DOCUMENTO COMPLETO

CONSENSUS DOCUMENT

Antimicrobial stewardship in hospitals: expert recommendation guidance document for activities in specific populations, syndromes and other aspects (PROA-2) from SEIMC, SEFH, SEMPSPGS, SEMICYUC and SEIP.

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ABSTRACT

In 2012, The Spanish Societies of Infectious Diseases and Clinical Microbiology (SEIMC), Hospital Pharmacy (SEFH), and Preventive Medicine, Public Health and Healthcare Management (SEMPSGS) lead a consensus document including recommendations for the implementation of antimicrobial stewardship (AMS) programs (AMSP; PROA in Spanish) in acute care hospitals in Spain. While these recommendations were critical for the development of these programs in many centers, there is a need for guidance in the development of AMS activities for specific patient populations, syndromes or other specific aspects which were not included in the previous document or have developed significantly since then.

The objective of this expert recommendation guidance document is to review the available information about these activities in these patient populations or circumstances, and to provide guidance recommendations about them. With this objective the SEIMC, SEFH, SEMPSPGS, the Spanish Society of Intensive Care Medicine (SEMICYUC) and the Spanish Pediatric Infectious Disease Society (SEIP) selected a panel of experts who chose the different aspects to include in the document. Because of the lack of high-level evidence in the implementation of the activities, the panel opted to perform a narrative review of the literature for the different topics for which recommendations were agreed by consensus. The document was open to public consultation for the members of these societies for their comments and suggestions, which were reviewed and considered by the panel.

Keywords: Antimicrobial stewardship; Antimicrobial stewardship in ICU; Antimicrobial stewardship pediatrics; Antimicrobial stewardship oncology-haematology; Antimicrobial stewardship clinical syndromes; Antimicrobial stewardship emergency; diagnostic stewardship.

Programas de optimización del uso de antimicrobianos en hospitales: guía de recomendaciones de expertos para actividades en poblaciones específicas, síndromes y otros aspectos (PROA-2) de la SEIMC, SEFH, SEMPSPGS y SEIP.

RESUMEN

En 2012, las Sociedades Españolas de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), Farmacia Hospitalaria (SEFH) y Medicina Preventiva, Salud Pública y Gestión Sanitaria (SEMPSPGS) lideraron un documento de consenso que incluía recomendaciones para la implementación de Programas de Optimización del Uso de Antimicrobianos (PROA) en hospitales de agudos en España. Si bien estas recomendaciones fueron críticas para el desarrollo de estos programas en muchos centros, actualmente es necesario establecer unas guías para la implementación de las actividades de los PROA en determinadas poblaciones de pacientes, síndromes clínicos y otros aspectos específicos que no se incluyeron en el documento previo o que desde entonces se han desarrollado significativamente.

El objetivo de esta guía de recomendaciones de expertos es revisar la información disponible acerca de esas actividades en estas poblaciones o circunstancias de pacientes y proporcionar unas recomendaciones que sirvan de guía sobre las mismas. Con este objetivo, la SEIMC, SEFH, SEMPSGS, así como la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC) y la Sociedad Española de Infectología Pediátrica (SEIP) seleccionaron un panel de expertos que eligieron los diferentes aspectos a incluir en el documento. Debido a la ausencia de evidencia de alto nivel en la implementación de las diferentes actividades, el panel optó por realizar una revisión narrativa de la literatura de los diferentes aspectos, en los que las recomendaciones se acordaron por consenso. El documento se abrió para consulta pública a los miembros de estas sociedades para sus comentarios y sugerencias, que fueron revisadas y consideradas por el panel.

Palabras clave: programas de optimización del uso de antimicrobianos; proa; PROA en UCI; PROA pediátrico; PROA en oncología-hematología; PROA en urgencias; PROA en síndromes clínicos; PRODIM

INTRODUCTION

In 2012, The Spanish Societies of Infectious Diseases and Clinical Microbiology (SEIMC), Hospital Pharmacy (SEFH), and Preventive Medicine, Public Health and Healthcare Management (SEMPSPGS) lead a consensus document including recommendations for the implementation of antimicrobial stewardship (AMS) programs (AMSP; PROA in Spanish) in acute care hospitals in Spain.[1] While these recommendations were critical for the development of these programs in many centers, there is a need for guidance in the development of AMS activities for specific patient populations, syndromes or other specific aspects which were not included in the previous document or have developed significantly since then.

The objective of this expert recommendation guidance document is to review the available information about these activities in these patient populations or circumstances, and to provide guidance recommendations about them. To do so, the SEIMC, SEFH, SEMPSPGS, the Spanish Societies of Critical Care Medicine and Coronary Units (SEMICYUC) and the Spanish Pediatric Infectious Disease Society (SEIP) selected a panel of experts who chose the topics to be included. Because of the lack of high-level evidence in the implementation of the activities, a systematic review and graded recommendations according to available evidence was not performed; the panel opted to perform a narrative review of the literature for the different topics for which guidance recommendations were agreed by consensus. The document was open to public consultation for the members of these societies for their comments and suggestions, which were reviewed and considered by the panel.

1. ANTIMICROBIAL STEWARDSHIP IN SPECIFIC POPULATIONS

CRITICALLY-ILL PATIENTS ADMITTED TO INTENSIVE CARE UNITS

While antimicrobial agents are essential in the care of critically ill patients with infections, their overuse can promote the emergence and spread of antimicrobial resistance with the consequent effects on morbidity, mortality and costs in intensive care units (ICUs).[2-5] Implementation of AMSP in ICUs is challenging because of the difficulties in taking decisions in severely ill patients, their pharmacokinetic-pharmacodynamic (PK-PD) particularities and the higher prevalence of resistance in these settings.

Differential characteristics of the critical patient for the application of AMSP

Clinical characteristics

Critically ill patients are by definition at high risk of death. In the ICON study, the mortality in ICU patients was 16.2%, and 25.8% in septic patients.[6] The importance of administering early active treatment in life-threatening infection triggers a high number of empirical treatments, as infection diagnosis is complex in this scenario.[7] Also, organ dysfunctions, which are frequent in critically-ill patients,[8] may modify the pharmacokinetic of antimicrobials, as discussed below. Invasive devices are frequently used in this population; in the ENVIN 2021 report of Spanish ICUs, the proportion of patients with mechanical ventilation, central venous catheter and urethral catheter were 48.55%, 69.57% and 79.68%, respectively.[5] Finally, antibiotic use in ICU patients is very frequent;in the same ENVIN report, 66.71% of ICU-admitted patients receive at least one antibiotic during their ICU stay.[5]

Microbiological and epidemiological characteristics

As a consequence of exposure to antimicrobial agents, nutrient deprivation and use of opioids, vasoactive agents and proton pump inhibitors, dysbiosis is frequent in ICU patients. Some studies are suggesting that microbiota patterns can be predictive of clinical outcomes.[9] Alterations in the microbiota pose patients at increased risk of colonization and subsequent infection by multidrug-resistant organisms (MDRO). Since infection by multidrug-resistant (MDR) bacteria, in particular Gram-negative organisms, confers a worse prognosis compared to susceptible microorganisms,[10] bundles of measures for the prevention and control of these have been developed.[11] Rapid diagnostics and efficient workflows in the microbiology laboratory should be implemented to allow early optimization of antimicrobial therapy[2, 13] or even delaying the initiation of antibiotics in hemodynamically stable patients.[14] Important challenges are discriminating colonization from infection and lack of etiological diagnosis in a high proportion of patients with infection, which frequently prevents streamlining of antibiotic treatments. To avoid this, appropriate sampling remains pivotal to AMSP in ICUs.

Fungal infections are also important in ICU patients, particularly invasive candidiasis,[15] for which early treatment is associated with improved survival but promotes overuse of antifungals, which has caused an increase in resistant *Candida* spp. However, the real epidemiology of invasive candidiasis is imprecise because its diagnosis is challenging.[16] Regarding aspergillosis, while emerging in ICU patients with specific risk factors, it should be noted that around half of *Aspergillus* spp. isolated from ICU patients are colonizers.[17] All these facts reinforce the need of clinical microbiology laboratories with 24/7 performance and evidence the benefits of a sustained partnership between the intensivists, clinical microbiologists and preventive medicine specialists, among other AMSP team specialists.

Pharmacokinetic characteristics

Early adequate antibiotic treatment in patients with septic shock is essential.[18] In septic shock, reaching the appropriate PK-PD target early enough is challenging; in fact, the results of randomized trials including mostly patients with stable hemodynamic conditions may not be extrapolated to critically ill patients.[19] While reviewing the PK-PD and dosing in critically ill patients is beyond the scope of this document, it is well stablished that, in these patients, hydrophilic antibiotics (i.e., aminoglycosides, beta-lactams, glycopeptides or lipopeptides) are affected by changes in renal function, require higher loading dose, and increases or decreases of maintenance dose depending mainly on the renal function. We warn against dose adjustments due to transient decreases in creatinine clearance in acute renal failure;[20] also, there is a risk of underdosing when data based on studies in patients with chronic renal failure are applied to patients with acute renal failure.[21] On the other hand, lipophilic antibiotics (fluoroquinolones, tigecycline, tetracyclines, lincosamides, macrolides or metronidazole) are affected by the liver function and usually accumulate in the intracellular tissue, not affecting the need to change loading or maintenance doses.

Although extended and continuous infusion of beta-lactams have been associated to better outcomes compared to intermittent perfusion in some studies,[22] the benefit of this strategy has been questioned.[23] On the other hand, antibiotics such as aminoglycosides or fluoroquinolones must be administered in intermittent infusion in order to reach their optimal PK-PD targets. Regarding therapeutic drug monitoring in critically ill patients, it is considered important for aminoglycosides, beta-lactams, linezolid, teicoplanin, vancomycin and voriconazole, but there are important barriers for its implementation.[24]

Methodological application of AMSP in the critical care setting

Successful AMSP in ICU includes three phases.[25] First, before starting, several aspects must be prepared: a multidisciplinary team integrated by intensivists, infectologists, pharmacists, microbiologists and preventive medicine specialists, with an ICU staff member as leader, must be formed; a bundle change package must be designed; and an appropriate data collection system with feedback to prescribers must be developed. Then, quality of antimicrobial use and resistance patterns should be analyzed in order to detect the main priorities; computer software can be useful for this analysis.[19] Finally, for the implementation phase, multifaceted intervention based on the specific needs of the ICU, and with clearly defined goals and indicators must be built. Three types of interventions[20-22] may be considered: (1) Restrictive, including formulary restrictions, pre-approval by a senior AMSP physician and automatic stop orders; except in very specific circumstances, these interventions are worse accepted and not preferred.[1] (2) Collaborative enhancement, including education of prescribers, implementation of treatment guidelines and prospective audit and feedback to providers. And (3) structural interventions, which can be added to the latter, such as computerized antibiotic decision support systems, faster diagnostic methods, ICU leadership commitment and ward rounds with multidisciplinary team. Besides, an updated, easily accessible dashboard with data on antimicrobial resistance rates, adherence to protocols, nosocomial infection rates, and antimicrobial consumption might be useful.[26-28] Among these types of interventions, collaborative strategies are the most commonly used and have been associated with a significant improvement in antimicrobial consumption without deleterious impact on mortality.[29-31]

One of the main challenges is addressing the fear of under-treatment in initial phases of infection. Therefore, many AMSP are focused on evaluating the appropriateness of therapy after 2-3 days of treatment, when information about the aetiology of the infection is already available; de-escalation has shown to be safe, but is

scarcely applied in ICUs.[14, 32] In addition, shortening of antimicrobial treatments is increasingly recognized as a feasible activity.[22]

Finally, the application of an AMSP will not be enough to control the spread of resistant pathogens in ICUs; to achieve this, the joint application of basic and advanced infection-control measures is absolutely needed.[33]

Evidence of the effectiveness of AMSP in the ICU

The studies performed in critical care settings have shown that AMSP are associated with a decrease in antimicrobial consumption and healthcare costs without causing deleterious effects on patients' outcomes. Their effect on the rate of MDRO has been scarcely studied and the results are heterogeneous (Table 1).[29, 34-43]

Guidance recommendations for antimicrobial stewardship programs in critically-ill patients admitted to Intensive Care Units (ICUs)

- Structured antimicrobial stewardship programs (AMSP) should be implemented in all ICUs.
- AMSP in the critical care setting should be led by an expert ICU staff member and implemented by a collaborative and multidisciplinary team including infectologists, microbiologists, pharmacists preventive medicine specialists, and other specialists as needed.
- Specialists of preventive medicine will form part of AMSP, for the coordination of outbreak control actions and other preventive measures to implant (patient hygiene, asepsis and antisepsis measures in taking samples, etc.) for invasive procedures device monitoring, for surveillance and monitoring of surgical prophylaxis, and for control of environmental biosafety in controlled environment

rooms in order to minimize infection transmission and prevent the appearance of outbreaks of environmental origin.

- The design and implementation of AMSP in critically ill patients should consider the specificities of this patient population. Infection severity, organ dysfunctions and changes in PK should be taken into account. Therapeutic drug monitoring, if available, is helpful for dose adjustments in ICU patients.
- Collaborative, non-compulsory interventions including audit and feedback should be prioritized. De-escalation and shortening of treatments should be the main targets.
- AMSP in critically ill patients should be fueled by real-time microbiological information and clinical microbiologists support.
- Updated knowledge of the local epidemiology is mandatory to design the antibiotic policy.

HAEMATOLOGIC AND SOLID-ORGAN CANCER PATIENTS, AND PATIENTS NEAR THE END OF LIFE

Patients with cancer and/or undergoing haematopoietic stem cell transplantation (HSCT) may benefit from AMSP as they are frequently exposed to broad-spectrum antibiotics and their antimicrobial treatments can frequently be optimized.[44] Patients with cancer developing infections caused by resistant organisms have much poorer outcomes than those with susceptible organisms.[45] However, AMSP efforts in immunocompromised patients are challenging because of their inherent complexity. Despite the most optimal approach to improving, antimicrobial use in these patients remains uncertain, the available data suggest that the AMSP principles for the general population are applicable. Several studies including patients with cancer and/or HSCT recipients showed an association of AMSP with decreased antimicrobial use and cost without resulting in harm.[46, 47] However,

there are barriers to standard interventions in these populations.[48, 49] A stable and successful collaboration between cancer clinicians (oncologists, haematologists) and the AMSP team may ensure the long-term success of AMSP in this patient population.

Antimicrobial stewardship in patients with haematological malignancies

Antimicrobial prophylaxis and early appropriate empiric antimicrobial therapy are key to prevent and/or minimize the impact of infectious complications in patients with haematological malignancies. As a consequence, antimicrobial consumption is high in hematologic wards,[50] contributing to an increased risk of colonization and subsequent infection by MDRO and a higher probability of inappropriate prophylactic or empirical regimens.[45, 51] In this context, optimization of antimicrobial use is a priority.[52]

Universal antibacterial prophylaxis with fluoroquinolones in neutropenic patients is associated with lower risk of febrile episodes and bacteraemia but has not demonstrated a benefit in mortality. In the setting of high quinolone-resistance, the benefit of universal antibacterial prophylaxis is associated with an increased risk of colonization/infection by MDRO.[45, 53-55] Therefore, a benefit-risk balance must be considered for the prophylactic use of quinolones.[55] Antifungal prophylaxis should be offered, along with other preventive measures, to patients at high risk of invasive fungal infections (IFI). The expected duration of neutropenia is one of the best predictors of IFI, but other factors[56] and the potential risks of new therapies should be considered.[57, 58]

The selection of empirical therapy in febrile neutropenia is an important opportunity to optimize antimicrobial therapy. At present, it should be individualized, as the "one-size-fits-all" model is associated with a significant risk of both over and under treatment. The severity of presentation, the suspected source of infection and the risk for

specific etiologies and resistant pathogens should be considered; by doing so, step-down (de-escalation) or step-up (escalation) approaches may be each indicated to specific patients.[59, 60] Finally, recent studies suggest that duration of antimicrobial therapy during febrile neutropenia could be safely reduced in many patients.[61-65]

Implementation of antimicrobial optimization practices in Haematology wards

Changing prescribing habits requires a detailed analysis of antimicrobial use patterns and of the potential barriers; measures or interventions aiming to improve antimicrobial prescribing should be locally tailored to overcome these barriers.[52] Antimicrobial prophylaxis, empirical treatment of febrile neutropenia and adjustment and duration of therapy, according to risk-stratified criteria, should be protocolized. Updated local antimicrobial resistance patterns and prior colonization/infection with certain MDRO should be considered.[52, 66] Protocols should be simple and accessible, and elaborated in multidisciplinary collaboration between haematologists and the AMSP team[63, 67-69] On-demand availability of infectious diseases specialists and clinical microbiologists should be warranted; additionally, multidisciplinary rounds might enhance adherence to local guidelines.[52]

Guidance recommendations for antimicrobial stewardship programs in haematological patients

- AMSP should be developed by a multidisciplinary team including haematologists, infectious diseases experts, microbiologists, preventive medicine specialists and pharmacists.
- Patterns of antimicrobial prescription and antimicrobial resistance should be monitored periodically.

