G.I.S.A.
GRUPPO ITALIANO PER LA STEWARDSHIP ANTIMICROBICA

DECALOGUE

FOR THE APPROPRIATE USE OF ANTIBIOTICS IN INFECTIONS AND THE CONTROL OF ANTIMICROBIAL RESISTANCE IN ITALY

DRAFT

INTRODUCTION

The worrying reality in the field of Italian epidemiology that combines a high consumption of antibiotics with an high level of antimicrobial resistance does not appear to be justified.

In fact, our National Health Service is not suffering from a relevant lack of resources, our hospital facilities are not generally inadequate and our health-care professionals (doctors, nurses) cannot be considered unprepared.

What would appear to be missing, therefore, is the capacity to transfer to daily care practice what is correctly reported in Recommendations and Guidelines (good use of antibiotics, good healthcare assistance).

Probably, the staff training on antibiotic use and infection control is inadequate or too theoretical and verification tools are often lacking: there is no feedback regarding the quality and the results of our work.

There is also a substantial disparity at a regional level: twenty-one different realities that can only produce inhomogeneous responses, nationwide and in the hospitals, that are reflected in a wide variation in the quality of the healthcare services provided, with a classic North-South gradient.

The idea of a specific "Guide" that sets out the priorities of action that help to transform good intentions into consolidated reality, would seem a natural choice for a recently-established, multidisciplinary scientific society such as GISA (*Gruppo Italiano per la Stewardship Antimicrobica* – Italian Group for Antimicrobial Stewardship) that promote the culture of appropriateness in the treatment of infections and in the control of antimicrobial resistance.

We have realize the Decalogue with the aid of top level specialists in the various fields (hygienists, microbiologists, pharmacologists,pharmacist, infectious diseases), and we are now proposing it to the national and international scientific community and to the representatives of the various institutions and political fields, firmly convinced that One Health approach, which focus on human and animal health, and also on environmental protection, is the only strategy potentially able to dealing with the challenge of antimicrobial resistance, which, according to current estimates, could cause up to 10 million deaths within the year 2050.

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DECALOGUE FOR THE APPROPRIATE USE OF ANTIBIOTICS IN INFECTIONS AND THE CONTROL OF ANTIMICROBIAL RESISTANCE IN ITALY

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Pier Luigi Lopalco

- Ensuring an appropriate immunization coverage for selected diseases has a positive impact on antimicrobial use and, consequently, on antimicrobial resistance.
- A multi-component vaccination strategy should be implemented in order to maximize the impact of vaccination on antimicrobial resistance.
- The following actions should be carried out:
  1. **Maintain high coverage levels with hexavalent vaccines and pneumococcal conjugate vaccines, and improve vaccination coverage for meningococcal vaccination during childhood.**
  2. **Reinforce the vaccination of risk groups**, implementing new and more effective strategies. Hospitalization can be an excellent opportunity, and **vaccine could be administered before hospital discharge to all patients belonging to risk groups.**
  3. Vaccine coverage for the **influenza and pneumococcal vaccine among people aged 65 and over** must be improved.
  4. **Healthcare workers must be vaccinated against influenza.**
  5. Effective communication strategies should be implemented, in order to **fight vaccine hesitancy.**

2. ANTIBIOTIC PROPHYLAXIS IN SURGERY AND IN THE COMPROMISED HOST page 14

Carlo Tascini

1. Promote **reference guidelines** either for bacterial prophylaxis in surgery or in the compromised host.
2. Promote the **multidisciplinary approach** needed to produce adequate guidelines.
3. Implementation of the **adherence to reference prophylaxis guidelines.**
4. Intervention **strategy, to reduce the inappropriate use of antimicrobials in surgical prophylaxis** (drug, dose, route of administration, duration).
5. Intervention **strategy, to increase the appropriate use of medical prophylaxis in the compromised host** (i.e. neutropenia).

CONTAINMENT OF ANTIMICROBIAL RESISTANCE (AMR)

3. INFECTION CONTROL page 18

Angelo Pan, Alessia Zoncada

1. **Define IC as a key priority of the health-care system, both at national and regional level**
   - **Support** actions on HAI & antimicrobial resistance, through communication and education at all levels within the health care system;
   - Involvement of Ministry of Health & Board of Heath (*Istituto Superiore di Sanità*)
   - Involvement of selected Scientific Societies;
   - Mandatory training programs during the various education degree, in school and within the ECM programs, on HAI for all health-care workers;
   - Definition of new national guidelines in critical settings (eg. carbapenemase-producing *Enterobacteriaceae* – CPE).

2. Awareness campaign for hospital administrators (*Direzioni Aziendali, Assessorati alla Salute, Agenzie di Sanità*)
- Regional IC teams with shared programs;
- Resources (budget, research funds).

3. Management of HAI data
- Evaluation of the adherence to already available IC national guidelines (eg. Compendium INF OSS, MRSA);
- Wider (mandatory?) participation in the already available national surveillance systems (SSI – SNICh and infections in intensive care unit – SITIN) by all regions;
- Definition of a program for new national surveillance systems on critical aspects: CLABSI, VAP, CAUTI, *C. difficile*.

4. CONTROL OF THE USE OF ANTIMICROBIALS IN FARMING ANIMALS AND RISK RELATED TO THEIR RESIDUES IN FOOD OF ANIMAL ORIGIN page 24

Luca Busani

1. Set targets for a reduction in the use of antimicrobials in farming animals.
2. Restrictions on the use of the critical antibiotics in farming animals and pets.
3. Reduction in the environmental dispersal of antibiotics through animal waste and manure and the residues of antibiotics in food of animal origin.
4. Improvement of the integrated surveillance on the use of antimicrobials and on the spread of the antimicrobial resistance in both medical and veterinary settings.
5. Raise awareness on the health risks related to antimicrobial resistance, including the incautious use and abuse of antimicrobials in animals.

RAPID DIAGNOSIS OF BACTERIAL INFECTIONS AND AMR

5. ROLE OF SURROGATE MARKERS page 28

Bruno Viaggi

1. There is clear evidence supporting the use of Procalcitonin (PCT) as part of a multi-parameter evaluation of the management of infections in septic patients
2. PCT-guided antibiotic therapy leads to a significant reduction in the number of days of antibiotic exposure, a lower drug-related effect, and a lower rate of antibiotic resistance.
3. PCT value should be contextualized and interpreted within the clinical context.
4. The dynamic change in PCT in the first 48-72 hours expresses the predictive value of survival and efficacy of the antibiotic therapy, with a significant impact on the patient's survival outcome.
5. Using PCT, a clinician can also differentiate, or rather hypothesize, a Gram-negative or a Gram-positive bacterial infection and, focusing on the *Negative Predictive Value* (NPV) of this biomarker, in the presence of septic conditions, a PCT value of <2 ng/mL can strengthen the clinical suspicion of fungal etymology, thus leading to a more targeted rapid diagnosis.
6. In the presence of sepsis/septic shock with negative or extremely low PCT, due to the severity of the clinical picture, a careful clinician should quickly address the diagnosis towards the exclusion of clinical pictures such as deep abscesses and/or compartmentalised collection, meningitis/ventriculitis, endocarditis without embolism, specific atypical pneumonia, BSI caused by CoNS or by fungi.

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Gian Maria Rossolini, Fabio Arena

1. To produce on a regular basis (at least at semi-annual intervals) reports on cumulative AST data stratified at the hospital level, to assist ASPs (*Antibiotic stewardship programs*) in developing local guidelines for empiric therapy.
2. To make any possible effort to reduce pathogen identification and AST Turn Around Times (adopt MALDI-TOF, fast phenotypic methods and molecular diagnostic systems for microbial ID and detection of key resistance mechanisms).
3. To design personalized diagnostic workflows and rationalize the use of new technologies adopting patient stratification criteria (severity of illness and/or risk of rapid clinical progression).
4. To actively support ASP components and other clinicians in the CML (*Clinical Microbiology Laboratory*) results interpretation.

APPROPRIATE USE OF ANTIBIOTICS AND AMR CONTAINMENT

8. ANTIBIOTICS MANAGEMENT STRATEGIES page 34

Francesco G. De Rosa, Silvia Corcione, Luca Scaglione, Giovanni Di Perri

1. **Fight the spiral of empirism** through the systematic search for bacterial etiology.
2. Always **monitor local epidemiological and resistance data** at hospital level, to adapt empiric antibiotic regimens.
3. Try to **gradually decrease empiric broad-spectrum combination antibiotic therapy** switching to a targeted, narrow-spectrum, antibiotic therapy as soon as possible.
4. Try to **identify high-risk patients** (i.e. rectal colonization by MDR bacteria) deserving a targeted empiric antibiotic approach.
5. Try to **reduce the duration of the antibiotic therapy course** (i.e. using PCT).

9. THE PHARMACOLOGY LABORATORY FOR ANTIBIOTICS OPTIMIZATION page 38

Andrea Novelli, Elia Rosi

1. **Raise awareness on the pharmacological factors related to the clinical & microbiological failure and the potential emergence of AMR**: inappropriate selection of the antimicrobial agent, unsuitable dosing, administration modality and duration of therapy. Select the most appropriate administration modality according to pharmacokinetic/pharmacodynamic parameters.
2. **Remember that standard susceptibility breakpoints, mainly in severely ill patients, may be inaccurate for the clinical scenario**, due to patient related modification of main kinetic parameters.
3. PD index for both concentration-dependent (C_{max}/MIC; AUC/MIC) and time-dependent antibiotics (T/MIC) may be influenced either increasing drug dosing or **reducing MIC through combination of antibiotics**.
4. In critically-ill patients **therapeutic drug monitoring (TDM)** may be useful to optimize drug dosing, both for increasing efficacy and reducing toxicity.
5. Promote **awareness of the need for pharmacological laboratories** for optimizing the use of antibiotic.

