategy to reduce the antimicrobials in animals, with particular focus on specific classes of antibiotics. Th objectives and the resources should be defined by the authorities, together with re national stakeholders (medical and veterinary associations, representatives of food an producers) and civil society representatives (consumers). 2) Improvement of integrated surveillance (One Health approach) on the u antimicrobials and on the spread of the antimicrobial resistance, in both the medic veterinary settings. 3) Development of communication and education programs to raise awareness amo general population and the health professionals in Italy on the health risks rela antimicrobial resistance, including the incautious use and abuse of antimicrob animals.
5. Use of biomarkers to guide antibiotic therapy	1) Use the available biomarkers within evidence-based guidelines, together with the c evolution of the patient, to systematically reduce the duration of the antibiotic th

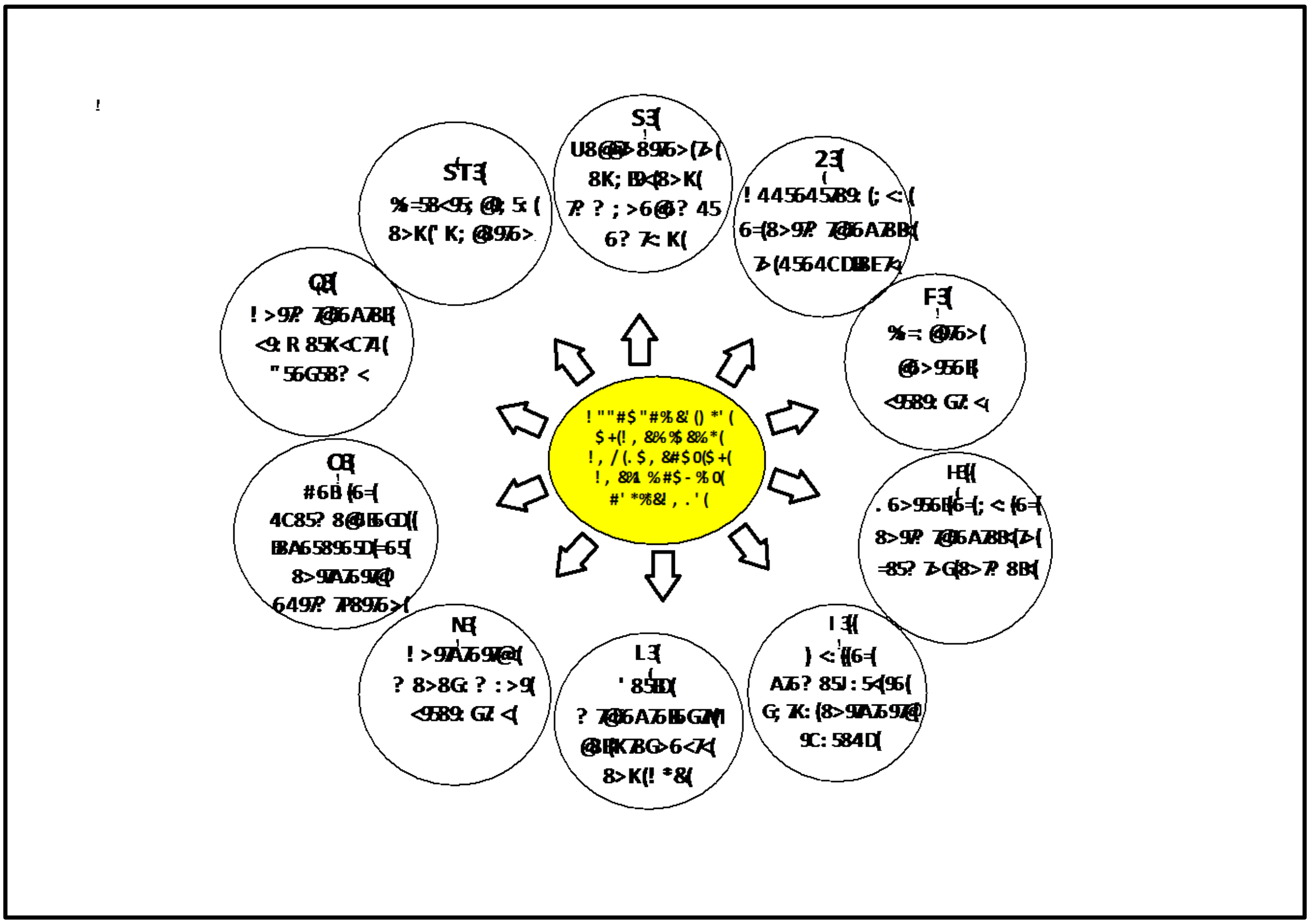
	especially in specific settings such as Intensive Care. 2) Raise awareness among both clinical and laboratory colleagues about the clinical of biomarkers such as PCT. 3) Develop appropriate training courses, which allow the clinician to understand the of PCT and other biomarkers within ASP.