- The implementation of screening samples to detect colonization by multidrug-resistant organisms (MDRO) may be considered, at least in patients at highest risk.
- Antimicrobial prophylaxis, empirical and streamlined therapy for febrile neutropenia should be protocolized considering local epidemiology and different patient risk profiles. Adherence to recommendations should be measured.
- On-demand availability of infectious diseases experts, clinical microbiologists and pharmacists should be warranted, at least for the most complex cases, and also specialists in preventive medicine in order to control outbreaks or isolation.
- Periodical, regular, multidisciplinary rounds are recommended.

Considerations for AMSP in Oncology wards

Similar to other immunocompromised hosts, patients with solid tumors are frequently exposed to the consequences of inappropriate use of antimicrobials and risk for MDRO.[70] However, experiences in implementation of specific AMSP in Oncology wards are scarce. A recent survey in 79 Spanish hospitals showed that only 36% had already implemented at least the basic measures in these departments.[71]

Infections in patients with solid tumors have singular clinical features. While febrile neutropenia is less frequent than in haematological patients, deep-seated infection (frequently with difficult-to-control source) is a leading cause of hospitalization.[72-74] Invasive fungal infections are also less frequent, and antifungal prophylaxis is not routinely recommended.[75] Thus, interventions targeting febrile neutropenia or antifungal stewardship may have a limited impact; despite this, most guidelines circumscribed their recommendations to febrile neutropenia.[76, 77] There is limited evidence regarding the management of the most prevalent infections including duration of therapy, which frequently leads to prolonged treatments.[48] Therefore, the development of specific local guidelines

developed with a multidisciplinary view is necessary.[46] AMSP will more probably succeed if developed in parallel with an accessible program of infectious diseases consultation.[78-80] Feasible targets for AMSP in oncology patients may include improved selection of empiric treatments, timely de-escalation, early switch to oral treatments, shortening durations and antimicrobial dose optimization.[46]

Some successful interventions in this population have been published. An educational AMSP based on short, weekly pedagogic interviews with prescribers in the Oncology ward associated with a stable infectious diseases consultation showed significant long-term improvements in the use of all-class antibiotics, and a reduction in mortality of bacteraemic infections.[73] Implementation of a nurse-led clinical pathway for patients developing sepsis at a comprehensive cancer center through different educational measures improved early management of sepsis, and was associated with significant benefits regarding hospital stay, mortality and hospitalization costs.[81, 82] Several interventions for de-labelling cancer patients with suspected antibiotic hypersensitivity have succeed improving antimicrobial use and reducing costs.[83, 84]. Rapid diagnostic tests associated with proper AMSP interventions might be useful in this population[85-87] although its clinical impact has not been proven yet in this setting.[88] Conversely, biomarkers have showed poor sensitivity and specificity in patients with solid tumors.[89]

Guidance recommendations for antimicrobial stewardship programs in solid cancer patients

- Specific local guidelines for the treatment of the most frequent infectious syndromes in patients with solid tumors (not only febrile neutropenia) based on local epidemiology, must be developed by the AMSP team and oncologists. Implementation of clinical pathways is more complex but also useful.

- The AMSP should include availability of infectious diseases specialists for consultation.
- Continuous active training on appropriate antimicrobial use must be implemented.
- Interventions specifically targeting febrile neutropenia, antifungal stewardship or biomarker-based algorithms may have a limited impact on patients with solid tumors and should not be prioritized.
- Research is needed regarding optimal duration of antimicrobial treatments or the clinical impact of rapid diagnostic tests in this setting.

Antimicrobial stewardship in patients near the end of life

Antibiotics are very frequently prescribed to patients at the end of life; 90% of hospitalized patients with advanced malignancies, and 40% of patients with advanced dementia in nursing homes receive antibiotics during their last week of life;[90] excessive use of antibiotics contributes to increased rates of MDRO in nursing homes.[91, 92] The complexity of decisions regarding treatments at the end of life requires multimodal interventions addressing scientific evidence and considering quality of life, patients and care-givers expectations, ethics and public health issues.[93] Therefore, it is mandatory that experts in palliative care participate in the guidelines development for these situations.

The goals of antimicrobial treatment should be balanced with the risk of prolonging suffering.[94] The risks of antibiotic treatments (e.g. toxicity, interactions, eventually need for a venous catheter, acquisition of MDRO, etc.) should be carefully considered if the main goal of care is patient comfort.[93] Antimicrobials have showed to improve symptoms of only 21 to 56% of palliative care patients,[95] and of less than 10% during the last week of life.[96] Experience in AMSP implementation in this setting is

limited. Patients and care-givers' expectations, and the difficulties to overcome the perception of desisting on patient care, are recognized barriers.[97]

Guidance recommendations for antimicrobial stewardship programs in patients near the end of life

- To develop local protocols with criteria helping in the identification of patients who will most probably benefit from antibiotics (i.e. improvement in survival or symptom relief while maintaining the quality of life) and those in which avoiding futile treatments, developed by palliative care experts and the AMSP team. The antibiotics and routes to be used in the most frequent syndromes and rules for early stopping should be included.
- A multimodal approach targeting physicians, patients and care-givers' perceptions is also recommended. Availability of consultation to palliative care and infectious diseases specialists is recommended.
- Research is needed about the optimal approach for developing and implementing AMSP in palliative care.

CHILDREN

Infectious diseases are the main reason for consultation and admission to hospital in children,[98, 99] and antibiotics are the most widely prescribed drugs in children: around 40% of admitted children receive at least one antibiotic, 60% in paediatric ICUs.[98-104] Antimicrobial resistance patterns are different to those in adults, and therapeutic options may be more limited in children.

Special considerations in children

Several features of infectious diseases and their management in children must be considered when planning an AMSP. Infectious diseases differ between adults and children in aetiology, clinical presentation, natural history, underlying comorbidities and mortality. Viral infections, mostly upper respiratory tract infections are more frequent in paediatric populations, mainly in children under 5 years.[105, 106] However, uncertainties regarding the causal pathogens is common as rapid diagnostic techniques are often unavailable.[107] In recent years, infections due to MDRO have increased in infants and children, which has been associated to higher morbidity and mortality;[108-112] of note, a 20% rise has been reported in the use of broad-spectrum antibiotics.[98, 113, 114]

An expert paediatrician in infectious diseases and antimicrobial use must be included in paediatric-AMSP teams. Specific guidelines for antimicrobial use are required; these should not be simple dosing adjustments of adult guidelines.[115, 116] Age-associated changes in body composition and organ function (absorption, distribution, metabolism, and elimination) are dynamic, especially in newborns and during the first decade of life and may affect the efficacy and safety of antimicrobial agents.[116, 117] Frequently, adequate evaluation of older antimicrobials in children is lacking, and those for new drugs may be delayed as less trials are performed in paediatric patients;[118-120] as a consequence, antimicrobial agents are often used off-label[120, 121]

The most frequently indicators used in AMSP in paediatric wards are length of stay, 30-day readmissions, mortality and resistance;[122-131] some indicators often used in adults are not appropriate in children (e.g., the rate of *Clostridioides difficile* infection, as carriers under two years of age are frequent). Also, consumption data based on defined daily dose(DDD) are inaccurate as dosing depends on body weight. The most widely standardized indicator in paediatrics is days of therapy (DOT) per 1000 patient-days, which may be calculated for specific drugs, for wards or groups of patients associated with a specific diagnosis.[99, 103, 122, 125, 132-137] Prescribed daily doses (PDD) can also be

used as asupplementary value, especially for monitoring adherence to protocols. Length of therapy(LOT) per 1000 patient-days and DOT/LOT can be used as advanced indicators in paediatrics. Switch from intravenous to oral rate can also be used as an advanced indicator for antimicrobial agents with high oral bioavailability as ratios between standardized antimicrobial agents in specific clinical settings.[103]

Antimicrobial stewardship strategies in children

Different scientific societies have emphasized the importance of AMSP in paediatrics in recent years; however, there is less data on the results of AMSP, and published studies show highly variable methods. However, most of the main strategies for AMSP in adults seem applicable to paediatric patients.[138]

Limiting the duration of antimicrobial therapy

There is an increasing interest in performing studies comparing short with long duration of treatment in the paediatric population. Randomized trials have shown that 5 days of therapy is enough for mild-moderate community-acquired pneumonia (CAP) [139, 140] (the SCOUT-CAP and SAFER trials have not yet been published at the time of this writing).

Recently developed paediatric guidelines and systematic reviews have launched recommendations for duration of therapy in different infections (Table 2)[141, 142]. Nevertheless, more data is still needed and an individually approach may be necessary.

Switch from intravenous to oral administration and dose optimization

The conditions for switching to oral therapy include clinical improvement, source control, lack of conditions compromising oral absorption (neonatal age, vomiting or mucositis, among others), availability of an appropriate oral drug and adherence.[138] This

strategy is feasible even in complex infections as bacteraemia, ventilator-associated pneumonia, brain or lung abscess, septic arthritis or acute osteomyelitis.[141, 143, 144] Dosing in life-threatening infections in children may be suboptimal. Therapeutic drug monitoring is an essential strategy in children to ensure effectiveness and reduce toxicity, but its availability may be limited.

Diagnostic stewardship in children

The role of microbiological diagnosis as support for AMSP has been studied in adults (see below),[145-151] but the experience in the paediatric field is less extensive. Because viruses are the main cause of infectious diseases in children, the use of rapid tests may help optimizing therapy.[148, 149] Also, methods for rapid identification of bacteriaand susceptibility testing directly from positive blood cultures help to reduce the time to optimal treatment.[145, 150, 151]

As for adults, obtaining optimal clinical samples for microbiological diagnosis is of utmost importance, but the sample volume is especially relevant in children. For blood cultures, sometimes a single bottle with lower-than-desired volume is what can be best obtained. There are systems and techniques adapted for paediatric blood cultures.[152, 153] Similarly, there is no simple and easy technique to obtain appropriate sputum or urine cultures from newborns and infants. The recommended suprapubic puncture is painful and the bag system is not helpful due to high rates of sample contamination.[154] The new microbiological techniques developed in recent years make diagnostic stewardship mandatory.[155]

Evidence for AMSP effectiveness in children

Several authoritative documents have defined key principles and strategies to develop AMSP in children,[132, 156-159] and some studies have evaluated the impact of

AMSP in paediatrics although to a lower extent than in adults.[129, 160] To date, the development of empirical antibiotic guidelines and infectious diseases consultation in the context of formal AMSP seem to be the most useful interventions in children.

Regarding the clinical indicators for AMSP, since in-hospital mortality in children is lower than in adults, its usefulness as indicator is poorer in this age group. Nevertheless, AMSP have been shown to be safe in terms of mortality in neonatal[161, 162] and pediatric[131, 163-164] populations. Length of hospital stay (LOS) and 30-day readmission are the most frequently used clinical indicators in paediatrics. McCulloh et al. demonstrated a significant reduction in LOS in children who received a recommendation from an AMSP team.[165] Also, AMSP have shown to reduce antibiotic consumption,[135, 140, 162, 166-169] mostly using prospective audits with feedback interventions with or without restrictions. A reduction of selected or broad-spectrum antibiotics has also been documented in other studies.[140]

Very few studies have been conducted to assess the reduction of antimicrobial resistance after AMSP implementation in children; two studies documented decreases in antimicrobial resistance in Gram-negative organisms.[166, 170] Regarding costs, at least three studies in paediatrics reported reduction in costs related to antimicrobial consumption after a formal AMSP.[162, 168, 171]

Guidance recommendations for antimicrobial stewardship programs in children

- The AMSP team should include an expert paediatrician in infectious diseases and antimicrobial use for the activities in paediatric population.
- Overall, the principles of AMSP in adults are applicable to children; however, two aspects must be considered: (a) local protocols for antimicrobial use in children should not be simple dose-adjusted transcriptions of protocols for adults but be

specifically developed, and (b) evidence for some interventions is more limited in children than in adults.

- The fact that viral infections are more frequent as cause of acute respiratory infections in children should be outlined, and availability of appropriate diagnostic methods must be considered in order to help avoiding the unnecessary use of antibiotics.
- For monitoring antimicrobial consumption, days of therapy (DOT) per 1000 patient-days is the preferred indicator.

PATIENTS ATTENDED AT EMERGENCY DEPARTMENTS

Importance of antimicrobial stewardship in Emergency Departments

Infections are among the 20 leading primary diagnosis groups at emergency department (ED) visits; prescription of antibiotics is frequent,[172, 173] and, as in other settings, frequently inapproppriate.[174, 175] Empirical therapy is the cornerstone of antimicrobial use in ED; it should be noted that patient-specific information available is often limited.[176] Since EDs sit at the interface of inpatient and outpatient settings, ED practitioners influence antimicrobial prescription in both locations. Therefore, ED is a strategic setting for AMSP. AMS teams must have a multidisciplinary composition and consider some specific characteristics of EDs in order to overcome potential barriers: these are areas with a high workload and patient turnover, where rapid decisions are taken usually without consultation, with and large and varied mix of providers who work in a shift-based scheduling format.[177]

Antimicrobial stewardship interventions in Emergency departments

As in other areas, AMSP activities in ED may be "horizontal" and "vertical".[178] Horizontal interventions are aimed at reducing the overall inappropriate use of antibiotics. The cornerstone is a properly training of the ED staff in identification and early treatment of patients with severe infections, proper collection of microbiological samples, and appropriate diagnosis and treatment of common infections. In a study, three aspects were associated with inappropriate prescription in ED: failure to obtain microbiological samples, lack of specifying the source of infection and lack of reporting the severity of infection.[175] Vertical interventions target specific antibiotics, infections or type of patients.

A specific challenge for adequate management in ED is sepsis. The appropriate identification of patients with severe infection is important both to provide adequate early treatment and to avoid overdiagnosis leading to excessive use of broad spectrum antibiotics.[179] To choose the appropriate empirical treatment, clinicians must be informed about the local epidemiology and data needed to assess the individual risk factors for a multi-drug resistant infection.[180-181] Empirical antimicrobial therapy should consider whether previous healthcare assistance may modify the microorganisms and resistance rates of the expected cause of infection. The importance of obtaining microbiological samples, source control and support must be emphasized.[181]

Patients evaluated at ED may be discharged, kept under observation in ED for a limited period of time, or be admitted to hospital. Therefore, when the results of microbiological cultures are available, the patient is not usually in the ED. Therefore, programs for appropriate follow-up of patients with infection are needed, in collaboration with primary care and hospital departments. In these cases, the coordination activity of preventive medicine specialists with primary care doctors or community centers or residences, responsible for the continuity of antibiotic treatments, will be essential. This

activity will make it possible to change the antibiotic when the patient has attended the ED where he has received the antibiotic of choice (in the case of urinary tract infections or others) and has gone home. Subsequently, observing in the culture the resistance of the microorganism, this coordination allows to stablish communication with the primary healthcare centers for the administration of the most appropriate antibiotic according to antibiogram results. These programs allow stopping, de-escalating, escalating, and/or switching to oral drugs as needed. An option is to organize a structured follow-up program for microbiologic results of patients attended at the ED, with daily review and assessment of the diagnosis and treatment provided.