10. ANTIMICROBIAL STEWARDSHIP PROGRAM

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Francesco Menichetti

1. Public awareness campaign at political and government level
   - **Support** actions on HCA-I & antimicrobial resistance, to promote new rules for a "fast-track" registration of new antibiotics (AIFA, EMA)
   - Involvement of Ministry of Health, Board of Health (*Istituto Superiore di Sanità*), Scientific Societies
   - National recommendations for the ASP
   - Lobbying activities
2. Awareness campaign for hospital administrators (*Direzioni Aziendali, Assessorati alla Salute, Agenzie di Sanità*)
   - Resources (budget, research funds)
3. Management of the new antibiotics
   - Multidisciplinary & fair guidelines and recommendations
   - Shared management of AIFA's form between ID consultant & specialist
   - Clear and consistent rules on the "off-label" use of the new antibiotics
   - Supervision of the hospital pharmacist
4. "One-Health" approach
   - Involvement of the general practitioner
   - DTP (diagnostic & therapeutic plan) for the more common infections (i.e. URTI).

PREVENTIN OF INFECTIONS

1. VACCINES IN ADULTS & THE COMPROMISED HOST

Pier Luigi Lopalco

Key actions

- Ensuring an appropriate immunization coverage for selected diseases has a positive impact on antimicrobial use and, consequently, on antimicrobial resistance.
- A multi-component vaccination strategy should be implemented in order to maximize the impact of vaccination on antimicrobial resistance. In particular the following actions should be carried out:
  - Maintain high coverage levels with hexavalent vaccines and pneumococcal conjugate vaccines, and improve vaccination coverage for meningococcal vaccination during childhood.
  - Reinforce the vaccination of risk groups, implementing new and more effective strategies. Hospitalization can be an excellent opportunity, and vaccine could be administered before hospital discharge to all patients belonging to risk groups.
  - Vaccine coverage for the influenza and pneumococcal vaccine among people aged 65 and over must be improved.
  - Healthcare workers must be vaccinated against influenza.
  - Effective communication strategies should be implemented, in order to fight vaccine hesitancy.

Definition of the problems

Vaccination plays a key role in infectious disease prevention and control. The impact of vaccination on the infectious disease burden is evident: smallpox has been eradicated; poliomyelitis spread is limited to few areas on the globe; tetanus and diphtheria virtually disappeared where effective vaccination programs are in place; pertussis, measles, rubella, invasive bacterial infections are under control in many areas in the world.
The benefits of the vaccination programs are not only limited to protecting individuals against dangerous diseases, but also include important positive side effects. First and foremost, the indirect protection of those that – either for medical reasons or for personal choice – are not vaccinated, thanks to the herd immunity effect. In addition, the reduced circulation of infectious agents should also lead to a decrease in the use of antimicrobial agents and the opportunities to select resistant strains.
The inappropriate antimicrobial use is the leading cause of antimicrobial resistance, a worldwide priority issue. Ensuring an appropriate immunization coverage at community level for selected diseases and the targeted immunization of risk groups may have a positive impact on antimicrobial use and, consequently, on antimicrobial resistance.

Scientific evidence and knowledge gaps

Haemophilus influenzae type b

The invasive disease caused by *Haemophilus influenzae* type b (Hib) strains is under control in those countries that successfully implemented specific immunization programs. In the pre-vaccination era, the annual average incidence of invasive Hib disease in children younger than five years of age was estimated at 41 per 100,000 people in Europe and 88 per 100,000 in the US. According to the latest surveillance data, notification rates for invasive *H. influenzae* cases range from 0 to 1.9 per 100,000 people in EU countries. Cases caused by type b strains are nowadays extremely rare. In Italy, over the six-year period 2011-2016, only 34 cases have been reported at national level. In the pre-vaccination era, Hib had already evolved a resistance to ampicillin, with consequent recommendations to use chloramphenicol and broad-spectrum cephalosporins for the empirical treatment of meningitis.
The impact of Hib vaccination on antibiotic consumption is difficult to assess, and there is little evidence available on this topic. On the other hand, considering that Hib infections were the leading causes of invasive bacterial infections among infants during the pre-vaccination era, the impact of Hib vaccination on antimicrobial use may be considerable.

Invasive meningococcal disease

Meningococcal C (MenC) vaccine programs have been implemented in 17 EU countries. The impact of such programs has been particular evident in those countries, like UK, where meningococcal endemicity was higher during the pre-vaccination era. In Europe, thanks to MenC vaccination, the incidence of the invasive meningococcal disease due to B strains is at the present the most relevant. Meningococcal B vaccination has been introduced very recently, and therefore its impact cannot be yet assessed. In Italy, the incidence of meningococcal invasive infections ranged between 0.23 and 0.38 per 100,000 during the period 2012-16, and serogroup B was predominant (48-65%), with the exception of 2015 and 2016, when the circulation of a hyper-virulent ST-11 strain in Tuscany made the serogroup C more prevalent.

The same goes for Hib: there is little evidence available on the impact of MenC vaccination on the antibiotic consumption. On the other hand, considering that every single case of meningococcal meningitis is followed by a large use of antimicrobials for the secondary prophylaxis of contacts, the impact of meningococcal vaccination on antimicrobial use may be considerable.

Pneumococcal infections

Streptococcus pneumoniae is the leading cause on invasive bacterial infections both in children and in the elderly. The burden of this pneumococcal disease is also relevant in adolescents and adult individuals at high risk of bacterial invasive disease, like those with chronic lung, heart, liver, or kidney disease; asthma; diabetes or conditions that weaken the immune system (splenectomy, HIV/AIDS, cancer). In addition to invasive disease like sepsis and meningitis, otitis media represents the major disease burden related to pneumococcal infections. *S. pneumoniae* is a common colonizer of the nasopharynx, and the rate of antimicrobial resistant strains in colonized patients can be up to 70%, in particular in special groups like children attending daycare centers. Acute otitis media (AOM) is a very common disease among infants and children and *S. pneumoniae* accounts for 28-55% of cases. AOM is one of the leading cause of antimicrobial consumption among children: in an Italian study, antibiotics were prescribed to more than 80% of the children diagnosed with AOM, and prescription rates did not decrease after the implementation of paediatric guidelines based on “vigilant waiting” strategy .

Pneumococcal conjugate vaccination with seven-valent vaccine (PCV7) has been progressively implemented worldwide, starting from 2003. Its impact on the reduction of antimicrobial resistant strains both in disease cases and in colonized patients has been demonstrated.

After the introduction of PCV7, serotype replacement of pneumococcal infections from serotypes not contained in PCV7 was observed. Of particular concern was the observation that the levels of antibiotic resistance increased in non-vaccine isolates responsible for the infections after the vaccine was introduced. In particular, type 19A, which also had high rates of penicillin non-susceptibility, emerged in most countries with high PCV7 coverage rates, and eroded the gains against the resistant disease. In order to cover six of the most prevalent serotypes which were not included in PCV7, including 19A, PCV13 was introduced. At present, it is unclear if serotype replacement and the increase in antimicrobial resistance rates will be observed for strains not covered by PCV13. In any case, the overall impact of PCV vaccination on the improper antimicrobial use and antimicrobial resistance is evident. It is important to note that S. pneumoniae is the leading cause of invasive bacterial disease (meningitis and sepsis) in Italy, despite the implementation of a successful paediatric vaccination program. In 2016, 1,462 cases of invasive infections (2.4 per 100,000) have been reported at national level.

Influenza

The influenza virus is the leading cause of respiratory illness during the winter season in the northern hemisphere. Vaccinations significantly reduce the incidence of influenza and, by preventing a portion of these cases, both the appropriate and inappropriate antimicrobial prescribing can be reduced. The use of fluoroquinolones is strongly associated with influenza, and it is estimated that a 20% reduction in influenza activity would decrease prescriptions by 8%. The inappropriate antimicrobial use is very common during the influenza season. In a study conducted in the US, antibiotics were prescribed to 21.6% of a large sample of patients with diagnosis of influenza. In 79% of these patients an inappropriate antibiotic treatment was confirmed.

Priority actions

Childhood routine vaccination program

Sustaining a high coverage level for the vaccines included into the childhood program is paramount. In particular, the following actions should be considered priority:

1. Keep under control Hib infections, maintain high coverage levels with hexavalent vaccines;
2. Keep under control pneumococcal infections among healthy children, by the means of routine childhood vaccination;
3. Maintain high coverage levels for meningococcal C vaccination and promote the introduction of meningococcal B vaccine, extending as much as possible the age groups with the active vaccine offer.

Vaccination of risk groups

Risk group vaccination need to be reinforced, implementing new and more effective strategies. In particular, influenza vaccine coverage in people with underlying conditions is very low. A proper targeted vaccination should be offered to every patient with underlying conditions when accessing health care services. In particular, the need for vaccination could be easily identified during hospitalization, and the vaccine could be administered before the hospital discharge, without any major impact on the hospital organization.

Vaccination of the elderly

Vaccine coverage for influenza and pneumococcal vaccine among people aged 65 and over must be improved. A strong collaboration between the different sectors of the health care system (general practitioners, vaccination services, hospitals, long term care settings, etc.) is needed and new strategies to remove all barriers to vaccination among the elderly should be elaborated.