6. Early microbiological diagnosis and antimicrobial susceptibility testing (AST)	1) Produce on a regular basis (at least at semi-annual intervals) reports on str cumulative AST data at hospital level, to assist the development of local guidelin empirical therapy. 2) Make every effort to reduce identification and AST Turn Around Times (adopt M TOF and molecular diagnostic systems for microbial identification and detection resistance mechanisms). 3) Design personalized diagnostic workflows and rationalize the use of new techno adopting patient stratification criteria (severity of illness and/or risk of rapid c progression). 4) Actively support ASP components and other clinicians in the interpretation Clinical Microbiology Laboratory results. 5) Implementation of the use of rapid diagnostics in primary care settings, in order to antibiotic prescription by general practictioners (GP).
7. Antibiotic Management Strategies	1) The automatic use of empirical broad-spectrum antibiotic therapy should be discou whenever possible, antibiotics should be prescribed on the basis of clinical jud combined with microbiologic data. In cases where empiric antibiotic are indicate example in immunocompromised hosts and in patients with multiple comorbiditi prolonged hospitalization, standardized evidence-based protocols should be used. 2) Empiric antibiotic treatment strategies should be based on local resistance patterns. 3) Strategies to rapidly decrease empirical broad-spectrum and combination ant therapies towards a targeted, narrow-spectrum treatment should be implemented. 4) Efforts to correctly identify patients at high risk of colonization by MDRO (i.e. colonization by MDRO), deserving a so called "targeted-empirical" antibiotic tre approach, should be pursued and implemented through the use of active scr cultures.[14]
8. Role of the pharmacology laboratory for antibiotic optimization	.1. Improve the knowledge about the target PK/PD parameter for the specific drug in u 2. Improve all strategies to help clinicians to select the most appropriate adminis method, according to the PK/PD parameters. 3. Promote the optimization of dosing, especially in severely ill patients, according t function, but limit the duration of therapy, where possible. 4. When appropriate, encourage the measurement of serum antimicrobial concentratio
9. Antimicrobial Stewardship Programs	1) Awareness campaigns for hospital administrators. 2) Management of new antibiotics. Knowledge of multidisciplinary recommendatio guidelines, and adoption of shared prescription policies. Institutional approval of rul procedures for the "off-label" use of antimicrobials (at national/regional level) in s clinical situations. To this purpose, the involvement of hospital pharmacists is crucial. 3) Reduction of antibiotic use in the community. Since 90% of the total antimicrob occurs at the patient's home, it is necessary to directly involve GP and pediatricia creating with them therapeutic-diagnostic pathways that reduce the need for an im use of antibiotics. 4) "One-health" approach. The use of antibiotics in animals for therapeutic purposes be further regulated, while the use for rapid growth purposes should be strongly res (veterinarians). The presence of antibiotics in food should be traced and contained.

10. Infrastructure and Education	1) Commitment to ASPs at national level (Ministry of Health, national authoriti providing economic and human support. 2) Rational use of hospital resources to ensure adequate infrastructure and dedicate for ASPs. 3) Continual educational programs for health professionals working in areas o prevalence of MDRO 4) Informative campaigns involving family practitioners and the general population.

Legend. MDRO= multi-drug resistant organisms; PK/PD = Pharmacokinetic/pharmacodynamics; ASP= Antimicrobial Stewardship Programs.

FIGURE 1. Core objective, Decalogue areas proposed by GISA



Legenda: AST: antimicrobial susceptibility testing.

Appendix 1

Endorsement

*This document is endorsed by the following italian national & international scientific societies & by the following colleagues representative of national health institutions:

Federazione Associazioni Dirigenti Ospedalieri Internisti (FADOI, Andrea Fontanella, Antonino Mazzone)**, Società Italiana di Medicina Interna** (SIMI, Francesco Perticone), **Società Italiana di Gerontologia e Geriatria** (SIGG, Raffaele Antonelli Incalzi, Francesco Landi); **Club Epatologi Ospedalieri** (CLEO, Alessandro Perrella) **Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica**, (SItI, Fausto Francia) **Gruppo Italiano Studio Igiene Ospedaliera,** (GISIO, Antonella Agodi) **Società Italiana Multidisciplinare per la Prevenzione delle Infezioni nelle Organizzazioni Sanitarie** (SIMPIOS, Gaetano Privitera) **Società Italiana di Farmacia Ospedaliera** (SIFO Eugenio Ciacco, Marcello Pani), **Società Italiana di Chemioterapia** (SIC, Teresita Mazzei, Francesco Scaglione), **Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva** (SIAARTI, Antonio Corcione, Antonino Giarratano)**, Federazione Italiana Micopatologia Umana e Animale** (FIMUA, Ercole Concia, Francesco Barchiesi) Associazione Microbiologi Clinici Italiani, (AMCLI, Pierangelo Clerici, Francesco Luzzaro)**; Società Italiana di Microbiologia** (SIM, Anna Teresa Palamara, Stefania Stefani); **Gruppo Italiano Trapianti Midollo Osseo** (GITMO, Francesca Bonifazi, Corrado Girmenia) **Global Alliance for Infections in Surgery** (Massimo Sartelli, Fausto Catena), **World Society of Emergency Surgery** (WSES, , Luca Ansaloni, Federico Coccolini) **World Association for Infectious Diseases and Immunological Disorders** (WAidid, Susanna Esposito).

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