Measuring the impact of AMSP in the Emergency department

Clinical outcomes should be defined; examples are early mortality of severe infections (e.g., 14-day mortality among patients with pneumonia, bloodstream infections or sepsis)[182-184] and rate of patients returning to the ED after first consultation for milder infections (e.g. urinary or upper respiratory tract infections).[184-185]

Traditional antibiotic consumption indicators cannot be measured in ED since there are not patient-days as denominator. The prevalence of patients with a prescription or the number of days of treatment per attended patients have been used[186-187] but these measures are time-consuming in centers without advanced information systems. Alternatively, monitoring pooled data of antimicrobial prescriptions in the ED weighted by the amounts of patients attended at the department has been used.[183]

Guidance recommendations for antimicrobial stewardship programs in patients attended at Emergency departments (ED):

- Multidisciplinary antimicrobial stewardship team with knowledge of the specific barriers for implementation of AMSP in the local ED must be formed.
- Local empirical treatment guidelines with input from local epidemiology must be available for ED faculty.
- Appropriate training for the basic aspects of infectious diseases diagnosis and treatment must be provided.
- Specific appropriate clinical outcome indicators and evaluations of quality of prescriptions must be measured.
- The coordination activity of preventive medicine specialists with primary care doctors or community centers or residences, responsible for the continuity of antibiotic treatments, will be essential. This activity will make it possible to change the antibiotic when the patient has attended the ED where he has received the antibiotic of choice and has gone home.
- If individualized data on antibiotic prescriptions are not automatically available, pooled data weighted by the number of patients attended at the department (DDD per 100 patients admitted in the observation area, DDD per 100 patients discharged from de ED) may be considered.

2. ANTIMICROBIAL STEWARDSHIP FOR SPECIFIC SYNDROMES AND SURGICAL PROPHYLAXIS

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is a leading cause of antibiotic

prescription in hospitals. The list of core microorganisms causing CAP is short and stable, being *Streptococcus pneumoniae* the main bacterial agent.[188] However, the importance of viruses as primary pathogens in CAP has been recently demonstrated.[189] Overtreatment in CAP is frequent, including use of broad-spectrum drugs and long durations, making CAP an important target for AMSP.[190] The key elements in hospitalized patients with CAP for AMSP include adherence to guidelines in empirical treatments, de-escalation, appropriate duration of treatment, switching to oral drugs therapy, improving the diagnostics, and appropriate use of biomarkers.

The selection of empirical therapy in CAP should be based on risk stratification and the most likely causative agents.[191] Adherence to guidelines is associated with improved outcomes in patients hospitalized with CAP,[192-195] and may be improved by implementation of stewardship interventions.[196-197] Antibiotic de-escalation is recommended in patients with CAP according to microbiological results, including bacteremic infections and CAP with negative cultures.[198-203] Barriers for the implementation of this strategy includes the lack of randomized trials, low rate of microbiological samples, distrust of the attending physician, and heterogenous definitions for "de-escalation". A study conducted in 164 US hospitals showed only a 13% rate of de-escalation at day 4 following negative microbiology results.[203]

Switch to oral therapy once clinical stability has been reached aims to reducing the LOS, catheter-related infection and costs. A meta-analysis showed equal efficacy for oral switch compared to continuing with intravenous therapy in terms of clinical success, mortality and recurrence, and a reduction in LOS.[204] In a later randomized clinical trial, Carratalà et al. demonstrated that the use of a 3-step critical pathway including early mobilization, switch to oral antibiotic and hospital discharge was safe and effective in reducing the duration of intravenous antibiotics and LOS without adversely affecting

outcomes.[205] However, early oral switch is not widely implemented.[206-207] Some barriers include the hierarchical structure of the medical teams and belief that intravenous route is more effective.[208] These barriers may be overcome by educational interventions.[209]

Several trials and meta-analysis have demonstrated the efficacy of short courses of antibiotics in CAP.[210-214] A recent systematic review and meta-analysis showed that clinical cure was similar between ≤6 days and ≥7 days of therapy, irrespective of patient setting or severity of pneumonia, and relapses were similar between groups. Of note, short treatment was associated with fewer serious adverse events and with lower mortality.

Beyond the importance of classical microbiological testing, implementation of novel rapid multiplexed molecular platforms may represent an opportunity for rapid decision on targeted antimicrobial therapy. Well-designed randomized clinical trials are warranted to assess the impact of these platforms on antibiotic use and patient outcome.[215]

Finally, the use of some inflammatory biomarkers such as procalcitonin, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), pro-adrenomedullin (proADM), and presepsin have been studied as specific biomarkers for bacterial infection. A Cochrane meta-analysis concluded that the use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with acute respiratory infections results in lower risks of mortality, antibiotic consumption, and antibiotic-related side effects, thus supporting the use of procalcitonin in the context of AMSP in these infections.[216] Nevertheless, all biomarkers must be used together with an appropriate clinical workout. Future biomarkers with higher sensitivity and specificity could be even more useful for the management of CAP.[217]

Guidance recommendations for antimicrobial stewardship programs in community-

acquired pneumonia (CAP)

- Increased adherence to CAP guidelines must be an objective of AMSP. Indicators for the measurement of adherence to the principles of treatment of CAP must be implemented.
- Empirical therapy in CAP must be locally protocolized according to guidelines, considering patients' severity and local epidemiology.
- Adherence to early antibiotic de-escalation, switch to oral therapy and short courses of therapy must also be objectives of AMSP. Overcoming of barriers for the implementation of these two strategies may be overcome by appropriate educational interventions.
- Research regarding the effectiveness of rapid diagnostic molecular tests as a stewardship tool in CAP is needed; however, these techniques should be considered in advanced AMSP with evaluation of results.
- The use of procalcitonin is useful to improve antibiotic use in patients with CAP, and may be incorporated as an aid tool together with appropriate clinical workout.

URINARY TRACT INFECTIONS

Urinary tract infections (UTI) are among the most frequent bacterial infectious diseases.[218] Microbiological cultures are frequently positive; although this helps antimicrobial selection, positive urine cultures in asymptomatic patients (asymptomatic bacteriuria) is a frequent cause of inappropriate use of antibiotics.[219] There is a dramatic spread of antimicrobial resistant uropathogens worldwide; an overinterpretation of this fact may contribute to an excessive use of broad spectrum antibiotics. For all these reasons, UTI is another important syndrome for AMSP. The key elements of AMSP in

UTI are adherence to guidelines of empirical antibiotic use, administering adequate directed antimicrobial therapy, avoiding treatment of asymptomatic bacteriuria with some exceptions, and reducing the duration of antimicrobial therapy. [220]

The selection of empirical therapy in UTI should be based on the most frequent etiologic agents and in the local antimicrobial resistance rates.[221] Guidelines should be adapted to local epidemiology. Importantly, data on antimicrobial resistance in UTI are obtained mostly from patients with complicated UTI (cUTI), which may not represent patients with uncomplicated infections. Adherence to local guidelines should be encouraged. In a recent study in 45 hospitals in Catalonia, adherence to local guidelines for empirical therapy of bacteremic UTI due to *E. coli* was 71%.[222] Appropriate definitive antimicrobial therapy may be complex in cUTI caused by MDRO; activities targeting this objective may be an important activity of AMSP.[222]

Asymptomatic bacteriuria should not be treated with antibiotics with the exception of pregnant women, patients undergoing urological procedures with high risk of mucosal bleeding, and renal transplant recipients during the first month after transplantation.[219, 221, 223] However, it is a frequent cause of inappropriate use of antibiotics. Therefore, interventions aimed at reducing the inappropriate use of antimicrobials in asymptomatic bacteriuria must be considered.

Duration of treatment in UTI can be shorter than previously thought. Acute uncomplicated cystitis can be treated for 1 to 5 days depending on the drug used.[221, 224] In Spain, fosfomycin trometamol 3 gr (one dose), or nitrofurantoin 50-100 mg every 8 hours (5 days) are the recommended therapies.[221] However, in complicated cystitis (immunosuppression, pregnancy, UTI in men, urological abnormalities, slow response), 7 days may be needed.[221, 224] This apply also to outpatient men with UTI after excluding urologic abnormalities, immunocompromising conditions, prostatitis, pyelonephritis,

nephrolithiasis and benign prostatic hyperplasia.[225-226] For acute pyelonephritis and febrile UTI with or without bacteraemia, a meta-analysis of 8 randomized clinical trials showed similar clinical and microbiological efficacy of 7 days compared to longer treatments except in the subgroup of patients with urogenital disorders, in whom microbiological efficacy was slightly higher with longer treatments.[227] Another meta-analysis of 10 randomized controlled trials suggests that 5-7 days of therapy are effective in acute non-complicated pyelonephritis.[228] In the Spanish guidelines[221], the recommended durations are: for uncomplicated pyelonephritis due to susceptible pathogens, 5-7 days of levofloxacin or ciprofloxacin, 7-10 days of third-generation oral or parenteral cephalosporin, 10 days for amoxicillin-clavulanic acid and co-trimoxazole, and a maximum of 5-day for aminoglycosides; for patients with severe or focal pyelonephritis or slow response to appropriate antibiotics, a longer duration of therapy may be required; in patients with catheter-associated UTI, 7 days for patients with prompt resolution of symptoms and patients with cystitis following urinary catheterization (5 days may be considered if levofloxacin is used); 10–14 days of treatment is recommended for those with delayed response. Adherence to these short regimens is challenging and need availability of guidelines and adequate training.

Audits with non-compulsory recommendations in targeted cases according to availability of resources may be implemented; some specific pathogens (e.g., multidrug-resistant bacteria, *Candida* spp., etc.) or patients-types (e.g., those with vesical catheter) may be prioritized.

Guidance recommendations for antimicrobial stewardship programs in urinary tract infections (UTI)

- Empirical antimicrobial therapy in UTI should be based on local guidelines. These guidelines should take into account local bacterial resistance rates, individual risk

and severity of infections.

- Antimicrobial stewardship teams should provide advice for optimizing directed therapy in UTI caused by MDRO.
- Interventions to avoid the inappropriate use of antibacterials in asymptomatic bacteriuria must be implemented.
- Interventions to improve adherence to short treatments according to specific type of infection and patients' characteristics must be implemented.
- Audits with feedback in selected patients or targeted microorganisms may be considered.

VASCULAR CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS

Vascular catheter-associated bloodstream infection (VCA-BSI) is one of the most frequent healthcare-associated infection. AMSP developed in ICU patients will include mostly central catheter-related infections; however, a higher number of VCA-BSI occur in conventional wards.

Because VCA-BSI frequently lack focalized signs of infection, particularly in infections associated with central catheters, a high suspicion index is needed in order to provide an adequate diagnostic and therapeutic management. Therefore, training of attending physicians on diagnostics and empirical therapy must be provided. Adherence to guidelines for the management of these infections must be promoted, including diagnostics, empirical and targeted therapy, duration of therapy and catheter removal [229, 230]

Regarding non-compulsory activities, bacteraemia programs are particularly relevant for VCA-BSI.[1] These programs include rapid, unsolicited advice for the management of patients with BSI, and have shown to improve the management and

outcomes of these patients.[231] In the case of VCA-BSI, aspects such as the need to remove the catheter, performance of follow-up cultures, de-escalation, and appropriate duration of therapy[232, 233] must be included using a structured bundle with measurement of adherence to quality-of-care indicators.[234, 235]

If a comprehensive bacteraemia program cannot be implemented, targeted audits for high-risk patients (e.g., immunocompromised, critically-ill, predisposing factors for endocarditis or other complications), and for patients with bacteraemia due to *Staphylococcus aureus* and *Candida* spp. may be an alternative.

Restrictive measures may be needed for the use of new drugs (i.e. daptomycin, dalbavancin) that may be used in these infections; in addition, programming automatic stop orders in pharmacy programs (i.e., automatic stopping of vancomycin after apredefined number of days in VCA-BSI due to coagulase-negative staphylococci in low risk patients) are also to be considered. However, restrictive measures are less well accepted and might cause safety problems if physicians avoid using restricted drugs in patients who would need them because of the restrictive barriers implemented. Finally, the duration of treatment is frequently too long, and shorter duration as appropriate according to etiology and clinical complexity must be reinforced [229, 233].

Guidance recommendations for antimicrobial stewardship programs in vascular catheter-related bloodstream infections (VCA-BSI):

- Promote the appropriate diagnosis and management of VCA-BSI by providing adequate training and adherence to guidelines.
- Specifically, appropriate duration of therapy of VCA-BSI should be promoted.
- Bacteraemia programs, in which unsolicited advice and follow-up is provided

for all patients with bacteraemia (or at least for high risk patients and pathogens) should be implemented; measurement of adherence to quality-of-care indicators is recommended.

SURGICAL PROPHYLAXIS

Surgical site infections (SSI) are associated with longer postoperative hospital stays, additional surgical procedures, and increased morbidity and mortality. The cumulative incidence of SSIs ranges 0.5% to 10.1% depending on the type of surgical procedure, with the highest rates found in colon surgery.[236] Surgical antimicrobial prophylaxis (SAP) reduces the incidence of SSI when properly indicated (clean-contaminated procedures, and clean procedures involving prosthetic material[237-241]).

However, SAP is frequently inappropriate, mostly because used in procedures in which they are not needed, use of not-recommended drugs, administration in the wrong moment or at inadequate dosing, not repeating the dose in prolonged interventions, and prolonging the antibiotic in the postoperative period.[233-244] Some of these errors are associated with increased risk of SSI and others with increased risk of adverse events, including *C. difficile* infection and superinfections caused by MDRO.[245] Because of the high number of procedures performed in hospitals, SAP is a key area for any AMSP.

Guidelines for an appropriate use of SAP are available.[237, 240, 241, 246, 247] Local recommendations for SAP should be established at each center for all types of surgery performed, adapting the guidelines to the local epidemiology. Indicators' measurement and interventions in SAP should be established by a multidisciplinary team involving surgeons, anesthesiologists, nurses, and the AMS team. Diverse strategies have been used to improve SAP including education, electronic-prescription protocols, automatic

interruption orders, SAP kits, checklists and specific bundles in the operating room.[244, 245] SAP should be audited regularly for a selected number of surgical procedures in which SAP is indicated and administered: choice of agent, timing of preoperative dose, and duration of appropriate postoperative prophylaxis. The proposed indicators are shown in Table 3.

Guidance recommendations for antimicrobial stewardship programs in surgical antimicrobial prophylaxis (SAP)

- Local adaptations of guidelines for SAP in all procedures performed in the hospital, agreed with surgeons and anesthesiologists, should be available. The local guidelines must include the antibiotics of choice and alternatives, as well as the appropriate timing, dosing and duration of antibiotic prophylaxis. It is important to enhance other prophylactic measures and their implementation carried out by preventivemedicine specialists.
- Training about the principles of SAP should be provided to all staff involved.
- Regular audits about adherence to local guidelines using standardized indicators must be performed, and feedback provided.
- Specific interventions to improve SAP must be considered according to local resources and problems detected.