Vaccination of healthcare workers

Healthcare workers (HCWs) must be vaccinated against influenza, in order both to reduce the risk to spread the disease in the healthcare environment during the influenza season, and also because HCWs should act as a role model in the healthcare system. An HCW not vaccinated against influenza cannot be a credible champion of flu vaccination.

Communication to fight hesitancy toward vaccination

Vaccine hesitancy is the new epidemic of the latest decades. Skepticism towards vaccination is spreading among the population and is reaching, in Italy, worryingly high levels. Fighting vaccine hesitancy is important, in order to plan and implement new strategies needed for improving the aforementioned vaccine programs.

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2. ANTIMICROBIAL PROPHYLAXIS IN SURGERY AND IN THE COMPROMISED HOST

Carlo Tascini

Key actions

1. Surgical antimicrobial prophylaxis could reduce the risk of surgical wound infections, in association with other measures.
2. Surgical antimicrobial prophylaxis should last no more than 24 hours.
3. Surgical antimicrobial prophylaxis should use narrow-spectrum antibiotics.
4. Active surveillance on the use of antimicrobials and on adverse events in surgery should be implemented.
5. Antimicrobial prophylaxis in special population might reduce the risk of infections.

General considerations

The expression "antimicrobial prophylaxis" refers to a short-term administration of an antibiotic in order to reduce the risk of infections in specific population without infection, such as those to be subjected to surgical interventions or immunocompromised patients, like those with splenectomy, sickle-cell disease, pregnancy or at high risk for endocarditis.

Surgical Antimicrobial Prophylaxis (SAP)

SAP's aim is to reduce the risk of surgical wound infections. SAP is usually appropriate only in case of clean-contaminated interventions (Table 1); in these cases:

- The antibiotic therapy should be addressed against the bacterial flora most likely to cause post-operative wound infections, not against every species and every infection;
- The selected antibiotic should i) have the narrowest spectrum necessary, ii) be as much tolerated as possible, iii) be easy to be administered, iv) not be usually used in the treatment of severe infections or sepsis;
- The antibiotic infusion should be started within 60 minutes before the surgical incision; **generally, a second administration is not required** (if surgical time does not exceed 2.5 half-lives of the antibiotic selected); antibiotics administered via other routes than the intravenous one are generally not recommended, except for the specific indication reported in the table;
- It is reviewed periodically, in consideration of the local epidemiology and resistance patterns.

In addition, to clearly organize the SAP and verify its usefulness:

- ❖ A definition of SAP (appropriateness, choice of the antibiotic, organization of the administration, etc) should be provided by the local committee on infection control, together with the surgeons representatives;
- ❖ The administration of the SAP should be managed by the anesthesiologist, who participates in the intervention;
- ❖ **Periodic audits on the consumption of antimicrobials, the incidence of *Clostridium difficile* colitis, SAP-related adverse events and pharmacovigilance should be periodically organized.**

Antimicrobial prophylaxis (AP) for patients with splenectomy and functional asplenia

Patients subjected to splenectomy or with a functional asplenia, such as those suffering from sickle-cell disease, are at an increased risk of infections, especially sepsis, due to capsulated bacteria. The main prophylactic measure is vaccination against these bacteria. In addition, in the following specific conditions, antimicrobial prophylaxis is recommended:

- Asplenic pediatric population: amoxicillin/clavulanate 125 mg every 12 hours from 2 months to 3 years of age, then amoxicillin/clavulanate 250 mg every 12 hours until 5 years of age or at least for 1 year after splenectomy
- Sickle-cell disease: penicillin V 125 mg every 12 hours from 2 months to 5 years of age and then penicillin V 250 mg every 12 hours. Discontinuation time has not been well established.
- For immunocompromised patients and those with thalassemia or previous episodes of sepsis, prophylaxis could be beneficial until 18 years of age.

Table 1 summarizes the recommended SAP regimens; unreported surgical interventions do not require the SAP

Type of Surgery	First line SAP[a]
Cardiovascular surgery: • reconstruction of the abdominal aorta • procedures with groin incision • procedures with foreign bodies insertion • cardiac surgery/heart transplantation • lower extremities amputation for ischemia • PMK/ICD implant • aneurism repair, revascularization	**Cefazolin 2 g**[b]
Gastro-duodenal/biliary surgery: • gastro-duodenal surgery • high risk PEG placement • pancreatic-duodenectomy • open cholecystectomy	**Cefazolin 2 g**
• ERCP with obstruction	**Piperacillin/tazobactam 4.5 g**
Colorectal surgery	**Cefazolin 2 g** *plus* **Metronidazole 500 mg**[c]
Head and neck surgery: • with oral/pharyngeal involvement • not necessary for clean interventions	**Cefazolin 2 g** *plus* **Metronidazole 500 mg**
Neurosurgical procedures: • clean procedures without implant • CSF shunt surgery, intrathecal pumps	**Cefazolin 2 g**
• clean-contaminated procedures with involvement of sinuses or naso/oropharinx	**Clindamycin 900 mg**
Obstetric and gynecologic surgery: • vaginal or abdominal hysterectomy • cesarean section for premature rapture of membranes or active labor	**Cefazolin 2 g**
• surgical abortion (first trimester)	**Doxicycline** *per os* **100 mg before procedure** *plus* **200 mg after procedure**
Orthopedic surgery: • joint replacement • arthroplasty	**Cefazolin 2 g**
• open reduction of closed fracture with internal fixation	**Ceftriaxone 2 g**
Urologic surgery: • cystoscopy with manipulation • transrectal prostate biopsy	**Ciprofloxacin 500 mg** orally *2 hours befor incision*
• clean intervention with or without entry into the urinary tract and with or without implanted prosthesis	**Cefazolin 2 g ± gentamycin 3 mg/kg**
• clean-contaminated intervention	**Cefazolin 2 g** *plus* **Metronidazole 500 mg**
Ophthalmic surgery	**Topical neomycin-garamycin-polymyxin B** *1 eye drop every 5-15 minutes per 5 doses*
Other: • breast surgery • herniorraphy • thoracotomy	**Cefazolin 2 g**

Notes: a) iv administration during the 60 minutes preceding the surgical incision (if not otherwise specified); b) some authors recommend to continue cefazolin 2 g every 8 hours for 1-2 days; c) generally associated with mechanical intestinal preparation and oral neomycin sulfate and oral erythromycin.

Antimicrobial prophylaxis during pregnancy

The aim of the AP during pregnancy is to prevent the early onset of group B streptococcal (GBS) disease in the newborn. The recommended regimen is the following:

- Penicillin G, 5 mlnU as initial dose, then 2.5-3 mlnU every 4 hours until delivery.

AP is appropriate in the following cases:

- Previous newborn with invasive GBS disease;
- GBS bacteremia during any trimester of the current pregnancy (not indicated if a caesarean is performed before labor onset and with intact amniotic membranes);
- GBS-positive vaginal or rectal screening culture in late gestation during the current pregnancy;
- Unknown GBS status at the onset of labor and any of the following conditions:
  - Delivery at <37 weeks of gestation;
  - Amniotic membrane rupture ≥18 hours;
  - Intrapartum temperature ≥38°C;
  - GBS-positive intrapartum NAAT.

Recently published guidelines also recommend vaccination against *Bordetella pertussis* and Influenza in the last part of the pregnancy.

Antimicrobial prophylaxis in subjects at high risk for endocarditis

AP to reduce the risk of infective endocarditis is nowadays recommended, only in few specific circumstances.
In case of dental procedures with manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa, AP is recommended in the following cases:

- Patients with any prosthetic valve or prosthetic material used for cardiac valve repair;
- Patients with prior infective endocarditis;
- Patients with congenital heart diseases (CHD) (any type of cyanotic CHD, any type of CHD repaired with a prosthetic material up to 6 months after the procedure or lifelong, if a residual shunt or valvular regurgitation remains).

Invasive procedures of the respiratory, gastrointestinal or urogenital tract and/or skin and soft tissues are not indications for AP to prevent infective endocarditis.
The AP recommended schedule is as follow:

- Amoxicillin 2 g *per os* or iv
- Clindamycin 600 mg *per os* or iv in case of allergy to penicillin.

Priority actions at national level

1. Definition and implementation of an effective intervention strategy, in order to reduce the use of antimicrobials in surgical prophylaxis. Control by the health authorities of the adherence to national guidelines.
2. Active surveillance of the use of antimicrobials in surgery departments and of the spread of antimicrobial resistances in the same units.
3. Proposal for surveillance of adverse events to the antibiotic prophylaxis included in the incidence of *Clostridium difficile* colitis, made by experts of the Ministry of Health.
4. Development of communication and education programs to increase awareness of the adverse events due to an inappropriate use of antibiotics for surgical prophylaxis.

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3. INFECTION CONTROL (IC)

Angelo Pan, Alessia Zoncada

Key actions

- Define IC as a key priority of the health-care system, both at national and regional level
- Organize awareness campaigns for hospital administrators, in order to increase their knowledge about this problem (*Direzioni Aziendali, Assessorati alla Salute, Agenzie di Sanità*)
- Define a core of skills on Infection Control (and Antimicrobial Resistance) for all health-care workers
- Improve or re-activate the projects that have already been organized by the Ministry of Health: improve adherence to hand hygiene, promote the adherence to prevention and control measures, as indicated in the Compendium INF OSS, reinforce the control of methicillin-resistant *Staphylococcus aureus* (MRSA), improve surveillance on carbapenamase-producing *Enterobacteriaceae* (CPE).
- Implement a wide use of the existing surveillance programs of the Italian Cente for Disease Control (*Centro per il Controllo delle Malattie* - CCM) of surgical site infection (*Sistema Nazionale di sorveglianza delle Infezioni del sito Chirurgico* - SNICh), and of the infections in intensive care units (*Sistema nazionale di sorveglianza delle Infezioni in Terapia Intensiva* - SITIN).