3. OTHER ASPECTS OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

ROUTES FOR ANTIBIOTICS ADMINISTRATION; MODES OF INTRAVENOUS PERFUSIONS

Overview of routes of administration

The route of administration of antimicrobials has gained relevance over time in AMSP. Several studies have been shown that intravenous-to-oral switch is associated with clinical benefits and shorter LOS.[248-251] However, there are barriers for its implementation, mainly in patients with moderate to severe infections.[252] Also, switching to oral drugs may lead to unnoticed longer treatments, with the consequent impact on microbiota.[253, 254] This effect may be higher for drugs with lower oral bioavailability, for which higher amounts of drug are present in the bowel lumen. This is also the case for intravenous drugs with high biliary excretion.[255, 256] Antibiotic nebulization is a useful route for many patients with cystic fibrosis but is controversial in patients with ventilator-associated pneumonia; however, it is considered when the dose of a specific antibiotic needed to reach the site of the infection is too high when administered by other routes. [257, 258] On the other hand, the intramuscular route of certain antimicrobials is an alternative to consider in patients undergoing ambulatory therapy, mainly when intravenous route is problematic and the oral route is not appropriate;[259] with this route, the speed of resorption may be delayed for some antibiotic preparations.[260] Other routes of administration such as intraventricular or intrathecal may be considered in infections of the central nervous system when in-site concentrations of the drug with intravenous administration is not satisfactory.[261-263] Finally, with certain antibiotics with a once daily dosing such as ertapenem, ceftriaxone or teicoplanin, when the intravenous route is not accessible or in palliative care situations, the subcutaneous can be a good alternative.[264]

Intermittent, extended and continuous intravenous perfusions

In the treatment of severe bacterial infections, antibiotics are mostly administered intravenously. In intermittent perfusions (IP), the antibiotic is administered along 30 to

60 minutes and repeated periodically. With this type of administration, a maximum plasma concentration (Cmax) is reached quickly with a subsequent exponential clearance proportional to the plasma concentration of the drug. IP facilitates achieving the PK/PD objectives of antibiotics with concentration-dependent activity (Cmax/MIC) and prolonged postantibiotic effect such as aminoglycosides, nitroimidazoles and rifamycins.[265] In the absence of a loading dose, the steady-state concentration (SSC) with IP is not reached until 3-5 times the half-life of the antibiotic.

In extended perfusion (EP), the drug is administered over at least 3 hours; and in continuous perfusion (CP), the drug is administered continuously at a constant rate. Both EP and CP aim at optimizing the achievement of the PK/PD targets for antibiotics which activity depend mainly on the time that the free plasma concentration of the antibiotic is above the MIC (*%f*T>MIC),[266] such as beta-lactams, macrolides and oxazolidinones. Despite their theoretical benefits, a meta-analysis including 29 randomized clinical trials of severe infections found no significant differences in mortality, clinical cure, recurrence, post-treatment superinfection or toxicity when CP/EP or IP were used.[267] In the case of beta-lactams, several studies have shown that CP improves the achievement of PK/PD objectives;[268, 269] however, the benefits in clinical outcome are unclear.[270] It is in infections caused by pathogens with borderline or high MIC[265] or in patients with increased renal clearance[271] where the potential impact of continuous infusion on clinical outcome is higher. In a recent meta-analysis that included 3 clinical studies and 632 patients with severe sepsis, patients who received CP had lower hospital mortality and higher clinical cure rate compared to IP.[271] Another meta-analysis that included 6 randomized trials and 4 observational studies comparing EP/CP with IP in severe infections treated with meropenem, patients treated with prolonged perfusions had a lower mortality and a better clinical resolution of infection.[272]

There is less experience with linezolid in CP compared to IP; CP showed better achievement of PK/PD target in a cohort of septic patients.[273] and in obese patients with ventilator-associated pneumonia.[274] Although the evidence is also very limited, vancomycin in CP is superior in reaching the PK/PD target compared to IP, especially in critically ill patients, without adding toxocity.[275, 276] However, the available studies do not provide definitive conclusions since they have important limitations in design and differences in type of patients, number and MIC of isolates, dosing and PK/PD objectives.

Use of infusion and elastomeric pumps

Infusion pumps provide better accuracy in the administration of intravenous drugs; however, errors caused by incorrect programming are not infrequent. Therefore, new management systems minimizing these errors, such as smart infusion pumps (SIP) are being developed.[277] These are conventional infusion pumps provided with a security software allowing the creation of drug lists with defined parameters as minimum and maximum concentration and infusion rates, which determine the so-called absolute and relative limits. They also allow generating specific lists for different therapeutic areas or groups of patients. On the other hand, elastomeric pumps facilitate intravenous outpatient treatments. The main concern for outpatient parenteral antimicrobial therapy programs is the degradation of antibiotics in the device, so the most optimal are those that have a longer half-life, which can be administered 1-2 times a day, and have a prolonged stability in this type of devices.[278, 279]

Implication of nurses in AMSP

Because of the importance of proper administration of antibiotics, implication of

nurses in AMS teams is important in order to appropriately apply the different methods of intravenous infusions, early administration of the first dose, extended perfusion, appropriate use of infusion pumps, avoiding administering incompatible drugs at the same time for the same catheter lumen, and avoiding missing doses. Their role in measuring indicators for appropriate administration of antibiotics and training other nurses is critical. A frequently unnoticed aspect is the residual volume (about 30 ml), which is the amount of volume with medication that remains in the infusion system at the end of antibiotic administration; this may mean up to a 20% underdosing in a 100 ml infusion and, even worse, 40% in a 50 ml infusion. Ensuring the administration of the complete dose should be added to other important dosing optimization considerations.[280]

Guidance recommendations for antimicrobial stewardship programs in aspects related to routes and ways of administration of antimicrobials:

- The different routes for antimicrobial administration, and the different modes of intravenous perfusions should be considered in local protocols; AMSP must include activities aiming at providing the most appropriate way to administer antibiotics to the patients.
- Timely switch to oral therapy when indicated must be an objective for AMSP, and activities encouraging this practice should be implemented; they should include actions to avoid longer treatments once the oral route is started.
- Infusion pumps facilitate the correct administration of intravenous antimicrobials and must be used in circumstances in which extended or continuous perfusions are considered critical for the patient. Handling of these devices must be carried out by trained personnel.

- Implication of nurses in AMSP is key in order to assure an appropriate administration of antibiotics.

NEW ANTIMICROBIALS

The scarcity in development of new antimicrobial agents covering real medical needs makes their use a specific target for AMSP in order to avoid rapid development of resistance to them. Optimizing their use must balance their potential advantages in serious infections caused by MDRO and avoiding their overuse in infections for which other similarly efficacious alternatives exist. AMS teams should support their introduction in hospital formularies as well as to implement interventions to facilitate their appropriate use.

Recently approved antimicrobials

Recently approved antimicrobials (Table 4) should be used almost exclusively as directed therapy for the approved indications. However, there are medical needs that frequently bring the question about their use off-label. As an example, ceftaroline is an attractive option for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia and endocarditis especially in cases of recurrence or failure of vancomycin or daptomycin;[281] ceftobiprole is also active against MRSA and shows activity against *Pseudomonas aeruginosa*.[282]

Potential empirical use of new drugs must balance the probability of pathogens not covered by other options and the implications of not providing an active drug up front. For instance, considering the high mortality rate of administering inadequate empirical therapy in patients with septic shock and according to recently published clinical trials,[283-

[285] ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam and imipenem-relebactam might be used empirically in patients with septic shock and high risk of MDR Gram-negative bacteria susceptible to these drugs, based on previous colonization or on local epidemiology data (e.g., in an outbreak setting). The details about their spectrum are shown in Table 4. Other drugs recently approved by the European Medicines Agency (EMA) are cefiderocol, [286] delafloxacin,[287] oritavancin,[288] and eravacycline[289] (Table 4).

Avoiding emergence of resistance to new antimicrobials: mechanisms, therapy failure, and related factors

Monitoring the impact of new drugs in the epidemiology of MDRO is a must for clinical microbiology laboratories. As an example, the introduction of ceftazidime-avibactam may influence the epidemiology of metallo-beta-lactamase- producing Gram-negative bacteria.[290] Of course, surveillance for the emergence ofresistance to new agents is also needed. As a matter of fact, the development of resistanceto ceftolozane-tazobactam and/or ceftazidime-avibactam during treatment of MDR/XDR *P. aeruginosa* are not infrequent, and the risk may be higher in infections caused by strains that are already resistant to classical beta-lactams, which is frequent.[291] The presence of AmpC overexpression as a first-step low level resistance, and MICs >2/4 mg/L of ceftolozane-tazobactam have been associated with treatment failure in *P. aeruginosa* infections.[292] Regarding Enterobacterales, while emergence of ceftazidime-avibactam resistance has been anecdotally documented among ESBL- or AmpC- producers, it has been more frequently documented among KPC-2 or KPC-3 mutants.[293] Control of the infection source appears to be a key aspect for avoiding treatment failure and resistance

development.[294] *P. aeruginosa* showing AmpC overexpression or KPC mutants described above are frequently susceptible to carbapenems. Therefore, carbapenem susceptibility must be tested in these isolates, as it might be used as rescue therapy or to avoid the emergence of resistance if used in combination, but this needs to be explored in future studies.

Inclusion of new antimicrobials in hospital pharmacies

The objective of hospital pharmacy committees is the selection of drugs to be included in the hospital formulary according to their clinical value.[295] A review of the pharmacy committees in different countries showed that their members frequently lack appropriate knowledge about the standards for the assessment of new drugs.[296] A document from the World Health Organization (WHO) describes the need for a critical assessment of drugs for their inclusion in pharmacological guides.[297] Daily cost of new antimicrobials is high in comparison to most drugs except biologicals and cancer therapies, but the overall cost for most of them is not that high, as they are infrequently used and for shorter periods of time; cost-effectiveness data must also be considered in the selection of new antimicrobials. The pressure of the pharmaceutical industry may lead to inappropriate use of new antibiotics, which may subsequently facilitate resistance development.[298] Finally, it would be desirable that the pharmacy committees of different hospitals in the same country or region apply similar criteria for the inclusion of new antibiotics in their formulary and that they include experts in antimicrobial therapy.

Antimicrobial stewardship interventions for new antimicrobials

As discussed above, some new antibiotics may offer therapeutic advances in orphaned clinical situations. Stewardship teams are tasked to minimizing barriers for their use in situations in which they can be beneficial for patients and therefore promote their inclusion in hospital formularies. However, the use of new antibiotics must always be very prudent for different reasons; first, because some adverse events may have been undetected in the pivotal trials; second, because their efficacy may have been overestimated if high-risk patients were underrepresented in the trials; and third, development and spread of resistance is a real threat. Therefore, it is very important to develop specific stewardship interventions aimed at facilitating their appropriate use.[299]

Among these interventions, AMSP should develop local guidelines for the use of new drugs; as off-label use of the new antibiotics is expected to be frequent particularly in settings in which MDRO are endemic,[300] consensus is needed for these indications. The local guideline must be easily available, and educational activities for prescribers should be performed. In addition, non-compulsory interventions such as audit and feedback activities, may also be implemented to facilitate adherence to the recommendations. Finally, the AMS teams have the responsibility to generate information by monitoring the outcomes of patients treated with these drugs in terms of mortality, failure, length of hospital stay, development of resistance or *C. difficile* infection; such information may be collective within multicenter initiatives.[301]

Guidance recommendations for antimicrobial stewardship programs in aspects related to new antimicrobials:

- AMSP should promote the inclusion of new drugs in hospital formularies according to local needs and best evidence, in order to provide patients with the best available therapy in infections caused by MDRO.

- AMSP should include local consensus guidelines including specific indications of use of new drugs according to the best available evidence and local epidemiology.
- AMSP should implement non-compulsory interventions as auditing and feedback to facilitate the adherence to the established guidelines.
- AMSP should monitor and evaluate the data concerning the outcomes of patients treated with new drugs, development of resistance to them and their impact in the overall epidemiology of MDRO.

SOCIAL SCIENCES AND BEHAVIOURAL CHANGE IN ANTIMICROBIAL STEWARDSHIP

AMSP should pay attention to knowledge from behavioural and social sciences

Prescribing is a final action resulting from deliberate and non-deliberate thinking and can be influenced by circumstances shaping prescribing patterns. Since prescribing falls within the realm of behaviour, and every behavioural improvement implies change, improving antimicrobial prescribing is clearly the expression of behaviour change. Interestingly, many of the circumstances that influence prescribing are not related to biomedical but to social and psychological factors. These are responsible for the gap between knowledge and clinical practice, the so-called implementation gap, which might account for 30-40% of antimicrobial prescriptions in hospitals.[186] While biomedical sciences (biological and clinical disciplines) contribute to define the standards of antimicrobial therapy, social and behavioural sciences are key to achieve the satisfactory implementation of these standards at the prescriber level.[302]

Unfortunately, according to a recent systematic review, very few AMS interventions employ behavioural change techniques.[303, 304] This might explain why similar interventions show highly variable success rates.[303] Therefore, AMS interventions

must be designed considering behaviour and social theories and employ behaviour change techniques. In fact, some authors suggest the inclusion of behaviour experts in the AMS team.[305] There are several models for behavioural change, some of which have been adapted and adopted for AMS. One of them is the behaviour change wheel (BCW), which is structured in three steps:[302, 306, 307]

Step 1. Understanding problematic and desired behaviours

The interventions should be designed taking into account the desired prescribing behaviour and what needs to change in order to achieve it.[302, 306] As many factors driving behaviours are context-dependent, the behavioural assessment must be performed in the setting where the interventions are to be applied. The prescribing behaviour should be defined in behavioural terms: what behaviour/s are being targeted, which should be changed, in which settings and when. Behaviours should be defined as specifically as possible to assist the intervention design and measurement of the impact of the intervention through specific metrics.[302, 306]

The next step is identifying the barriers and enablers for the change in behaviour. To do this, there are several approaches. Flottorp et al. defined a 57-item check-list in seven domains: guideline factors, individual health professional factors, patient factors, professional interactions, incentives and resources, capacity for organizational change, and social, political, and legal factors.[308] Michi et al used the so-called COM-B approach integrating sources of behaviour (barriers and enablers), intervention functions (type of interventions) and policies.[302, 306] COM-B postulates that there are three basic aspects that must be met in order for a change in behaviour to occur: capability (physical and psychological), opportunity (physical and social) and/or motivation (reflective and automatic). The range of potential factors influencing behaviour, summarized in 14 theoretical domains, are displayed within the COM-B components (Tables 5 and 6). The

3 COM-B components and the corresponding theoretical domains should be assessed in the target population.[306]

Step 2. Identifying the most appropriate intervention functions

The interventions should be designed with the aim of overcoming the barriers and/or taking advantage of the enablers for the desired behaviour. Thereby, for every barrier and enabler there are one or more matching intervention functions that should ideally been selected when designing the intervention (Table 5).

Step 3. Selecting content and implementation options

Once the intervention functions have been identified, one or more behaviour change techniques (BCT) have to be selected. A BCT is the smallest component of an intervention that may have the potential to change behaviour.[307] Each intervention function is likely to be addressed by several BCTs; on the other hand, each BCT may fit in more than one function (Table 6). The BCT taxonomy, developed to standardize potentially 'active ingredients' of interventions to change behaviour, might help to select the most suitable BCT for each prescribing problem.[309]

Nudge is a behavioural theory popularized by Thaler and Sunstein that tries to address the misalignment between actual and desired behaviour due to non-rational decision-making attributable to judgmental heuristics. Interestingly, nudging comprises BCTs that aim to use judgmental heuristics in order to increase the likelihood of certain choices, which in AMSP are those representing appropriate antimicrobial prescribing, in what has been named "antibiotic judo".[310, 311] Nudges are easy and inexpensive to implement in an environment that disrupt the cues triggering inappropriate antimicrobial prescribing in what has been called "choice architecture". According to the nudge theory,

nudges are acceptable if they lean the individuals towards a choice that is consistent with their values or preferences (appropriate antimicrobial use), but respect their freedom of choice, meaning that they do not significantly increase the cost of alternative choices.[312] Defaults are one of the most popular nudge techniques, based on the fact that people are more likely to choose a particular option if it is the default option. Default options have been successfully used, among others, to decrease antimicrobial use in asymptomatic bacteriuria.[313] Social nudges are based on the tendency for individuals to look at other persons' behaviour to help guide their own; therefore, social comparisons and modelling BCTs fit in the nudge category.

Behaviourally designed incentives can also be used to change prescribing behaviour. Given the array of human motivations that can lie behind prescription behaviours, incentives can incorporate the need individuals have to feel they are acting "correctly", their contribution to a socially desirable outcome, their sense of responsibility or the fact that they are behaving better than their peers.

In addition to flawed design, interventions may achieve limited effects because the intervention is inadequately implemented. The main implementation faults are inadequate fidelity (the intervention was not implemented as intended) and inappropriate intensity or poor coverage of target participants, among others. On the other hand, unintended consequences of the intervention may yield satisfactory outcome despite inconsistent or poor implementation. Because of these discrepancies, conducting process evaluations while the intervention is ongoing is recommended[302, 314] and testing pilot measures before setting on larger interventions (Table 6 [302, 307, 315-320]).

Guidance recommendations for application of social sciences and behavioural change in antimicrobial stewardship programs:

- Antimicrobial stewardship interventions should be designed considering knowledge from behavioural and social sciences and should employ behaviour change techniques. Whenever possible, behaviour experts should be part of antimicrobial stewardship teams.
- The prescribing behaviours that are intended to be changed should be precisely defined, and barriers and promoters should be analysed locally.
- Behaviour change techniques (BCTs) should be selected taking into account the main determinants of the desired and/or undesired behaviours. The interventions must combine several BCTs.
- There are several behaviour's change theories and models that can be applied in the field of AMS. One of the most frequently adopted models for AMS is the behaviour change wheel.
- It is advisable to conduct process evaluations of ongoing interventions in order to learn why they fail or succeed.

E-TOOLS FOR ANTIMICROBIAL STEWARDSHIP

The use of technological advances, such as health information technology (HIT), clinical decision support systems (CDSS), electronic medical record, mobile applications, and social media may provide clinicians with patient-specific data and recommendations to aid clinical decision-making, and can be used to optimize antibiotic use[321, 322]. Several studies have shown that information technology interventions can improve antimicrobial prescribing in hospitals, but analyzing clinical outcomes is necessary.[323]

E-tools in the Pharmacy department

Electronic prescribing (EP), electronic hospital pharmacy (EHP) or computerized physician order entry (CPOE) systems reduce medication errors and adverse drug events,[324] and may also support AMSP.[325] They are also useful for audits in AMSP, providing better documentation of the prescription and reducing the time needed for auditing.[326]

CDSS could be integrated information systems, among other applications, such as pharmacy dispensing systems and CPOE. In fact, it is possible to create alerts for antibiotics prescribed, critical laboratory results, discrepancies between a prescribed antibiotic and the results of antibiograms, dosing, drug interactions or allergies, and also provide links to guidelines.[327, 328] It is also possible to incorporate a stop date or other specific elements, such as providing dosage or administration recommendations for each antibiotic, need to monitor plasma levels, and even prompting providers with treatment recommendations after prescription based on local patient and microbiological data.[329] CDSS that integrate EP systems with medical notes, pharmacy systems and laboratory results are more effective to support antibiotic use, developing interventions that support all key decisions within the antibiotic prescribing process.[330]

E-tools in microbiology laboratories

CDSS in microbiology laboratories integrate patient information with clinical knowledge bases and laboratory data to generate specific recommendations aimed at better patient management.[331] These systems have been used successfully in daily clinical practice, often within an AMSP. Their implementation has shown a significant reduction

in LOS, adequacy of antibiotic treatments and hospital costs.[332] Because microbiology departments handle large amounts of analytical data,[333, 334] their contribution is essential for CDSS in supporting AMSP tasks. CDSS applications obtain data from the electronic medical records, Pharmacy and laboratory information system (LIS), and may be capable of exporting periodically cumulative susceptibility reports and generate microbiological alerts; these alerts should include early outbreaks alerts, positive culturesof sterile samples, prescription alerts (drug-microorganism mismatches, redundant antibiotic treatment, PK/PD optimization, and adequacy and duration of antibiotic prescription). The incorporation of microbiological alerts to CDDS decreased the time toadequate treatment in the experience of an Italian hospital.[334] In addition, user-friendly applications for cell phones are well accepted and widely used by hospital staff and are becoming useful auxiliary tools for AMSP activities.[335] These technological resources open new ways of analyzing and interpreting the data to improve the management of patients. For example, Morales et al. described a CDDS for empirical antibiotic therapy and proposed a new concept: the number needed to fail, representing the "number of patients that would need to be treated with a specific antibiotic for one to be inadequatelytreated" and could be calculated by integrating microbiological and pharmacy data.[336]

In summary, e-tools provide an important support to the microbiology laboratory, not only organizing and presenting generated data, but also integrating these data in CDDSs in order to facilitate the optimization of antimicrobial treatments.

Evidence for the implementation of antimicrobial stewardship e-tools

Many e-tools have emerged in the last years. As indicated above, many of them are been developed to assist pharmacies and microbiology laboratories to optimize their processes or to organize data. Regarding AMS interventions, many electronic resources

have been implemented to facilitate guidelines access, clinical pathways, and post-prescription audits.[337] One of the most popular are the CDSS focused on antimicrobial prescription targeting the prescribers. These CDSS allow real-time data entry as it is the case CDDS based on local cumulative susceptibility reports.[337] In addition, electronic guidelines directed to wide populations led to sustained reductions in antibiotic prescribing.[338] However, a recent Cochrane review argued that most studies evaluating AMS interventions used weak methods,[303] mostly before-after, quasi-experimental designs with no control group and inappropriate statistical analyses. Cluster randomized control trials (the preferred designs to evaluate AMS interventions[303]) focused on e- tools applied to specific syndromes and populations have shown an important decrease in antimicrobial use.[339-341] Gulliford et al. developed a cluster randomized trial to evaluate an electronic stewardship intervention over 79 practices. The intervention comprised a brief training webinar, automated monthly feedback reports of antibiotic prescribing, and aCDSS; the electronically delivered interventions were integrated into practice workflow. A significant reduction of antibiotic prescribing for respiratory tract infectionsin adults was demonstrated.[342] A recent systematic review evaluating the effectiveness, the acceptability and the usability of CDSS also showed a positive impact on antibiotic prescription for respiratory tract infections.[343]

When evaluating e-tools, evaluating their feasibility according to local resources is important. Some electronic medical records allow for alerts and clinical pathways, but these functionalities are not widely available. For this reason, social media may play an important role as tools for disseminating stewardship resources. Pisano et al. used social media platforms (Facebook and Twitter) to increase internal medicine residents' antibiotic knowledge and awareness of AMSP resources. Residents knowing how to access the AMSP web site increased from 70% to 94%, and also increased using the clinical pathways "sometimes, frequently, or always" from 33% to 61%.[344]

Guidance recommendations for e-tools implementation in antimicrobial stewardship programs:

- Whenever possible and feasible, e-tools should be included in AMS interventions to facilitate guidelines, clinical pathways and post prescriptionreview.
- The efficacy and safety of AMS e-tools should be validated through cluster randomized control trials or adequately controlled quasi-experimental designs.
- AMS e-tools should be available for prescribers. Social media may be considered as tools to disseminate the AMSP resources.

4. DIAGNOSTIC STEWARSDHIP

The role of clinical microbiologists in antimicrobial stewardship programs

The activity of clinical microbiologists (CMs) has undergone an important transformation in recent years. CMs must leave part of their traditional bench activity to dedicate to conceptual, organizational and research tasks, joining transversal multidisciplinary teams and focusing part of their efforts on promoting the rational use of antimicrobials and combating antibiotic resistance.[333] The role of CMs in AMSP is to provide the team with information on the antimicrobial susceptibility testing (AST) of microorganisms, the optimization of microbiological diagnosis of infections and performing the surveillance of emerging pathogens and their resistance to antimicrobials. The active contribution of CMs is fundamental in hospital, primary care and long-term care facility settings, and at local, regional and national levels.

Microbiological diagnostic stewardship programs

The process of diagnostic stewardship begins with the evaluation, selection, and implementation of appropriate diagnostic tests in the clinical setting for individualpatients including suitable sample collection, transport, processing and timely reporting of results.[345] Microbiological diagnostic stewardship programs (MDS or PRODIM, in Spanish) promote the adequate use of microbiology diagnostic methods.[346, 347] MDS include from choice and indication of a microbiological study to decision-making based on the results. These programs must also be considered as a fundamental part of AMSP. According to ESGMD and ESGAP (European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Groups for Genomic and Molecular Diagnostics and for Antimicrobial Stewardship), a good prescription starts with aprecise diagnosis, which is needed to ensure prompt appropriate clinical action and to rapidly translate diagnostic test results in the laboratory into improved outcomes at the bedside.[346]

Pre-analytical sample procedures

a. Promoting adequate test indications and specimen handling

The impact of proper specimen handling on patient care is enormous and is key to achieving accurate laboratory diagnosis and confirmation.[348] While the collection of microbiology specimens depends on another group of professionals, CMs must be available for advice on the diagnosis of infectious diseases to ensure the correct indication and management of tests and the selection of the best quality samples and their collection, transport, and storage. They also must guide physicians to resolve problems with specimen submissions. Moreover, assurance of adequate conservation and immediate delivery to the microbiology laboratory is necessary to guarantee the continuity of the process regardless of the reception time.

Management of the adequacy of the laboratory test requests

CMs must provide clinician's guidance to ask for conventional or new diagnostic tests and appropriate testing strategies. They should monitor the use of these tests and introduce educational programs to reduce overuse among high test users.[345] For this purpose, electronic or on-line laboratory request forms also favor adequate decision-making.

Analytical phase

a. Improved culture and identification systems and rapid diagnostic techniques

Recent advances in microbiological diagnostics are providing clinicians with rapid identification of microorganisms and their susceptibility, leading to use the most adequate antimicrobial therapy to improve clinical outcomes and reduce unnecessary treatments. Since diagnostic uncertainty is a significant contributor to the overuse of antibiotics, microbiologists must advocate for the introduction of adequately assessed new technologies to enhance patient care, taking into account which microbiological testswill be implemented, based on prevalent or problematic organisms within the hospital setting.[349] Consideration should also be given to the sensitivity and specificity of each test, as variability exists among different rapid diagnostic technologies and organisms.[350] On the other hand, evaluation of the cost-effectiveness of new diagnostic tests is mandatory.[351, 352] CMs should discuss with the AMS team the justification of expenditures on new technologies and must also update clinicians about the new rapid diagnostic techniques implemented in their laboratory in order to achieve a positive impact on infection management.[353]

The following recommendations on specific clinical indications related to rapid diagnostic techniques were published in the 2016 by the Infectious Diseases Society of

America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA)[127] and are discussed:

1.Rapid identification of organisms from blood is a critical component in providing quality healthcare. The combined use of matrix-assisted laser desorption and ionization time-of-flight (MALDI-TOF) from blood-cultures and real-time AMS intervention allow early optimization of antimicrobial therapy and provides significant hospital savings.[147, 354] New technologies provide rapid identification and detection of resistance markers directly from blood (nuclear magnetic resonance testing) or rapid identification and antimicrobial susceptibility from positive blood cultures (Gram stain, peptic nucleic acid fluorescent, morphokinetic fluorescent cellular analysis, nephelometry, syndromic rapid multiplex polymerase chain reaction, microarray-based or nanoparticle probe technology). These diagnostic techniques improve the management of patients with bloodstream infections, particularly those infected with resistant organisms such as extended-spectrum beta-lactamase-producing or carbapenem-resistant Enterobacterales. They are relatively easy to implement and most seem to have a favorable cost-benefit balance. Their use is associated with statistically significant improvements in time to initiation of appropriate antibiotic therapy, rates of recurrent infection, mortality, length of stay, and hospital costs in several studies. Their implementation needs to be adapted to local resources and be fully integrated into the AMSP of the hospital.[355, 356] The use of a rapid diagnostic test can also reduce unnecessary antimicrobial exposure and increase the appropriateness of empirical antibiotic therapy in pneumonia,[357] central nervous system and gastrointestinal infections, although more studies to evaluate their full impact are needed.[358]

2. The use of rapid viral testing for respiratory pathogens (antigen, immunoassay, direct fluorescent antigen or molecular test) seems to reduce inappropriate antibiotic use in addition to the indication of other ancillary test orders.[127]

3. Invasive fungal infections (IFI): experts recommend incorporating non-culture-based fungal markers to optimize antifungals use in patients with haematological malignancies at risk of IFI.[127] The results of these tests should be included in a decision algorithm, together with the suspected pathogens, the possibility of colonization, the medical history of the patient (clinical presentation, historical microbiological data and risk factors for multidrug-resistant infection) and local epidemiology.

b. Fast-track protocols for selected patients

CMs should improve laboratory workflows to reduce time to microorganism identification and AST and obtain results on the first day of diagnosis in selected patients based on the severity of infection or individual risk (sepsis alert, admission to an intensive care unit or immunocompromised patients).[359] A timely reporting of the diagnosis in these cases is as important as the use of rapid diagnostic tests, and time between processing and transmission of critical results should be as short as possible.

Post-analytical considerations

CMs should provide the information of the results to the responsible physician and the AMS team in a way that decision making is facilitated. Strategies include cascade reporting of AST results, the introduction of advisory statements, and not reporting the identification and susceptibility data in case of commensal microbiota[349]. Microbiologists must keep up with changes regarding susceptibility breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and provide reports on

local patterns of susceptibility by periodic elaboration of accurate cumulative antibiogram reports.

a. Interpretation of microbiological results. Information pathways

Special attention should be paid to the form and way results are reported to clinicians. Microbiology laboratories must issue intelligible, judicious, clinically relevant reports within the shortest possible time. These reports must be clear, especially if they include new species, unusual mechanisms of resistance or information about specific resistance genes. If explanatory comments are necessary, they should not be excessively long, but rather easy and quick to read.