Infections Control

As stated by the father of medicine Hippocrates of Kos over 2400 years ago, one of the primary goal of all health-care workers is to not cause harm to patients. Between 5 and 10% of all patients admitted in acute care hospitals (ACH), and 3 to 7% of patients in long-term care facilities (LTCF), develop a healthcare-associated infection (HAI). To reduce the risk of HAI acquisition, strategies must be implemented aiming at preventing and controlling these infections in susceptible populations, in both the ACH and LTCF settings: namely the infection control (IC) strategies. The antimicrobial resistance (AMR) highly increases the complexity of HAI prevention, control and management.

The IC procedures, a core part of the patient safety programs, are central in order to limit AMR: a) by directly limiting the cross transmission of multi-drug resistant organisms (MDRO) in the various health-care settings, and b) by limiting the AMR selection by reducing the use of antibiotics through the prevention of HAI. It is estimated that 50% or more of HAI may be prevented through adequate IC policies.

In order to have an effective IC program, a high level coordination between the central and the peripheral level is necessary: this is a crucial point, and we will go back to it in the text. A lack of coordination may determine an uncontrolled increase of AMR, as it has been the case with the rapid diffusion 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.

To confirm the strong need for a coordinated intervention is the fact that many strategies necessary for an adequate IC have already been planned and organized by the Ministry of Health (MdS, *Ministero della Salute*), including for example a national hand hygiene (HH) promotion campaign or the surveillance of surgical site infections (SSI). In any case, these projects probably did not have enough support from the central Institutions, nor a wide diffusion in the Regions to have a strong impact on national epidemiology. Parallel to this point, different Regions organized effective programs, but often without any strong collaboration. Therefore, the coordination and extension of already available systems seems to be the most needed and promising strategy to improve IC in Italy.
This paper analyzes eight areas where the implementation of new strategies could have a positive impact on IC programs, both at a central – MdS and Regions – and peripheral level, in this case dealing with strategies that should be applied at the single structure level.

Organization of the program

As stated above, without a well-organized program, the possibility to adequately control AMR are extremely limited.

Central level: central programs aiming to control HAI have been in place for over 30 years. Despite the time elapsed, in many parts of the country there still is a lack of central involvement in HAI control. First, the MdS should define IC as a key priority of the healthcare system, both at national and regional level. The MdS should identify a simple set of programs to be implemented and audited at the national and regional level, with definite timeframes. Similarly, at the regional level, standardized critical information from the individual hospitals should be collected. Data regarding the interventions should regularly be communicated to the scientific community, as well as to tax payers.
A similar strategy should be applied to the other healthcare settings, including LCTF, rehabilitation facilities, and the community context. This extension of the IC borders is due to the changes observed in medicine over the last decades, with an important portion of the patients being managed outside the ACH.

Peripheral level: at this level, an effective IC system needs to be under the responsibility of the hospital Management, and should include the *Infection Control Committee* (ICC) and the *Infection Control Team* (ICT), with formally dedicated resources. Depending on the characteristics of each facility, a network of link nurse and doctors, in close collaboration with the ICT and the ICC, could be implemented. Due to the universality of the HAI risk, the IC programs need a full multidisciplinary approach, with professionals from many different areas, as well as regular meetings of both the ICC and the ICT. These should identify the most critical issues for their institution, based on real world data, and regularly monitor, audit and provide feedback on the critical issues.

Education

Education on IC and AMR plays a central role in having a well-structured system and, along with a good organization, is the basis for long lasting results.

Central level. Among the different options possible in this setting, a core curriculum on IC and AMR for all health-care workers (HCWs) should be defined and rapidly implemented. In addition, IC and AMR should be a relevant part of continuing education programs in all specialties, focusing first on those at high risk of IC and AMR, such as intensive care units, internal medicine, pneumology, nephrology and dialysis, organ transplantation, general surgery.

Peripheral level. Each single facility or health-care trust should include, in the educational programs, IC and AMR subjects that are closely related to the characteristics of the facility itself and the local epidemiology.

Guidelines and recommendations

The availability of national guidelines and local guidelines and protocols is a crucial part of any control program. To date, national guidelines focusing on the main IC problems are already available. The recent laws on medical responsibility provide the chance to rapidly improve the spread and use of guidelines on IC.

Central level. National guidelines on IC were published in 2009, while those on the control on methicillin-resistant *Staphylococcus aureus* (MRSA) were published in 2011. In other settings, such as the prevention and control of CPE, *Clostridium difficile* associated diarrhoea (CDAD), or SSI – where guidelines by Regions and by Scientific Societies were published – individual national shared documents should be drafted.
The Regions should promote the implementation of the guidelines available at facility level.

Peripheral level. Each facility should draft local protocols that should adapt the guidelines indications to the characteristics and needs of each individual hospital. On the other hand, audits on adherence to IC protocols should be regularly performed.

CONTAINMENT OF ANTIMICROBIAL RESISTANCE (AMR)

Surveillance

It is necessary to have wide view of the reality, in order to identify the priorities both at central and peripheral level. The collection and dissemination of data on AMR and HAI are therefore of the utmost importance in controlling AMR. Data show that the implementation of a surveillance system, *per se* is associated with a decline in the surveyed infection, as also confirmed by the data of SSI surveillance system in Italy.

Central level. Within the programs of the CCM on IC there are two ongoing surveillance systems established in 2010, one on SSI, the *Sistema Nazionale di sorveglianza delle Infezioni del sito Chirurgico* (SNICh), and the other on infections in the intensive care units (ICU), the *Sistema nazionale di sorveglianza delle Infezioni in Terapia Intensiva* (SITIN). To date, only one Region defined as mandatory the data collection for SSI. It should be responsibility of the MdS to extend the data collection for these two ongoing projects, giving strong indications to the Regions to promote the organization of adequate surveillance systems.
Another existing surveillance program is that of CPE blood-stream infections. Due to the epidemiological relevance of CPE in Italy today, this system should be strongly sponsored by the MdS. Surveillance data should be regularly published, possibly every three to six months, in order to identify improvements and critical areas.
Regional studies should be implemented on the prevalence of points on HAI and antimicrobial use, based on the ECDC protocol: despite all the limitations of prevalence surveys, this type of study is relatively easy to perform and gives general information on HAI; in addition, it can increase HCWs' awareness on this problem.
In addition, regional surveillance experiences – such as those of 2012-2013 on CDAD performed in Emilia-Romagna and Lombardy – should be resumed, and other Regions should be involved.

Peripheral level. When single institutions deal with critical epidemiological threats and implement a local surveillance system, it is strongly recommended to build the surveillance program around available national, European or international protocols, in order to make data comparable.

Hand hygiene

Hand hygiene (HH) plays a central role in the prevention and control of all HAIs. A wide HH campaign was started in 2006 by the CCM, within a project of the World Health Organization (WHO), called *Le cure pulite sono cure più sicure* ("Clean care is safer care"), with a significant change in the system organization and an improvement in HH adherence. Despite the improvements observed in this project, HH adherence remains quite low in the country, both in the ACH and in the LTCF, with the consumption of alcohol hand rub solution (AHRS) at the lowest levels in Europe.

Central level. A new launch of the HH project should be sponsored by the MdS and every Region should be formally involved. Easy-to-produce indicators, such as the consumption of AHRS, should be regularly monitored and added to the information debt that the Regions have with the MdS, in parallel with that of antibiotic consumption.

Peripheral level. Each and every facility, including LTCF, should have access to AHRS. Adherence to hand hygiene should be calculated following WHO indications, especially in the wards with high risk patients or with a high spread of MDRO.

Environmental hygiene

Over the last years, the importance of a clean environment in the prevention and control of HAI gained a lot of interest. Problems concerning this point that need to be analyzed are the lack of national guidelines, the difficulty in verifying the level of cleanliness beyond the standard visual inspections, the limited availability of new technologies, and a high turn-over of the cleaning personnel, who often work for subcontractors. A full revision of this chapter was announced by the MdS.

Use of medical device use and bundles of interventions

The use of medical devices has significantly improved patients' outcomes, but with a marked increase in the risk of HAI. As reported above, to date in our country the surveillance systems on these infections are limited. Interventions to reduce the most common HAI, including SSI, central line associated blood-stream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), ventilator-associated pneumonia (VAP), or CDAD, have generally proven effective. For example, programs on CLABSI have been associated with a decline in BSI as high as 67%. Most of the interventions are based on the introduction of a bundle of interventions, i.e. 3-6 procedures of evidence-based efficacy, to be performed jointly on the same patient.

Central level. As indicated above, the MdS published guidelines on the management of medical devices in 2010. These indications need to be widely spread, both for an educational purpose and to assess the adherence to the recommended practices.

Peripheral level. Each facility should identify its own critical areas and implement a strategy aimed at reducing HAI. It is of paramount importance that a common surveillance system is used to collect data, in order to make comparisons with other facilities. Auditing at least the most critical practices is strongly recommended.

Interventions for specific multi-drug resistant organisms

Italy has among the highest European rate for many MDRO, including MRSA, CPE, extended-spectrum beta-lactamase (ESBL) - producing *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*. The interventions to limit the spread of many MDRO are strongly needed and, as previously stated, need to be well coordinated. A National program is feasible, based on the excellent results, in terms of a significant reduction of resistance, that have been observed in other countries.