When the laboratory implements a rapid diagnostic test, providers must be alerted to results in real-time.[346] Also, results from blood cultures and other sterile samples, and first isolates of epidemiological relevant microorganisms such as *Mycobacterium tuberculosis, C. difficile* or MDRO must also be reported in real time. Negative results may be of particular relevance in patients with suspected sepsis, unknown source of infection or for monitoring severe infections. Active read-back reporting on alert systems ensures that results have been received in a timely manner, and are better than passive reporting requiring the clinician to continually check the medical records.[345, 360] Other traditional information channels such as phone calls or message systems are alternatives; they are complementary to face-to-face advice during daily ward rounds. Person-to-person communication provides reliable transfer of information optimally, increases team feeling, and heightens appreciation of the CMs value. In a recent Danish study,[361] the investigators observed an improvement in the reassessments of the antibiotic treatments at a hospital where a CM was present at ward round.

b. Interpretation and selective information of antibiograms

The method used by the microbiology laboratory to communicate the results, selective reporting and instructions on the interpretation of results can have an important impact on prescribing habits. According to the ECDC,[362] CMs should ensure that AST and reporting of results are in accordance to treatment guidelines and EUCAST standards. Selective reporting of AST is the practice of reporting susceptibility results for a limited number of antibiotics instead of all the antibiotics tested.[363] Previous studies suggested that selective reporting may improve the quality of antibiotic prescriptions, mainly in urinary tract infections.[364] Cascade reporting is a type of selective reporting in which susceptibility results of secondary antibiotics (either more costly or with broader spectrum) are only reported if an organism is resistant to the primary antibiotic within a particular antibiotic class. Regulatory authorities provide guidance for testing and reporting susceptibilities for specific organisms but do not cover all organism-antibiotic combinations.[364] Although data that demonstrate the direct impact of these strategies on prescribing are limited, some form of selective or cascade reporting is reasonable. Written AST reports usually also include specific commentaries to guide clinicians in their antibiotic prescriptions. These commentaries or additional messages have not been studied extensively but must follow general recommendations and should provide clear and concise messages based on local experience.[333] Nonetheless, a recent ESCMID survey conducted in 36 European countries and Israel reported that selective reporting was in place in only 11 of these nations. The most frequent application was in uncomplicated community-acquired infections, particularly urinary tract and skin and soft-tissue infections. Several barriers to implementation were reported, mainly the lack of precise guidelines, poor system support, insufficient resources, and lack of professional capacity.[353]

c. Cumulative antimicrobial susceptibility reports. Stratified antibiograms

Microbiology laboratories must provide at least an annual cumulative antimicrobial susceptibility report for specific antibiotic-organism combinations, which is critical for the local guidelines for empirical therapy[127, 365] and monitoring over time the local resistance trends.[366] Although there is currently limited evidence that stratified antibiograms (e.g., by ward or age if at least 30 isolates are available for each organism) lead to improved empiric antibiotic therapy, stratification can provide significant differences in susceptibility, which can help the AMS team to develop optimized treatment recommendations and guidelines for different wards. A single institutional or hospital-wide antibiogram may mask significant susceptibility differences across units within an institution (ICU *vs* non-ICU settings, or medical *vs* surgical wards), or by population age group, infection site, patient comorbidities, acquisition (community *vs* healthcare-associated).

d. Clinical decision support system for the prescription of antibiotics

In the 2012 PROA consensus document,[1] computerized support systems were described as a tool for clinical decisions in the prescription of empirical antibiotic treatment. As indicated in the section dealing with e-tools of this manuscript (see above), these systems use patient-specific data including microbiological results and integrate this information with local epidemiological data and therapeutic site-guidelines through artificial intelligence or machine learning to make more precise recommendations.

Currently, there is limited information about the impact of using these systems. Nevertheless, before implementing such a system in a center or a network of centers, it is necessary to adapt the system to the LIS, and to know the structure of information available and the preferential work approaches of the users.[367]

Epidemiological surveillance of multidrug-resistant pathogens

The microbiology laboratory plays a central role in epidemiological surveillance because it is the generator of the essential information, by establishing if any bacterium meet the multidrug-resistance criteria, detecting the responsible mechanism, determining if a hospital outbreak has occurred or, in specific cases, the clone causing the outbreak and if is imported or emerging.[368] Antimicrobial resistance surveillance systems are a fundamental tool as long as they analyze microbiological, clinical, and epidemiological data from a One Health approach (humans, animals and environment).

Institutional role. Integration in the AMS team

AMS multidisciplinary teams are a critical component of any AMSP.[369] The participation of CMs in these teams is mandatory, and their tasks in the team must be considered as an additional healthcare activity. As full members of the team, the responsibilities of CMs include tasks related to coordination, planning, post-prescription review and feedback activities.

Guidance recommendations for diagnostic stewardship:

- Diagnostic stewardship principles should be part of any AMSP.
- The adequacy of laboratory test requests and correct handling of specimens should be promoted among the activities of the AMSP.
- Rapid microbiological diagnostic techniques for the adequate samples and patients, and rapid identification and susceptibility testing from positive blood cultures should be implemented and associated with rapid active reporting and antimicrobial stewardship interventions.

- The use of rapid viral diagnostic testing for respiratory pathogen should be promoted in the appropriate settings.
- Non-culture-based fungal markers in patients with haematological malignancies at risk of IFI must be implemented and associated with appropriate interpretation criteria to both improve diagnosis and facilitate adequate use of antifungals.
- Fast-track protocols for selected patients (critical or immunocompromised patients) must be designed and implemented.
- Provide cascade or selective reporting instead of over-reporting all tested antimicrobials.
- Provide periodical data on cumulative antimicrobial susceptibility for optimizing empirical therapy, with appropriate stratification of data whenever possible.
- Surveillance programs of multidrug-resistant pathogens for the detection of outbreaks and emerging new clones must be implemented.

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REFERENCES

1. Rodríguez-Baño J, Paño-Pardo JR, Álvarez-Rocha L, Asensio A, Calbo E, Cercenado E, et al. Programas de optimización de uso de antimicrobianos (PROA) en hospitales españoles: documento de consenso GEIH, SEIMC, SEFH y SEMPSPH. Enferm Infecc Microbiol Clin. 2012;30(1):22.e1-22.e23.
2. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA J Am Med Assoc. 1999;281:61–6.
3. Paruk F, Richards G, Scribante J, Bhagwanjee S, Mer M, Perrie H. Antibiotic prescription practices and their relationship to outcome in South Africa: findings of the prevalence of infection in South African intensive care units (PISA) study. South Afr Med J. 2012;102:613–6.
4. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care. Reasons for caution. N Engl J Med. 2014;370:1673–6.
5. Estudio nacional de vigilancia de infección nosocomial en servicios de medicina intensiva (ENVIN-HELICS). Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC). Informe 2021. Available at: https://hws.vhebron.net/envin-helics/Help/Informe%20ENVIN-UCI%202021.pdf (Accessed March, 2022).
6. Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med. 2014;2:380-6.

7. Klein Klouwenberg PMC, Cremer OL, van Vught LA, Ong DSY, Frencken JF, Schultz MJ, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015;19:319.
8. Vincent JL, Lefrant JY, Kotfis K, Nanchal R, Martin-Loeches I, Wittebole X, et al. Comparison of European ICU patients in 2012 (ICON) versus 2002 (SOAP). Intensive Care Med. 2018;44:337–44.
9. Akrami K, Sweeney DA. The microbiome of the critically ill patient. Curr Opin Crit Care. 2018;24:49-54.
10. MacVane, S.H. Antimicrobial resistance in the intensive care unit: a focus on Gram-negative bacterial infections. J Intensive Care Med. 2017;32:25-37.
11. Garnacho-Montero J, Álvarez-Lerma F, Ramírez P, Palomar M, Álvarez-Rocha L, Barcenilla F, et al. Combatting resistance in intensive care: the multimodal approach of the Spanish ICU "*Zero Resistance*" program. Critical Care 2015;19:114.
12. Frattari A, Savini V, Polilli E, Di Marco G, Lucisano G, Corridoni S, et al. Control of Gram-negative multi-drug resistant microorganisms in an Italian ICU: rapid decline as a result of a multifaceted intervention, including conservative use of antibiotics. Int J Infect Dis. 2019;84:153-62.
13. Bassetti M, Peghin M, Vena, A, Giacobbe DR. Treatment of infections due to MDR Gram-negative bacteria. Front Med (Lausanne). 2019;6:74.
14. Tabah A, Bassetti M, Kollef MH, Zahar JR, Paiva JA, Timsit JF, et al. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). Intensive Care Med. 2020;46:245-65.
15. Eggimann P, Pittet D. *Candida* colonization index and subsequent infection in critically ill surgical patients: 20 years later. Intensive Care Med 2014;40:1429-48.
16. Guinea J. Global trends in the distribution of *Candida* species causing candidemia. Clin Microbiol Infect. 2014;20 (Suppl 6):5-10.
17. Álvarez-Lerma F, Álvarez-Rocha L, Blanquer J, Galván B, Rodríguez A, Zaragoza R, et al. Epidemiology, diagnosis and treatment of fungal respiratory infections in the critically ill patient. Rev Esp Quimioter. 2013;26:173-88.
18. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-96.
19. De Bus L, Gadeyne B, Steen J, Beolens J, Claeys G, Benoit D, et al. A complete and multifaceted overview of antibiotic use and infection diagnosis in the intensive care unit: results from a prospective four-year registration. Critical Care. 2018;22:241-50.
20. Pulcini C, Binda F, Lamkang AS, Trett A, Charani E, Goff DA, et al. Developing core elements and checklist items for global hospital antimicrobial stewardship programs: a consensusapproach. Clin Microbiol Infect. 2018;25:20–25.
21. Kollef MH, Bassetti M, Francois B, Burnham J, Dimopoulos G, Garnacho-Montero J, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. Intensive Care Med. 2017;43:1187-97.

22. De Waele JJ, Akova M, Antonelli M, Canton R, Carlet J, De Backer D, et al Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multidrug resistance. Intensive Care Med. 2018;44:189-96.
23. Bates A, Joffe AR. Is there a role for continuous infusion of β-lactam antibiotics in severe sepsis? J Thorac Dis. 2016 Jun;8:E437-9.
24. Abdul-Azis MH, Alffenaar JWC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically-ill adult patients: a position paper. Intensive Care Med. 2020;46:1127-53.
25. Timsit JF, Bassetti M, Cremer O, Daikos G, Waele J, Kallil A, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med. 2019;45:172-89.
26. Bailly S, Meyfroidt G, Timsit JF. What's new in ICU in 2050: big data and machine learning. Intensive Care Med. 2018;44:1524-7.
27. Salluh JIF, Chiche JD, Reis CE, Soares M. New perspectives to improve critical care benchmarking. Ann Intensive Care. 2018;8(1):17.
28. Naidus E, Celi LA. Big data in healthcare: are we close to it? Rev Bras Ter Intensiva. 2016;28:8-10.
29. Ruiz J, Ramírez P, Gordon M, Villareal E, Frasquet J, Poveda-Andrés JL, et al. Antimicrobial stewardship program in critical care medicine: A prospective interventional study. Med Intensiva. 2018;42:266-73.
30. Morris AM, Bai A, Burry L, Dresse LD, Ferguson ND, Lapinsky SE, et al. Long-term effect of phased implementation of antimicrobial stewardship in academic ICUs: 2007-2015. Crit Care Med. 2019;47:159-66.
31. Onorato L, Macera M, Calò F, Monari C, Russo F, Iovene MR, et al. The effect of an antimicrobial stewardship programme in two intensive care units of a teaching hospital: an interrupted time series analysis. Clin Microbiol Infect. 2020;26(6):782.e1-782.e6.
32. De Bus L, Depuydt P, Steen J, Dhaese S, De Smet K, Tabah A, et al. Antimicrobial de-escalation in the critically ill patient and assessment of clinical cure: the DIANA study. Intensive Care Med. 2020;46:1404-17.
33. Teerawattanapong N, Kengkla K, Dilokthornsakul P, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Prevention and control of multidrug-resistant Gram-negative bacteria in adult intensive care units: a systematic review and network meta-analysis. Clin Infect Dis. 2017;64(suppl. 2):S51-60.
34. Arena F, Scolletta S, Marchetti L, Galano A, Maglioni E, Giani T, et al. Impact of a clinical microbiology-intensive care consulting program in a cardiothoracic intensive care unit. Am J Infect Control. 2015;43:1018-21.
35. Bornard L, Dellamonica J, Hyvernat H, Girard-Pipau F, Molinari N, Sotto A, et al. Impact of an assisted reassessment of antibiotic therapies on the quality of prescriptions in an intensive care unit. Med Mal Infect. 2011;41:480-5.
36. Diaz-Granados CA. Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. Am J Infect Control. 2012;40:526-9.

37. Elligsen M, Walker SA, Pinto R, Simor A, Mubareka S, Rachlis A, et al. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. Infect Control Hosp Epidemiol. 2012;33:354-61.
38. Hohn A, Heising B, Hertel S, Baumgarten G, Hochreiter M, Schroeder S. Antibiotic consumption after implementation of a procalcitonin-guided antimicrobial stewardship programme in surgical patients admitted to an intensive care unit: a retrospective before-and-after analysis. Infection. 2015;43:405-12.
39. Katsios CM, Burry L, Nelson S, Jivraj T, Lapinsky SE, Wax RS, et al. An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial prescribing in critically ill patients. Crit Care. 2012;16(6):R216.
40. Leung V, Gill S, Sauve J, Walker K, Stumpo C, Powis J. Growing a "positive culture" of antimicrobial stewardship in a community hospital. Can J Hosp Pharm. 2011;64:314-20.
41. Rimawi RH, Mazer MA, Siraj DS, Gooch M, Cook PP. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. Crit Care Med. 2013;41:2099-107.
42. Álvarez-Lerma F, Grau S, Echeverría-Esnal D, Martínez-Alonso M, Gracia-Arnillas MP, Horcajada JP, et al. A before-and-after study of the effectiveness of an antimicrobial stewardship program in critical care. Antimicrob. Agents Chemother. 2018;62(4):e01825-17.
43. Taggart LR, Leung E, Muller MP, Matukas LM, Daneman N. Differential outcome of an antimicrobial stewardship audit and feedback program in two intensive care units: a controlled interrupted time series study. BMC Infect Dis. 2015;15:480.
44. Bow EJ. There should be no ESKAPE for febrile neutropenic cancer patients: the dearth of effective antibacterial drugs threatens anticancer efficacy. J Antimicrob Chemother. 2013;68:492-5.
45. Gudiol C, Tubau F, Calatayud L, García-Vidal C, Cisnal M, Sánchez-Ortega I, et al. Bacteraemia due to multidrug-resistant gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother. 2011;66:657-63.
46. Robilotti E, Holubar M, Seo SK, Deresinski S. Feasibility and applicability of antimicrobial stewardship in immunocompromised patients. Curr Opin Infect Dis. 2017;30:346-53.
47. Webb BJ, Majers J, Healy R, Jones PB, Butler AM, Snow G, et al. Antimicrobial stewardship in a hematological malignancy unit: carbapenem reduction and decreased vancomycin-resistant *Enterococcus* infection. Clin Infect Dis. 2020;71:960-7.
48. Wolf J, Sun Y, Tang L, Newland JG, Gerber JS, Van Dyke CJ, et al. Antimicrobial stewardship barriers and goals in pediatric oncology and bone marrow transplantation: a survey of antimicrobial stewardship practitioners. Infect Control Hosp Epidemiol. 2016;37:343-7.
49. Seo SK, Lo K, Abbo LM. Current state of antimicrobial stewardship at solid organ and hematopoietic cell transplant centers in the United States. Infect Control Hosp Epidemiol. 2016;37:1195-200.
50. Bitterman R, Hussein K, Leibovici L, Carmeli Y, Paul M. Systematic review of antibiotic consumption in acute care hospitals. Clin Microbiol Infect. 2016;22(6):561.e7-561.e19.
51. Gudiol C, Albasanz-Puig A, Laporte-Amargós J, Pallarès N, Mussetti A, Ruiz-Camps I, et al. Clinical predictive model of multidrug resistance in neutropenic cancer patients with bloodstream

infection due to *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2020;64(4):e02494-19.

52. Gyssens IC, Kern WV, Livermore DM, et al. The role of antibiotic stewardship in limiting antibacterial resistance among hematology patients. Haematologica. 2013;98:1821-5.
53. Hakki M, Humphries RM, Hemarajata P, Tallman GB, Shields RK, Mettus RT, et al. Fluoroquinolone prophylaxis selects for meropenem-nonsusceptible *Pseudomonas aeruginosa* in patients with hematologic malignancies and hematopoietic cell transplant recipients. Clin Infect Dis 2019;68:2045-52.
54. Alexander S, Fisher BT, Gaur AH, Dvorak CC, Luna DV, Dang H, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation a randomized clinical trial. JAMA. 2018;320:995-1004.
55. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018;76:20-37.
56. Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation. Intern Med J. 2014;44:1283-97.
57. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with Ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. Clin Infect Dis. 2018;66:140–8.
58. Facchinelli D, Marchesini G, Nadali G, Pagano L. Invasive fungal infections in patients with chronic lymphoproliferative disorders in the era of target drugs. Mediterr J Hematol Infect Dis. 2018;10(1):e2018063.
59. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: Summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013;98:1826–35.
60. Morrissey CO, Gilroy NM, Macesic N, Walker P, Ananda-Rajah M, May M, et al. Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy. Intern Med J. 2014;44:1298-314.
61. Aguilar-Guisado M, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4(12):e573-83.
62. Stern A, Carrara E, Bitterman R, Yahav D, Leibovici L, Paul M. Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer. Cochrane Database Syst Rev. 2019;1(1):CD012184.
63. la Martire G, Robin C, Oubaya N, Lepeule R, Beckerich F, Leclerc M, et al. De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome. Eur J Clin Microbiol Infect Dis. 2018;37:1931-40.