Central level. Since the spread of CPE, that has now reached an endemic level, is a national problem, the specific intervention aimed at reducing the incidence of carbapenem-resistant *Enterobacteriaceae* should be mandatory for each individual Region. Similarly, a national strategy to control MRSA should be strongly encouraged.

Peripheral level. Each individual facility should strive to limit the spread of MDRO, each focusing on the most common pathogen among the patients who refer to it. A close connection with the facilities that have high mutual transfer of patients is strongly needed, in order to better deal with this problem.

In conclusion, many are the strategies necessary to improve IC. The theoretical and practical basis of IC has already been set up by different projects, both at national and regional level. A strong commitment by both the MdS and the Regions is necessary to improve IC and reduce AMR. High level projects and a high degree of collaboration are absolutely necessary to deal with this significant problem.

Priority actions

1. Define IC as a key priority of the healthcare system and identify specific funding by 2018.
2. Implement a national campaign on hand hygiene in all healthcare institutions of the National Health Care System, both in the acute and long term care facilities by 2018.
3. Increase the diffusion of surveillance programs (CPE, SSI) by 2018.

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4. CONTROL OF THE USE OF ANTIMICROBIALS IN FARMING ANIMALS AND RISK RELATED TO THEIR RESIDUES IN FOOD OF ANIMAL ORIGIN

Luca Busani

Key actions

- Define targets for the reduction of antimicrobials use in farming animals.
- Restrictions on the use of the critically important antibiotics in farming animals and pets.
- Improvement of the integrated surveillance on the use of antimicrobials and on the spread of antimicrobial resistance in both the medical and veterinary settings.
- Raise awareness on the health risks related to antimicrobial resistance, including the incautious use and abuse of antimicrobials in animals.

Definition of the problems

In the production of food of animal origin, antimicrobial agents are used for different purposes:

1. Specific treatment of infections in clinically sick animals, preferably with a bacteriological diagnosis (therapeutic use);
2. Treatment of clinically healthy animals belonging to the same flock or pen as animals with clinical signs (metaphylactics);
3. Treatment of healthy animals in a period where they are either stressed or in other ways susceptible, in order to prevent diseases (prophylactics);
4. Continuous inclusion of antimicrobial agents in animal feed, to improve their growth (growth promotion).

Prophylaxis use can be a sign of management problems, and in many countries it is not considered legal or prudent.
The use of antimicrobials as growth promoters is banned in Europe (EU) since 2006, but this practice is still allowed in many other countries.
In many countries, the amount of antimicrobial use in animals outweigh that in human beings.
Although gaps in the evidence undoubtedly remain, there is an increasingly robust consensus that the unnecessary use and abuse of antibiotics in animals and agriculture is a significant concern for human health. It promotes the development of antibiotic-resistant bacteria and resistance genes that can be transferred to people through the consumption of food, but also through direct contact with food animals or environmental mechanisms. Also, because food animals and foods of animal origin are traded worldwide, they contribute to create antibiotic resistance in countries far from those where the problem has originated.

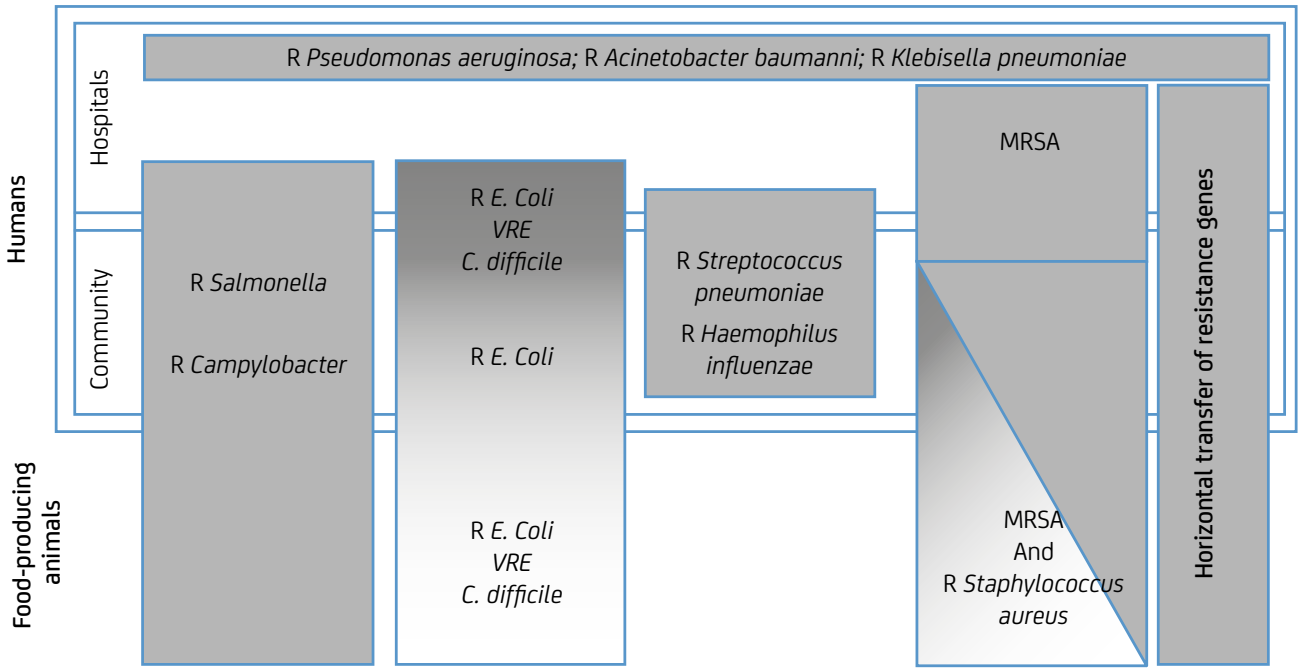
Use of critically important antimicrobials in livestock

The World Health Organization (WHO) classified certain antimicrobial classes as “Critically Important Antimicrobials for human medicine” (WHO, 2012).
According to the European Medicines Agency (EMA-ESVAC), the World Health Organization critically important antimicrobials appear to be in frequent use on farm animals across the major EU countries.

Emerging public health threats with a potential relationship with antimicrobial use in livestock

The increasing use of these antibiotics in agriculture over the past decade is widely recognized to have contributed to the emergence of a range of highly resistant bacteria in farm animals, such as Extended-Spectrum Beta-Lactamase (ESBL) *E. coli*, ESBL *Salmonella*, fluoroquinolone-resistant *Campylobacter* and methicillin-resistant *S. aureus* (MRSA).
Recently, in *E. coli* and *Salmonella* isolates from pigs, chickens and, to a lesser extent cattle, a transferable resistance to the polymyxin antimicrobial colistin, mediated by a “family” of genes (*mcr* genes) has been identified. The emergence of plasmid-mediated resistance to colistin is a cause of great concern, due to the importance of colistin as “last resort” antimicrobial, and emphasizes the urgent need for a coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

Figure 1. Overview of some of the most important antimicrobial-resistant pathogens and the overlap between the different reservoirs (food-producing animals and humans, in both community and hospital). Shades of gray indicate the relevance of the reservoir (darker: high relevance; lighter: low relevance)



Adjusted to the Italian situation by Aarestrup, 2015

Residues of antibiotics in food

The use of antibiotics in animals might result in the deposition of residues in food (meat, milk and eggs) intended for human consumption. Concern over antibiotic residues in food of animal origin occurs for two reasons; one is whether it produces a potential threat to direct toxicity in human, another is whether the low levels of antibiotic exposure could result in an alteration of the microflora, cause disease and the possible development of resistant strains, which cause the failure of the antibiotic therapy in clinical situations.

The search for residues in food of animal origin is routinely performed by the national food safety authorities; in 2016 in Italy over 13,000 samples were tested, and 0.04% was found to contain residues of antimicrobials above the established limits.

Antibiotic use in Italian farms

Data on the sales of farm antibiotics are available for Italy for 2010 to 2014 (ESVAC), and in this period farm antibiotic use in Italy has been exceptionally high, well above the EU average. About 94% of farm antibiotic use in Italy is for mass medication, in animal feed or drinking water.

In addition, farm use of antibiotics classified as "critically important in human medicine" –fluoroquinolones and 3rd and 4th generation cephalosporins – is also high. Furthermore, the farm use of the antibiotic colistin is exceptionally high in Italy.

Regulatory situation in Italy

In Italy, as in the rest of the European Union, antibiotics cannot be used for growth promotion since 2006, and 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 incautious in animals.

So far, Italy has taken limited actions to reduce farm antibiotic use and antimicrobial resistance in the veterinary sector.

With regard to the perception of the risk of antimicrobial resistance and the knowledge on antibiotics among the general population, Italy is among the countries with the lowest risk perception and the lowest knowledge.

CONTAINMENT OF ANTIMICROBIAL RESISTANCE (AMR)

Scientific evidence and gaps in knowledge

Although an absolute proof of a cause/effect relationship in this field can be extremely difficult to establish, because so many of the same antibiotics are used in both veterinary and human medicine, scientists established a clear relation between antibiotic use in farm animals and resistance in humans. Here a list of examples:

- For some major human bacterial infections, such as *Salmonella* and *Campylobacter*, farm animals are the most important source of antimicrobial resistance.
- For certain other human infections, such as *E. coli* and enterococci, there is strong evidence that farm animals are an important source of antibiotic resistance.
- For some infections, like MRSA and *Clostridium difficile*, human reservoirs have been created, and there is evidence that the farm use of antibiotics contributes to treatment problems in human medicine.
- For a further small number of antimicrobial-resistant human pathogens, there is as yet no evidence of any relation with farm antimicrobial use at all, however there is a solid theoretical suspicion that the horizontal transmission of resistance genes of farm-animal origin could contribute to the rise of potentially untreatable cases in humans.
- For many other infections – such as multi-drug resistant tuberculosis and the wide range of infections caused by antibiotic-resistant strains of *Streptococcus pneumoniae* – the use of antibiotics in farms plays no part in the problem of resistance in human medicine.

Even though the precise burden of the selection for antimicrobial resistance in the food animal reservoir has not been established, there is sufficient evidence to conclude that it is a burden on human health that requires immediate attention and intervention.

Priority actions at national level

1. Definition and implementation of an effective intervention strategy to reduce the use of antimicrobials in animals, with particular focus on the critically important antibiotics. The strategy, the main objectives and the resources will be defined by the authorities (the Ministry of Health, the Board of Health [*Istituto Superiore di Sanità*] and the national reference center/laboratory for antimicrobial resistance in veterinary medicine), together with national relevant stakeholders (medical and veterinary associations, representatives of food and drug producers) and civil society representatives (consumers). Current experience suggests that reducing the routine use of antimicrobial agents for food animals is associated with either very limited negative effects or possibly even positive effects for the animal health and welfare, as well as for economy. Different models of intervention are available at international level, and they should be considered and adapted to the national situation.
2. Improvement of integrated surveillance (*One Health* approach) on the use of antimicrobials and on the spread of the antimicrobial resistances, in both the medical and veterinary settings. The proposal for surveillance priorities and the evaluation of the results should come from an agreed evaluation made by experts of the Ministry of Health, the Board of Health (*Istituto Superiore di Sanità*), the national reference center/laboratory for antimicrobial resistance in veterinary medicine and the representatives of the medical scientific societies competent on the matter. Such measure would be beneficial in providing additional information to tailor intervention strategies and to follow-up the impact of the measures implemented.
3. Development of communication and education programs to raise awareness among the general population and the health professionals in Italy on the health risks related to antimicrobial resistance, including the incautious use and abuse of antimicrobials in animals. This activity should involve both the institutions (Ministry of Health, Board of Health [*Istituto Superiore di Sanità*] and other relevant institutions) and representatives of civil society.
   The knowledge of the problem and the measures to be undertaken, also at individual level, to fight the spread of the antimicrobial resistance are an integrated part of the overall national strategy.

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5. ROLE OF SURROGATE MARKERS

Bruno Viaggi

Procalcitonin: the evidence

There is remarkable evidence supporting procalcitonin (PCT) as part of a multi-parameter assessment of the management of infections in septic patients.

- **Liliana Simon** (2004): first review and meta-analysis comparing PCT and CRP as markers of bacterial infection, **concluding that PCT was more sensitive (88% vs. 75%) and more specific (81% vs. 67%) than CRP in differentiating a bacterial infection of non-infective origin.**
- The **proCAP study**: it used PCT in the decision **to discontinue the antibiotic therapy at an earlier stage**, showing that on average the 151 PCT patients discontinued the antibiotic therapy during CAP (**C**ommunity **A**cquired **P**neumonia) after only 5 days, compared with 12 in the control group, with a 99-85% reduction in the prescription upon admission.
- The **ProHOSP study (2009)** – which extended the analysis to all lower respiratory tract infections by analyzing 1,359 patients in a RCT multicenter trial – confirmed that the PCT group had a lower exposure to antibiotics and a lower percentage of drug-related adverse events compared with the control group for a similar outcome.
- The **PRORATA trial**: it supported the current clinical use of PCT, definitively confirming that the mortality rate among the 307 patients in the PCT group (algorithm for initiating and/or discontinuing PCT-guided antibiotic therapy) at 28 and 60 days fully overlapped that of the 314 patients in the control group, but with a significantly lower daily exposure to antibiotics.
- The **Cochrane Collaboration (2012)** published a review of 14 randomized and controlled clinical trials on acute respiratory tract infections, concluding that the use of PCT at the beginning or discontinuation of the antibiotic therapy did not show a higher mortality and/or therapeutic failure rate, whereas there was a significant reduction in the number of days of antibiotic exposure, a lower drug-related effect, and a lower rate of antibiotic resistance.
- A further **meta-analysis carried out in 2013** introduced the concept that the **PCT value** should be contextualized and interpreted **within the clinical context**; it is not a single absolute value that should be considered, but rather the meaning that such value has in that specific clinical setting. It is the **dynamic change** in **PCT** in the **first 48-72 hours** that expresses the predictive value of survival and the efficacy of the antibiotic therapy. It shows that, on the fourth day, a decrease of over 80% in the PCT value compared to baseline is related to the efficacy of the ongoing antimicrobial therapy, with a significant impact on the patient's survival outcome, especially in a ICU setting.
- PCT has also been **associated with with new microbiological diagnostic and rapid identification technologies** to optimize the treatment of serious infections in the critical patient. PCT has also been included in all the most advanced **Antimicrobial Stewardship programs.**
- Data on the **reduction in mortality in the PCT-guided group** was *published* with the results of a large Dutch, open-label, RCT conducted on 1,575 patients divided into two groups (PCT-guided and standard therapy-guided), where the mortality rate at day 28 in the PCT group amounted to 19.6% vs. 25% in the control group.
- Using PCT, a clinician can also differentiate, or rather hypothesize, a **Gram-negative or a Gram-positive bacterial infection**, since the former normally shows much higher values.
- Where values are only slightly higher, just over 1 ng/mL, the bacterial infection could have originated from **coagulase-negative staphylococcus or fungi.**
- There is evidence that a value of 2 ng/mL marks a **threshold between bacterial and fungal infections**. In the presence of well-understood septic conditions, in patients with risk factors, a PCT value of <2 ng/mL can strengthen the clinical suspicion of a fungal cause, thus leading to more rapid targeted diagnosis.

Procalcitonin: a modern and rational use

- Currently, those using PCT in an advanced and innovative way focus their attention on the **marker's high NPV**, in the absence, however, of known and common infectious outbreaks, such as a **BSI** (*Blood Stream Infection*) of known origin and/or an **IVAC** (*Infection-related Ventilator-Associated Complication*).
- In the presence of a patient with sepsis/septic shock with negative or extremely low PCT, syndromes such as deep and/or compartmental abscesses, meningitis/ventriculitis, endocarditis without embolism, specific atypical pneumonia, BSI caused by CoNS or by mycoses in which PCT is known to remain very low or even negative should be considered.
- Instrumental diagnostics can be used, with advanced contrast-enhanced CT scans and MRI. Another reference diagnostic test is the transthoracic – or, rather, trans-oesophageal – echocardiography, which aims to exclude valvular vegetation.

Summary of clinical trials

Bibliographic references		Conclusions
Clin Infect Dis 2004; 39:206-217	Review and metanalysis	PCT superior to CRP as a marker of bacterial infection Sensitivity 88% vs. 75% Specificity 81% vs. 67%
Am J Respir Crit Care Med 2006; 174:84-93	ProCAP trial	Lower exposure to antibiotics in the PCT group, during CAP, 5 days vs. 12 days for the control group with a similar outcome
JAMA 2009;302(10):1059-1066	ProHOSP trial	Lower exposure to antibiotics in the PCT group, during LRTI*, and lower percentage of drug-related adverse events for a similar outcome compared to the control group
Lancet 2010;375(9713):463-74	Prorata trial	Significant reduction in daily exposure to antibiotics in the PCT group compared to the control group for a similar outcome
The Cochrane Library 2012; issue 9	Review of RCTs	Significant reduction in antibiotic exposure, in the drug-related effect and in the antibiotic resistance rate in the PCT group compared to the control group, while discontinuing the antibiotic therapy early, in the absence of higher rates of mortality and/or therapeutic failure
Lancet Infect Dis 2013;13(5):426-35	Metanalysis	The value of PCT must be interpreted carefully within the context of the clinical history and has no meaning if the test is performed on a single point outside the clinical context
Crit Care Med 2017;45(5):781-789 *J Shock 2011;36(6):570-574* *J Crit Care 2011;26(3): 331.e1-7*		The importance of the PCT's kinetic rate variation in the first 48-72 h in determining the efficacy of a therapy and in initiating early the discontinuation thereof (importance of the trend compared to the single initial value)
Clin Infect Dis 2013;56(1):996-1002 *Intensive Care Med 2014; 40:1580-1582* *Intensive Care Med 2015;41(5):776-95* *Intensive Care Med 2016;42(12):2063-2065*		Strong confirmation of the role played by PCT in advanced antimicrobial stewardship programs in ICU on the rapid discontinuation of antimicrobial therapy due to an improved clinical status (stopping rules)

**LRTI: Low respiratory tract infection*

Priority actions to be undertaken

1. Present the appropriate use of PCT and its kinetics (daily monitoring at least for the first 48-72 hours from the diagnosis of the septic event), together with the clinical evolution of the patient, to systematically reduce the duration of the antibiotic therapy, especially in an intensive environment.
2. Develop appropriate training courses, that allow the clinician to understand the use of PCT within antimicrobial stewardship programs
3. Raise awareness among laboratory colleagues about the clinical utility of PCT.