64. Orasch C, Averbuch D, Mikulska M, Cordonnier C, Livermore DM, Gyssens IC, et al. Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical. Clin Microbiol Infect. 2015;21(3):e25-7.
65. Le Clech L, Talarmin JP, Couturier MA, Ianotto JC, Nicol C, Le Calloch R, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Lond). 2018;50:539-49.
66. Castañón C, Fernández Moreno A, Fernández Verdugo AM, Fernández J, Martínez Ortega C, Alaguero M, et al. The value of adding surveillance cultures to fluoroquinolone prophylaxis in the management of multiresistant Gram-negative bacterial infections in acute myeloid leukemia. J Clin Med. 2019;8:1985.
67. Schiavino D, Nucera E, De Pasquale T, Roncallo C, Pollastrini E, Lombardo C, et al. Delayed allergy to aminopenicillins: clinical and immunological findings. Int J Immunopathol Pharmacol. 2006;19:831-40.
68. Niessen FA, Van Mourik MSM, Bruns AHW, Raijmakers RAP, De Groot MCH, Van Der Bruggen T. Early discontinuation of empirical antibiotic treatment in neutropenic patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome. Antimicrob Resist Infect Control. 2020;9:74.
69. Van de Wyngaert Z, Berthon C, Debarri H, Bories C, Bonnet S, Nudel M, et al. Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: A prospective cohort. Int J Antimicrob Agents. 2019;53:781-8.
70. Aitken SL, Nagel JL, Abbo L, Alegria W, Barreto JN, Dadwal S, et al. Antimicrobial stewardship in cancer patients: the time is now. J Natl Compr Canc Netw. 2019;17:772-5.
71. Molina J, Fernández-Gamarra E, Gómez MA, Larrosa N, Arrazubi V, Cercenado E, et al. Encuesta nacional sobre el nivel de implementación de los programas de optimización de antimicrobianos (PROA) en los hospitales españoles. Situación específica en las unidades de oncología. XXXIII Congress of the Spanish Society of Infectious Diseases and Clinical Microbiology. Enferm Infecc Microbiol Clin. 2019 May;37 Supl Congr(1):310-1.
72. Rolston KVI. Infections in cancer patients with solid tumors: a review. Infect Dis Ther. 2017;6:69-83.
73. Gudiol C, Aguado JM, Carratalà J. Bloodstream infections in patients with solid tumors. Virulence. 2016;7:298-308.
74. Ñamendys-Silva SA, González-Herrera MO, Texcocano-Becerra J, Herrera-Gómez A. Clinical characteristics and outcomes of critically ill cancer patients with septic shock. QJM Mon J Assoc Physicians. 2011;104:505-11.
75. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol. 2018;36:3043-54.
76. Carmona-Bayonas A, Jiménez-Fonseca P, de Castro EM, Mata E, Biosca M, Custodio A, et al. SEOM clinical practice guideline: management and prevention of febrile neutropenia in adults with solid tumors (2018). Clin Transl Oncol. 2019;21:75-86.
77. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology

and Infectious Diseases Society of America clinical practice guideline update. J Clin Oncol. 2018;36:1443-53.

78. Molina J, Noguer M, Lepe JA, Pérez-Moreno MA, Aguilar-Guisado M, Lasso de la Vega R, et al. Clinical impact of an educational antimicrobial stewardship program associated with infectious diseases consultation targeting patients with cancer: results of a 9-year quasi-experimental study with an interrupted time-series analysis. J Infect. 2019;79:206-11.
79. Yeo CL, Wu JE, Chung GW-T, Chan DS-G, Fisher D, Hsu LY. Specialist trainees on rotation cannot replace dedicated consultant clinicians for antimicrobial stewardship of specialty disciplines. Antimicrob Resist Infect Control. 2012;1:36.
80. Granwehr BP, Kontoyiannis DP. The impact of infectious diseases consultation on oncology practice. Curr Opin Oncol. 2013;25:353-9.
81. Hiong A, Thursky KA, Venn G, Teh BW, Haeusler GM, Crane M, et al. Impact of a hospital-wide sepsis pathway on improved quality of care and clinical outcomes in surgical patients at a comprehensive cancer centre. Eur J Cancer Care (Engl). 2019;28(3):e13018.
82. Thursky K, Lingaratnam S, Jayarajan J, Haeusler GM, Teh B, Tew M, et al. Implementation of a whole of hospital sepsis clinical pathway in a cancer hospital: impact on sepsis management, outcomes and costs. BMJ Open Qual 2018;7(3): e000355.
83. Foolad F, Berlin S, White C, Dishner E, Jiang Y, Taremi M. The impact of penicillin skin testing on aztreonam stewardship and cost savings in immunocompromised cancer patients. Open Forum Infect Dis. 2019;6(10):ofz371.
84. Trubiano JA, Grayson ML, Phillips EJ, Stewardson AJ, Thursky KA, Slavin MA. Antibiotic allergy testing improves antibiotic appropriateness in patients with cancer. J Antimicrob Chemother. 2018;73:3209-11.
85. Morneau K, Chisholm GB, Tverdek F, Bruno J, Toale KM. Timing to antibiotic therapy in septic oncologic patients presenting without hypotension. Support Care Cancer. 2017;25:3357-63.
86. Szymankiewicz M, Nakonowska B. Rapid detection of bloodstream pathogens in oncologic patients with a filmarray multiplex PCR assay: a comparison with culture methods. Pol J Microbiol. 2018;67:103-7.
87. Brazelton de Cárdenas JN, Su Y, Rodríguez A, Hewitt C, Tang L, Garner CD, et al. Evaluation of rapid phenotypic identification and antimicrobial susceptibility testing in a pediatric oncology center. Diagn Microbiol Infect Dis. 2017;89:52-7.
88. Rosa R, Suarez JF, Bravo G, Morillas-Rodríguez JA, Anderson AD, Camargo JF, et al. Challenges in antimicrobial stewardship: rapid diagnostics and optimization of therapy among immunocompromised patients. Open Forum Infect Dis. 2019;6(7):ofz239.
89. El Haddad H, Chaftari AM, Hachem R, Chaftari P, Raad II. Biomarkers of sepsis and bloodstream infections: the role of procalcitonin and proadrenomedullin with emphasis in patients with cancer. Clin Infect Dis. 2018;67:971-7.
90. Juthani-Mehta M, Malani PN, Mitchell SL. Antimicrobials at the end of life. JAMA. 2015;314:2017-8.
91. Aliyu S, Smaldone A, Larson E. Prevalence of multidrug-resistant Gram-negative bacteria among nursing home residents: a systematic review and meta-analysis. Am J Infect Control. 2017;45:512-8.

92. Mitchell SL, Shaffer ML, Loeb MB, Givens JL, Habtemariam D, Kiely DK, et al. Infection management and multidrug-resistant organisms in nursing home residents with advanced dementia. JAMA Intern Med. 2014;174:1660-7.
93. Kwon KT. Implementation of antimicrobial stewardship programs in end-of-life care. Infect Chemother. 2019;51:89-97.
94. Baghban A, Juthani-Mehta M. Antimicrobial use at the end of life. Infect Dis Clin North Am. 2017;31:639-47.
95. Rosenberg JH, Albrecht JS, Fromme EK, Noble BN, McGregor JC, Comer AC, et al. Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. J Palliat Med. 2013;16:1568-74.
96. Nakagawa S, Toya Y, Okamoto Y, Tsuneto S, Goya S, Tanimukai H, et al. Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? J Palliat Med. 2010;13:535-40.
97. Gaw CE, Hamilton KW, Gerber JS, Szymczak JE. Physician perceptions regarding antimicrobial use in end-of-life care. Infect Control Hosp Epidemiol. 2018;39:383-90.
98. Gerber JS, Newland JG, Coffin SE, Hall M, Thurm C, Prasad PA, et al. Variability in antibiotic use at children's hospitals. Pediatrics. 2010;26:1067-73.
99. Versporten A, Bielicki J, Drapier N, Sharland M, Goossen H, et al. The worldwide antibiotic resistance and prescribing in European children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother. 2016;71:1106-17.
100. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J. 2005;24:766-73.
101. Levy ER, Swami S, Dubois SG, Wendt R, Banerjee R. Rates and appropriateness of antimicrobial prescribing at an academic children's hospital, 2007-2010. Infect Control Hosp Epidemiol. 2012;33:346-53.
102. Rutledge-Taylor K, Matlow A, Gravel D, Embree J, Le Saux N, Johnston L, et al. A point prevalence survey of health care-associated infections in Canadian pediatric inpatients. Am J Infect Control. 2012;40:491-6.
103. Newland JG, Gerber JS, Kronman MP, Meredith G, Lee BR, Thurm C, et al. Sharing antimicrobial reports for pediatric stewardship (SHARPS): a quality improvement collaborative. J Pediatric Infect Dis Soc. 2018;7:124-8.
104. Kronman MP, Hersh AL, Feng R, Huang YS, Lee GE, Shah SS. Ambulatory visit rates and antibiotic prescribing for children with pneumonia, 1994-2007. Pediatrics. 2011;127:411-8.
105. Esposito S, Bianchini S, Argentiero A, Neglia C, Principi N. How does one choose the appropriate pharmacotherapy for children with lower respiratory tract infections? Expert Opin Pharmacother. 2020;21: 1739-47.
106. McMullan BJ, Hall L, James R, Mostaghim M, Jones CA, Konecny P, et al. Antibiotic appropriateness and guideline adherence in hospitalized children: results of a nationwide study. J Antimicrob Chemother. 2020;75:738-46.

107. Cantarero-Arévalo L, Hallas MP, Kaae S. Parental knowledge of antibiotic use in children with respiratory infections: a systematic review. Int J Pharm Pract. 2017;25:31-49.
108. Suwantarat N, Logan LK, Carroll KC, Bonomo RA, Sinmer PJ, Rudin SD, et al. The prevalence and molecular epidemiology of multidrug-resistant *Enterobacteriaceae* colonization in a pediatric intensive care unit. Infect Control Hosp Epidemiol. 2016;37:535-43.
109. Fanelli U, Chiné V, Pappalardo M, Gismondi P, Esposito S. Improving the quality of hospital antibiotic use: impact on multidrug-resistant bacterial infections in children. Front Pharmacol. 2020;11:745.
110. Tsai MH, Chu SM, Hsu JF, Lien R, Huang HR, Chiang MC, et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. Pediatrics. 2014;133(2):e322-9.
111. Kosecka-Strojek M, Sadowy E, Gawryszewska I, Klepacka J, Tomasik T, Michalik M, et al. Emergence of linezolid-resistant *Staphylococcus epidermidis* in the tertiary children's hospital in Cracow, Poland. Eur J Clin Microbiol Infect Dis. 2020;39:1717-25.
112. Basmaci R, Bielicki J, Daniels R, Kissoon N, Ellis S, Balasegaram M, et al. Management of children with multidrug-resistant sepsis in low-income and middle-income countries. Lancet Child Adolesc Health. 2018;2:8-10.
113. Hersh AL, Shapiro DJ, Zhang M, Madaras-Kelly K. Contribution of penicillin allergy labels to second-line broad-spectrum antibiotic prescribing for pediatric respiratory tract infections. Infect Dis Ther. 2020;9:677-81.
114. Brogan TV, Thurm C, Hersh AL, Gerber JS, Smith MJ, Shah SS, et al. Variability in antibiotic use across PICUs. Pediatr Crit Care Med. 2018;19:519-27.
115. Halpern SA. American Pediatrics: The Social Dynamic of Professionalism, 1880– 1980. Berkeley. University of California Press, 1988.
116. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology - drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157-67.
117. Kearns GL. Impact of developmental pharmacology on pediatric study design: overcoming the challenges. J Allergy Clin Immunol. 2000;106(Suppl 3):S128-38.
118. Berdkan S, Rabbaa L, Hajj A, Eid B, Habbour H, El Osta N, et al. Comparative assessment of off-label and unlicensed drug prescriptions in children: FDA versus ANSM Guidelines. Clin Ther. 2016;38:1833-44.
119. Folgori L, Bielicki J, Ruiz B, Turner MA, Bradley JS, Benjamin Jr DK, et al. Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review. Lancet Infect Dis. 2016;16(9):e178-e189.
120. Thompson G, Barker CI, Folgori L, Bielicki JA, Bradley JS, Lutsar I, et al. Global shortage of neonatal and paediatric antibiotic trials: rapid review. BMJ Open. 2017;7(10):e016293.
121. Gidey MT, Gebretsadkan YG, Tsadik AG, Welie AG, Assefa BT. Off-label and unlicensed drug use in Ayder comprehensive specialized hospital neonatal intensive care unit. Ital J Pediatr. 2020;46(1):41.
122. Donà D, Barbieri E, Daverio M, Lundin R, Giaquinto C, Taoutis T, et al. Implementation and impact of pediatric antimicrobial stewardship program: a systematic scoping review. Antimicrob Resist Infect Control. 2020;9(1):3.

123. Principi N, Esposito S. Antimicrobial stewardship in paediatrics. BMC Infect Dis. 2016;16:1-8.
124. Tersigni C, Venturini E, Montagnani C, Chiappini E, de Martino M, Galli L. Antimicrobial stewardship in children: more shadows than lights? Expert Rev Anti Infect Ther. 2019;17:871-6.
125. McPherson C, Lee BR, Terrill C, Hersh AL, Gerber JS, Kronman MP, et al. Characteristics of pediatric antimicrobial stewardship programs: current status of the sharing antimicrobial reports for pediatric stewardship (SHARPS) collaborative. Antibiotics (Basel). 2018;7(1):4.
126. Goldman JL, Newland JG, Price M, Yu D, Lee BR. Clinical impact of an antimicrobial stewardship program on high-risk pediatric patients. Infect Control Hosp Epidemiol. 2019;40:968-73.
127. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51-e77.
128. Newland JG, Hersh AL. Purpose and design of antimicrobial stewardship programs in pediatrics. Pediatr Infect Dis J. 2010;29:862-3.
129. Hersh AL, Newland JG, Gerber JS. Pediatric antimicrobial discharge stewardship: an unmet need. JAMA Pediatr. 2016;170:191-2.
130. Hersh AL, De Lurgio SA, Thurm C, Lee BR, Weissman SJ, Courter JD, et al. Antimicrobial stewardship programs in freestanding children's hospitals. Pediatrics. 2015;135:33-9.
131. Dyar OJ, Beović B, Pulcini C, Tacconelli E, Hulscher M, Cookson B, et al. ESCMID generic competencies in antimicrobial prescribing and stewardship: towards a European consensus. Clin Microbiol Infect. 2019;25:13-9.
132. Tamma PD, Avdic E, Keenan JF, Zhao Y, Anand G, Cooper J, et al. What is the more effective antibiotic stewardship intervention: preprescription authorization or postprescription review with feedback? Clin Infect Dis. 2017;64:537-43.
133. Benić MS, Milanič R, Monnier AA, Gyssens IC, Adriaenssens N, Versporten A, set al. Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. J Antimicrob Chemother. 2018;73 (suppl 6):vi50-vi58.
134. Mostaghim M, Snelling T. Bajorek B. Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data. Pharm Pract (Granada). 2019;17(3):1482.
135. Kreitmeyr K, von Both U, Pecar A, Borde JP, Mikolajczyk R, Huebner J. Pediatric antibiotic stewardship: successful interventions to reduce broad-spectrum antibiotic use on general pediatric wards. Infection. 2017;45:493-504.
136. Hufnagel M, Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H. High rates of prescribing antimicrobials for prophylaxis in children and neonates: results from the antibiotic resistance and prescribing in European children point prevalence survey. J Pediatric Infect Dis Soc. 2019;8:143-51.
137. Chakravorty A, Binder E, Rawlins M, Trevenen M, Ingram PR, McKeogh A, et al. Antibiotic allergy labels and optimal antimicrobial stewardship. Intern Med J. 2020 Aug 3. doi: 10.1111/imj.15003. Online ahead of print.