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6. 7. MICROBIOLOGICAL DIAGNOSIS AND ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)

Gian Maria Rossolini, Fabio Arena

General concepts and rationale on recommendations

The identification (ID) of the microbial pathogens and the antimicrobial susceptibility testing (AST) are among the oldest and most common tasks performed by the Clinical Microbiology Laboratory (CML) in support of the choice of the antimicrobial chemotherapy targeted on the individual patient. Their clinical usefulness is further increased in the current scenario of growing antibiotic resistance, where the antimicrobial stewardship has become increasingly more important for the improvement of the clinical outcomes, while minimizing the selective pressure, cause of the development of resistance. In addition, cumulative AST data are important for the compilation of epidemiological surveillance reports on antimicrobial resistance, which are used as a guidance for the selection of empirical antimicrobial regimens and to monitor the evolution of antimicrobial resistance over time.

The impact of microbiological diagnosis on the antimicrobial stewardship is expected to be higher when the rapidity of data reporting is increased. In fact, recent studies showed that the more rapid is the laboratory data reporting, the shorter is the patients' hospitalization (both in the Intensive Care Unit and in the hospital in general) and the antibiotic consumption, resulting in cost savings for the healthcare system and a containment of the selective pressure.

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 antimicrobial stewardship of the MALDI-TOF-based identification have been clearly documented. Also on the AST scenario there are several novel technologies that allow to reduce 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 antimicrobial resistance. The molecular methods for the microbial identification and the detection of resistance genes can also be performed directly from clinical samples (eg. respiratory samples or positive blood culture broth), providing relevant information for the antimicrobial stewardship in a shorter turn-around time (1-5 h). Some of these systems were designed to combine rapid ID and detection of resistance mechanism with a syndromic approach. However, these methods provide qualitatively different and limited information in comparison with conventional ID and AST. Indeed, molecular methods are unable to distinguish between dead and viable pathogens and their ability to predict the antibiotic susceptibility or resistance is influenced by the test design and coverage.

In a limited resources context, given their higher cost compared to conventional methods, the use of new approaches (at least in the near future) should be limited to samples obtained from severely ill patients and/or patients with a higher risk of rapid clinical progression.

Specific recommendations for clinical microbiology laboratories

- Produce on a regular basis (at least at semi-annual intervals) reports on stratified cumulative AST data at hospital level, to assist the ASPs (*Antibiotic Stewardship Programs*) in developing local guidelines for the empirical therapy.
- Make any possible effort to reduce ID and AST Turn Around Times (adopt MALDI-TOF and molecular diagnostic systems for microbial ID and detection of key resistance mechanisms).
- Design personalized diagnostic workflows and rationalize the use of new technologies, adopting patient stratification criteria (severity of illness and/or risk of rapid clinical progression).
- Actively support ASP components and other clinicians in the interpretation of the CML (Clinical Microbiology Laboratory) results.

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8. ANTIBIOTICS MANAGEMENT STRATEGIES

Francesco G. De Rosa, Silvia Corcione, Luca Scaglione, Giovanni Di Perri

Key actions

1. A paradigm arises: how to fight the spiral of empirism through the systematic search for the etiology and how to apply empirical treatments to decrease mortality, especially in immunocompromised hosts and in patients with multiple comorbidities and prolonged hospitalization.
2. Empiric antibiotic treatment strategies are mandatory in the presence of febrile neutropenia, intra-abdominal infections, severe sepsis or septic shock and in the majority of pneumonia syndromes.
3. Empiric antibiotic treatment strategies should be based on local resistance patterns.
4. Pursue any effort to rapidly decrease empirical broad-spectrum and combination antibiotic therapies towards a targeted, narrow-spectrum treatment.
5. Efforts to correctly identify patients at high risk of colonization by MDR pathogens (i.e. rectal colonization by MDR), deserving a so called "targeted-empirical" antibiotic treatment approach, should be pursued and implemented.
6. Reduce the duration of the antibiotic therapy course (i.e. with biomarkers, such as PCT).
7. The issues of bacterial prophylaxis in high-risk group (i.e. neutropenia) should be adapted and discussed with the local epidemiology, especially of Gram-negative resistance.

Empiric antibiotic therapy vs. targeted empirical antibiotic therapy

Empiric antibiotic therapies are essential in critical settings, such as sepsis or septic shock; as suggested by the most recent Surviving Sepsis Campaign (SSC) guidelines, the goal of the therapy is the administration of broad-spectrum antibiotics within three hours from the ED triage.

In clinical practice, physicians must often begin to administer broad spectrum empirical antibiotics in order to maximize the chance of treating the causative organisms and minimize the chance of missing a treatable infection. Traditional bacterial diagnostic techniques require the organism to be grown on culture media, which typically takes 2-3 days to occur, therefore physicians are forced to make "educated guesses" while awaiting more definitive diagnostic data.

However, overuse of broad-spectrum antibiotics therapy may lead to an increased selection pressure, promoting antimicrobial resistance. Therefore, a gradual decrease of antibiotics towards a narrower spectrum, as soon as the microbiological results are available, has been recommended, in order to minimize the emergence of drug-resistant organisms, as well as to reduce costs, during the treatment of patients with severe infections. Empiric antibiotic treatment regimens are still extremely important clinical tools in the context of the daily clinical practice, and should be accompanied by a periodic microbiological review or an assessment report, if possible with local manuals and critical guidelines.

Unfortunately, there are "persistently empirical" antibiotic regimens which may be reduced with clinical efforts, differential diagnosis and strategies aimed at reducing toxicity, side effects and collateral damage. While most hospitals have available recommendations widely promoted in specific settings, such as febrile neutropenia, intra-abdominal infections, pneumonia and meningitis, few hospitals have a therapeutic formulary or even a Manual of empirical antibiotic treatment based on local epidemiology (*http://www.cittadellasalute.to.it/images/stories/MOLINETTE/area_documentale/linee_guida/Terapia_antibiotica_empirica_vers_2_Tabelle.pdf*). Empiric treatments are administered and selected on the basis of a series of factors, such as disease severity, likelihood of certain bacterial etiologies, source of infection, availability of microbiological tests such as Gram staining or other rapid tests when appropriate, host factors and their pharmacology. Widely adapted strategies of empirical antibiotic treatment exist in patients with febrile neutropenia, where the presence of fever leads to the administration, after the proper collection of samples for microbiological studies, of empirical regimens in patients from both high- or low-risk groups. Febrile neutropenia treatment strategies are the milestone of empirism, since among the factors specific to this population it is easily understandable the balance between the high risk of delaying antibiotic treatment and the theoretical risks of toxicities and secondary antibiotic resistance. Moreover, the strategy is mainly based on the detection of body temperature, which should be correctly evaluated in patients with and without mucositis.

The rate of empirical antibiotic treatment may be evaluated under the stewardship perspective in a variety of clinical syndromes, with variable severity: sepsis (with a clear definition for the attending physicians), intra-abdominal infections, pneumonia, immunosuppressed patients. Empiric regimens should be continuously reevaluated, with the clinical status, microbiological results and possibly with biomarkers. Procalcitonin (PCT) is a serum biomarker produced in the presence of bacterial infections. PCT correlates with the severity of the disease and is not impaired by neutropenia or other immunocompromised states, which makes it more beneficial when compared to other clinical biomarkers. Due to these advantages, PCT has been studied to aid clinicians in the tapering therapies. PCT should always be interpreted in the clinical context of the patient and it can be used in stewardship programs to aid physicians in the interpretation of PCT values and the subsequent antibiotic changes based on PCT levels.

The antimicrobial choice and spectrum should be narrowed as needed, the dose adjusted as needed and a careful re-evaluation on the infection status and the differential diagnosis should be done. Factors that have been consistently associated with a successful de-escalation approach include the choice of the right empirical antibiotic(s), adherence to the guidelines for the treatment of neutropenic patients, evidence of a microbiological etiology (i.e. positive blood culture, invasive sampling in ventilator-associated pneumonia), lower severity of the illness scores, and compliance with national prescribing guidelines. Moreover, de-escalation has no detrimental impact on the mortality of patients, as compared to the continuous administration of broad-spectrum antibiotics.

There are different treatment strategies in patients who are known to be colonized by resistant bacteria, such as MRSA, ESBL-producing Gram-negative bacteria, carbapenemase-producing *Enterobacteriacae* or complex antimicrobial resistance profiles produced by *P. aeruginosa* or *A. baumannii*. Although there is no simple and universal answer, a “targeted empirical treatment” has been sometimes proposed to highlight a special antimicrobial spectrum in hosts colonized by specific microorganisms, when specific strategies for the appropriate screening of risk hosts are implemented in the hospital setting. The appropriate management of these patients is complex and requires infection control protocols, as well as timely and appropriate therapeutic strategies, with a multistep approach. The production of an empirical antibiotic treatment manual may be associated with an improvement of the definition of targeted empirical antimicrobial treatment, at least in the local setting. Targeted treatments are an opportunity to measure and optimize any antimicrobial stewardship program, by the means of the appropriate choice of antibiotic, dosage, duration of infusion, days of treatment and even tapering treatment or toxicity.

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9. THE PHARMACOLOGY LABORATORY FOR ANTIBIOTICS OPTIMIZATION

Andrea Novelli, Elia Rosi

Introduction

The increased bacterial resistance to antibiotics, as well as the emergence of new pathogens, have several causes. Among them, three key factors are related to the pharmacological aspects, and they include: Inappropriate selection of the antimicrobial agent, inappropriate dosing, and excessive duration of the therapy.
The available evidence suggests that, when the use of antibiotics is warranted, the appropriate use and the shortest treatment time to achieve clinical and microbiological efficacy will result in a lower incidence of failure or relapse, as well as a lower emergence of antibiotic resistance.

Pharmacological principles for optimal drug dosing and duration

The pharmacokinetic (PK) and pharmacodynamic (PD) properties differ among the various classes of antimicrobial drugs and even among antibiotics within the same class, thus altering their ability to eradicate bacteria at drug concentrations or drug exposure attained during therapy.
Based on their different patterns of bactericidal activity, we can divide antibiotics into two major groups: time-dependent or concentration-dependent drugs. Antibiotics such as fluoroquinolones, semi-synthetic macrolides, aminoglycosides, colistin, daptomycin, the new lipo-glycopeptides dalbavancin and oritavancin, and the antifungal polyenes show maximal bactericidal activity when their concentrations are high (high Cmax/MIC or AUC/MIC ratio), even if they are maintained for a relatively short time, and are considered concentration-dependent drugs. Therefore, in order to maximize the exposure, these drugs are generally administered at high doses and long intervals (i.e. one single daily dose or no more than two daily doses). Thus, the dosing of drugs exhibiting this pattern of activity is optimized through the administration of high doses. In addition, dosing intervals can be lengthened, because of the prolonged post-antibiotic effect (PAE).
On the other hand, antibiotics such as betalactams, carbapenems, natural macrolides, glycopeptides, oxazolidinones, tigecycline and antifungael triazoles show time-dependent activity and the concentrations of the free drug should be maintained above the MIC for the specific pathogen at the infection site for a relatively prolonged time, in order to optimize exposure. Time-dependent killing and prolonged persistent effects characterize the final pattern of activity. Although higher drug concentrations do not increase the killing of organism, higher concentrations produce a prolonged suppression of organism regrowth. The goal of dosing with these drugs is to optimize the amount of drug (Table 1).

Pharmacokinetics, 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, it is to be remembered that for hydrophilic antibiotics only a fraction of the plasma concentration may diffuse into tissue, and the penetration may be even reduced in the presence of co-morbidities 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.
On the contrary, lipophilic agents may achieve tissue concentrations higher than in the plasma and their penetration into the interstitial fluid is usually high and often is unaffected by the underlying pathophysiological status. Therefore, for these drugs a standard dosing approach might be successful in the majority of cases.

In some cases, mainly in intensive care patients, a therapeutic drug monitoring (TDM) may be extremely useful to evaluate the antimicrobial concentration, in order to optimize the therapeutic approach. Though TDM has traditionally been designed as a process to reduce the risk of adverse events in patients receiving toxic drugs, at present its importance is being recognized in the optimization of the therapeutic outcomes, either in terms of cure or resistance suppression.
In recent years, a clinical evidence that many breakpoints are still too high has started to emerge.
Examples can be obtained among both time-dependent (i.e. glycopeptides) and concentration-dependent (i.e. aminoglycosides) drugs, since their generally accepted PK/PD goals cannot be clinically achieved for many pathogens included in the higher levels of their susceptibility ranges.

MICs can also vary according to the infection site and type of patient (co-morbidities, immune status, organ function and so on), since these greatly influence the possibility of reaching and maintaining the optimal PK/PD goal, which can vary in itself. On the other hand, the restriction programs to reduce resistance have often failed. The association between a reduction in prescribing and resistance is not straightforward. Resistance levels will depend on the pattern of antibiotic use, the specific interaction between the microorganism and the antibiotic and the potential for transmission.
Since restricting antibiotic use is important, but not sufficient to reduce resistance, physicians need to pay more attention to the appropriate dose and duration of therapy. Low dose and long duration are two of the main drivers of resistance.
Physicians should pay great attention to the safety and efficacy of the drugs when treating patients. Clinically applicable treatment strategies should be chosen, to maximize efficacy while minimizing side effects. Safety profiles vary for the different classes of antibiotics, as well as for antibacterial agents within each class.

Finally, costs can be reduced when the antibiotic therapy is administered for the proper amount of time. Using an optimal course of antibiotics can have economic as well as clinical advantages. Many studies showed that the correct selection of an antibiotic and its correct dosing, which involves shorter courses of treatment for pneumonia, bronchitis, sinusitis, and urinary tract infections, can be as effective as longer treatments.
While antibiotic turnover is not definitively recommended and restrictive policies can have the paradoxical effect of increasing resistance, there are some strategies that can be applied to everyday care which can help contain antimicrobial resistance, either directly or by increasing the likelihood of clinical success. Table 2. summarizes these suggestions, most of which are widely known and generally accepted as single strategies but have not necessarily previously been considered as an overall therapeutic approach. Indeed, the application of pharmacokinetic/pharmacodynamic (PK/PD) principles has been shown to be of help optimize the antimicrobial therapy in terms of clinical success and minimal toxicity. Evidence is currently being gathered (both from trials and clinical practice) that the application of PK/PD principles can also help control antimicrobial resistance, by avoiding the exposure of microorganisms to antimicrobial doses that exert a selective pressure, instead of eradicating them.

Table 1. **Antimicrobial drugs: PK/PD parameters predictive of the therapeutic outcome**

Parameter correlated with efficacy	C_{max}/MIC	AUC/MIC	T > MIC
Examples	Aminoglycosides Fluoroquinolones Metronidazole Fosfomycin	Fluoroquinolones Glycopeptides Daptomycin Quinup./Dalfopristin	Penicillins Cephalosporins Carbapenems Nitrofurantoin TMP/SMX **Tigecycline** **Linezolid** **Tedizolid**
Organism kill	Concentration-dependent		Time-dependent
Therapeutic goal	Maximize exposure		Optimize the duration of exposure

Table 2. **What can be done in the clinical setting**

Adjust the use of antimicrobials according to local epidemiology
Know the target pharmacokinetic/pharmacodynamic parameter for the specific drug in use
Select the most appropriate administration method, according to the pharmacokinetic/pharmacodynamic parameters
Remember that standard susceptibility breakpoints may be inaccurate for the clinical scenario
Maximize dosing, especially in severely ill patients, according to renal function, but limit the duration of therapy, where possible
Assess serum antimicrobial concentrations, whenever possible
Adopt the combination therapy for 48-72 hours, and then reassess the empirical therapy
Carry out an active surveillance

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10. THE ANTIMICROBIAL STEWARDSHIP PROGRAM

Francesco Menichetti

Definition

Management of the antimicrobial therapy through a fair exchange of ideas between specialists (infectious disease specialist, microbiologist, pharmacologist, pharmacist, hygienist) and prescribers (ICUs', internal medicine specialists, surgeons, transplant surgeons, onco-hematologists etc.), who express shared recommendations for the appropriate use of the antimicrobial therapy in the various care settings and in agreement with local epidemiology.

Rationale

Antimicrobial Stewardship Programs (ASP) are necessary and useful to manage the complex issues related to infections, antimicrobial resistance and the fair and shared management of new antibiotics. A multidisciplinary and equal approach may generate consensus and permanent results, while the apparently simpler hierarchical approach produces instead less consistent and durable results.

Objectives

- Antimicrobial Stewardship Programs (ASP) have as their goals:
- Improve the patient's outcome;
- Reduce the inappropriate use of antimicrobials;
- Reduce the side effects of antimicrobials;
- Control the emergence of antimicrobial resistance.

Tools (constituting element of an ASP)

1. "Ad hoc" programs
2. Workgroup: core of the ASP + prescribers
3. Shared therapeutic recommendations
4. Microbiological laboratory (rapid methods)
5. Pharmacology laboratory (TDM etc.)
6. ID consultation, supported by the "microbiological alert" system
7. Adequate and integrated "Infection Control" system
8. Supervision by the hospital pharmacist
9. Overall management software platform

Organizational models

The following are distinguished:

1. "Front-end" ASP model: restricted antibiotic list, need for approbatory ID consultation; prescription freedom for ICUs & onco-hematologists;
2. "Back-end" ASP model: free use of all antimicrobials for 48-72 hours, and intervention of the ID consultant to continue with "special" therapies.

The ASP must be "locally tailored", thus built on the resources and skills available in the specific setting.

Process and outcome indicators

Necessary for properly assessing the impact of ASPs.

Process indicators are:

1. Antibiotic consumption
2. Antibiotic expenditure.

Outcome indicators are:

1. Duration of hospitalization;
2. Mortality.

Analysis of the issues and priority actions

1. Awareness initiatives at political and government level:

- Targeted **ADVOCACY** actions on the issues related to antimicrobial resistance, ICAs, the need for "fast-track" registrations for new antibiotics (AIFA, EMA);
- Role of the MdS and the ISS;
- National guidelines for ASP;
- Role of Scientific Societies (SS);
- Lobby of PIs.

2. Awareness campaign for hospital administrators *(Direzioni Aziendali, Assessorati alla Salute, Agenzie di Sanità)*

- Role of professionals in the sectors involved (leadership);
- Regional guidelines for ASP;
- Resources (allocation of specific budgets, research funds).

3. Management of the new antibiotics

- Shared multidisciplinary recommendations and guidelines;
- "Shared management" of AIFA's sheet for the request of the drug;
- Unified rules and procedures for the "off-label" use (at national/regional level);
- Involvement of hospital pharmacists.

4. "One-Health" approach

- Since 90% of the total antimicrobial use occurs at the patient's home, it is necessary to directly involve GPs and pediatricians, by creating with them and with the ASLs therapeutic-diagnostic pathways (TDPs) that reduce the need for an improper use of antibiotics (diagnostics for viral IRSs, implementation of vaccination programs in adults and in fragile patients, etc.).
- The use of antibiotics in animals for therapeutic purposes should be further regulated, while the use for rapid growth purposes should be strongly restricted (veterinarians).
- The presence of antibiotics in food should be traced and contained.

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