138. Australian Commission on Safety and Quality in Health Care. Antimicrobial stewardship in the care of children. [Internet]. Sydney: ACSQHC; 2020. Available from https://www.safetyandquality.gov.au/sites/default/files/2020-10/chapter_14_ams_book_paediatric.pdf [accessed December 9, 2021].
139. Wald-Dickler N, Spellberg B. Short-course antibiotic therapy-replacing constantine units with "shorter is better". Clin Infect Dis. 2019;69:1476-9.
140. Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-courseantibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. Pediatric Infect Dis J. 2014;33:136-42.
141. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis. 2016;16(8):e139-52.
142. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD, et al. Comparative effectiveness of antibiotic treatment duration in children with pyelonephritis. JAMA Netw Open. 2020;3(5):e203951.
143. Dagher M, Fowler Jr. VG, Wright PW, Staub MB. A narrative review of early oral stepdown therapy for the treatment of uncomplicated *Staphylococcus aureus* bacteremia: yay or nay? Open Forum Infect Dis. 2020;7(6):ofaa151.
144. Same RG, Hsu AJ, Tamma PD. Optimizing the management of uncomplicated Gram-negative bloodstream infections in children: translating evidence from adults into pediatric practice. J Pediatric Infect Dis Soc. 2019;8:485-88.
145. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis. 2013;57:1237-45.
146. Wabe N, Li L, Lindeman R, Yimsung R, Dahm MR, McLennan S, et al. Impact of rapid molecular diagnostic testing of respiratory viruses on outcomes of adults hospitalized with respiratory illness: a multicenter quasi-experimental study. J Clin Microbiol. 2019;57:1355-6.
147. Pliakos EE, Andreatos N, Shehadeh F, Ziakas PD, Mylonakis E. The cost-effectiveness of rapid diagnostic testing for the diagnosis of bloodstream infections with or without antimicrobial stewardship. Clin Microbiol Rev. 2018;31(3):e00095-17.
148. Alter SJ, Bennett JS, Koranyi K, Kreppel A, Simon R. Common childhood viral infections. Curr Probl Pediatr Adolesc Health Care. 2015;45:21-53.
149. Aguilera-Alonso D, Illán-Ramos M, Daoud Z, Guinea V, Culebras E, Ramos JT. Análisis del impacto de los test de diagnóstico virológico en el consumo de antibióticos en pacientes pediátricos ingresados por neumonía adquirida en la comunidad. Enferm Infecc Microbiol Clin. 2020;38:230-3.
150. Veesenmeyer AF, Olson JA, Hersh AL, Stockmann C, Korgenski K, Thorell EA, et al. A retrospective study of the impact of rapid diagnostic testing on time to pathogen identification and antibiotic use for children with positive blood cultures. Infect Dis Ther. 2016;5:555-70.

151. Reuter CH, Palac HL, Kociolek LK, Zheng XT, Chao YY, Patel RM, et al. Ideal and actual impact of rapid diagnostic testing and antibiotic stewardship on antibiotic prescribing and clinical outcomes in children with positive blood cultures. Pediatr Infect Dis J. 2019;38:131-7.
152. Tran P, Dowell E, Hamilton S, Dolan SA, Messacar K, Dominguez SR, et al. Two blood cultures with age-appropriate volume enhance suspected sepsis decision-making. Open Forum Infect Dis. 2020;7:635-6.
153. Buttery JP. Blood cultures in newborns and children: optimising an everyday test. Arch Dis Child Fetal Neonatal Ed. 2002;87(1):F25-8.
154. Cataldi L, Zaffanello M, Gnarra M, Fanos V, Neonatal Nephrology Study Group of the Italian Society of Neonatology. Urinary tract infection in the newborn and the infant: state of the art. J Matern Fetal Neonatal Med. 2010;23(Suppl 3):90-3.
155. Dik JH, Poelman R, Friedrich AW, Niesters HGM, Rossen JWA, Sinha B. Integrated stewardship model comprising antimicrobial, infection prevention, and diagnostic stewardship (AID Stewardship). J Clin Microbiol. 2017;55:3306-7.
156. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-77.
157. Fishman N. Policy statement on antimicrobial stewardship by the Society of Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33:322-27.
158. Brett A, Bielicki J, Newland JG, Rodrigues F, Schaad UB, Sharland M. Neonatal and pediatric antimicrobial stewardship programs in Europe-defining the research agenda. Pediatr Infect Dis J. 2013;32(12):e456-65.
159. Bielicki J, Lundin R, Patel S, Paulus, s. Antimicrobial stewardship for neonates and children. A global approach. Pediatr Infect Dis J. 2015;34:311-3.
160. Godbout EJ, Pakyz AL, Markley JD, Noda AJ, Stevens MP. Pediatric antimicrobial stewardship: State of the art. Curr Infect Dis Rep. 2018;20(10):39.
161. Holzmann-Pazgal G, Khan AM, Northrup TF, Domonoske C, Eichenwald EC. Decreasing vancomycin utilization in a neonatal intensive care unit. Am J Infect Control. 2015;43:1255-57.
162. Cantey JB, Wozniak PS, Pruszynski JE, Sánchez P. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis. 2016;16:1178-84.
163. Molloy L, McGrath E, Thomas R, Kaye KS, Rybak MJ. Acceptance of pharmacist-driven antimicrobial stewardship recommendations with differening levels of physician involvent in a children´s hospital. Clin Pediatr (Phila). 2017;56:744-51.
164. Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. J Pediatric Infect Dis Soc. 2015;4(4):e127-35.
165. McCulloh RJ, Queen MA, Lee B, Yu D, Stach L, Goldman J, et al. Clinical impact of an antimicrobial stewardship program on pediatric hospitalist practice, a 5-year retrospective analysis. Hosp Pediatr. 2015;5:520-27.

166. Lighter-Fisher J, Desai S, Stachel A, Pham VP, Klejmont L, Dubrovskaya Y. Implementing an inpatient pediatric prospective audit and feedback antimicrobial stewardship program within a larger medical center. Hosp Pediatr. 2017;7:516-22.
167. Hurst Al, Child J, Pearce K, Palmer C, Todd JK, Parker SK. Handshake stewardship highly effective rounding-based antimicrobial optimization service. Pediatr Infect Dis J. 2016;35:1104-10.
168. Willis ZI, Gillon J, Xu M, Slaughter JC, Di Pentima MC. Reducing antimicrobial use in an academic pediatric institution: evaluation of the effectiveness of a prospective audit with real-time feedback. J Pediatric Infect Dis Soc. 2017;6:339-45.
169. Donà D, Zingarella S, Gastldi A, Lundin R, Perilongo G, Frigo AC, et al. Effects of clinical pathway implementation on antibiotic prescriptions for pediatric community-acquired pneumonia. PLoS One. 2018;13:e0193581.
170. Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis. 2017;64:69-73.
171. Gillion J, Xu M, Slaughter J, Di Pentima MC. Vancomycin use: room for improvement among hospitalized children. J Pharm Pract. 2017;30:296-9.
172. Tagashira Y, Yamane N, Miyahara S, Orihara A, Uehara Y, Hiramatsu K, et al. Misuse of discharge antimicrobial prescription in the emergency department: an observational study at a tertiary care center. Open Forum Infect Dis. 2019;6(2):ofz016.
173. Frost HM, Knepper BC, Shihadeh KC, Jenkins TC. A novel approach to evaluate antibiotic utilization across the spectrum of inpatient and ambulatory care and implications for prioritization of antibiotic stewardship efforts. Clin Infect Dis. 2020;70:1675-82.
174. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA. 2016;315:1864–73.
175. Oltra Hostalet F, Núñez-Núñez M, Portillo Cano MDM, Navarro-Bustos C, Rodríguez-Baño J, Retamar Gentil P. Analysis of quality antimicrobial agent use in the emergency department of a tertiary care hospital. Emerergencias. 2018;30:297-302.
176. Santarossa M, Kilber EN, Wenzler E, Albarillo FS, Sterk EJ. BundlED Up: a narrative review of antimicrobial stewardship initiatives and bundles in the emergency department. Pharmacy (Basel). 2019;7(4):145.
177. May L, Cosgrove S, L'Archeveque M, Talan DA, Payne P, Jordan J, et al. A call to action for antimicrobial stewardship in the emergency department: approaches and strategies. Ann Emerg Med. 2013;62(1):69-77.e2.
178. Patel PK. Applying the horizontal and vertical paradigm to antimicrobial stewardship. Infect Control Hosp Epidemiol. 2017;38:532–3.
179. Fitzpatrick F, Tarrant C, Hamilton V, Kiernan FM, Jenkins D, Krockow EM. Sepsis and antimicrobial stewardship: two sides of the same coin. BMJ Qual Saf. 2019;28:758–61.
180. Burillo A, Muñoz P, Bouza E. Risk stratification for multidrug-resistant Gram-negative infections in ICU patients. Curr Opin Infect Dis. 2019;32:626–37.

181. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. 2018;44:925–8.
182. Viale P, Scudeller L, Pea F, Tedeschi S, Lewis R, Bartoletti M, et al. Implementation of a meningitis care bundle in the emergency room reduces mortality associated with acute bacterial meningitis. Ann Pharmacother. 2015;49:978-85.
183. Hortmann M, Heppner HJ, Popp S, Lad T, Christ M. Reduction of mortality in community-acquired pneumonia after implementing standardized care bundles in the emergency department. Eur J Emerg Med. 2014;21:429-35.
184. Praena J, Gil-Navarro MV, Aguilar-Guisado M, Toral J, Montero E, Álvarez-Marín R, et al. Uso de antimicrobianos en urgencias de un hospital: propuesta de un nuevo indicador de consumo y descripción del perfil de prescripción. XX Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Enferm Infecc Microbiol Clin. 2016 May;34 Esp Congr(1):51-2.
185. MacMillan KM, MacInnis M, Fitzpatrick E, Hurley KF, MacPhee S, Matheson K, et al. Evaluation of a pharmacist-led antimicrobial stewardship service in a pediatric emergency department. Int J Clin Pharm. 2019;41:1592–8.
186. Jorgensen SCJ, Yeung SL, Zurayk M, Terry J, Dunn M, Nieberg P, et al. Leveraging antimicrobial stewardship in the emergency department to improve the quality of urinary tract infection management and outcomes. Open Forum Infect Dis. 2018;5(6):ofy101.
187. Yadav K, Meeker D, Mistry RD, Doctor JN, Fleming-Dutra KE, Fleischman RJ, et al. A multifaceted intervention improves prescribing for acute respiratory infection for adults and children in emergency department and urgent care settings. Acad Emerg Med. 2019;26:719–31.
188. Wunderink RG, Waterer DW. Clinical practice. Community-acquired pneumonia. N Engl J Med 2014;370: 543-51.
189. Jain S, Self WH, Wunderink S, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415-27.
190. Viasús D, Milly Vecino-Moreno M, De la Hoz JM, Carratalà J. Antibiotic stewardship in community-acquired pneumonia. Expert Rev Anti Ther. 2017;4:351-9.
191. Metlay JP, Waterer GW, Long AC, Anzueto A, Brocek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America.Am J Respir Crit Care Med. 2019; 200 (7):e45-e67.
192. Arnold FW, LaJoie AS, Brock GN, Peyrani P, Rello J, Menéndez R, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med. 2009;169:1515-24.
193. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DL. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med. 2009;169:1525–31.
194. Wathne JS, Harthug S, Kleppe LKS, The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrob Resist Infect Control. 2019;8:63.

195. Frei CR, Attridge RT, Mortensen EM, Restrepo MI, Yu Y, Oramasionwu CU, et al. Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit. Clin Ther. 2010;32:293–9.
196. Høgli JU, Garcia BH, Skjold F, Skogen V, Småbrekke L. An audit and feedback intervention study increased adherence to antibiotic prescribing guidelines at a Norwegian hospital. BMC Infect Dis. 2016;16:96.
197. McIntosh KA, Maxwell DJ, Pulver LK, Horn F, Robertson MB, Kaye KI, et al. A quality improvement initiative to improve adherence to national guidelines for empiric management of community-acquired pneumonia in emergency departments. Int J Qual Health Care. 2011;23:142-50.
198. Yamana H, Matsui H, Tagami T, Hirashima J, Fushimi K, Yasunaga H. De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia. J Infect. 2016;73:314–25.
199. Khasawneh FA, Karim A, Mahmood T, Ahmed S, Jaffri SF, Mehmood M. Safety and feasibility of antibiotic de-escalation in bacteremic pneumonia. Infect Drug Resist. 2014;7:177–82.
200. Carugati M, Franzetti F, Wiemken T, Kelley RR, Peyrani P, Blasi F, et al. De-escalation therapy among bacteraemic patients with community-acquired pneumonia. Clin Microbiol Infect. 2015;21(10):936.e11-8.
201. Viasus D, Simonetti AF, Garcia-Vidal C, Niubó J, Dorca J, Carratalà J. Impact of antibiotic deescalation on clinical outcomes in community-acquired pneumococcal pneumonia. J Antimicrob Chemother. 2017;72:547-53.
202. Uda A, Tokimatsu I, Koike C, Osawa K, Shigemura K, Kimura T, et al. Antibiotic de-escalation therapy in patients with community-acquired nonbacteremic pneumococcal pneumonia. Int J Clin Pharm. 2019;41:1611-7.
203. Deshpande A, Richter SS, Haessler S, Lindenauer P, Yu PC, Zibelberg MD, et al. De-escalation of empiric antibiotics following negative cultures in hospitalized patients with pneumonia: rates and outcomes. Clin Infect Dis. 2021;72:1314-22.
204. Athanassa Z, Makris G, Dimopoulos G, Falagas ME. Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. Drugs. 2008;68:2469-81.
205. Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med. 2012;172:922-8.
206. Engel MF, Postma DF, Hulscher MEJL, van Berkhout FT, Emmelot-Vonk MH, Sankatsing S, et al. Barriers to an early switch from intravenous to oral antibiotic therapy in hospitalised patients with CAP. Eur Respir J. 2013;41:123-30.
207. Kimura T, Ito M, Onozawa S. Switching from intravenous to oral antibiotics in hospitalized patients with community-acquired pneumonia: a real-world analysis 2010-2018. J Infect Chemother. 2020;26:706-14.

208. Broom J, Broom a, Adams K, Plage S. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. J Antimicrob Chemother. 2016;71:2295-9.
209. Engel MF, Bruns AH, Hulscher MEJL, Gaillard CAJM, Sankatsing SUC, van Berkhout FT, et al. A tailored implementation strategy to reduce the duration of intravenous antibiotic treatment in community-acquired pneumonia: a controlled before-and-after study. Eur J Clin Microbiol Infect Dis. 2014;33:1897-908.
210. Li JZ, Winston LG, Moore DH, Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med. 2007;120:783-90.
211. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos KP, Athanassa Z, Falagas ME. Short versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. Drugs. 2008;68:1841-54.
212. Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. JAMA Intern Med. 2016;176:1257-65.
213. El Moussaoui R, de Borgie CA, van den Broek P, Hustinx WN, Bresser P, van den Berk GEL,et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ 2006; 332(7554):1355.
214. Tansarli GS, Mylonakis E. Systematic review and meta-analysis of the efficacy of short-course antibiotic treatments for community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2018;62(9):e00635-18.
215. Poole S, Clark TW. Rapid syndromic molecular testing in pneumonia: The current landscape and future potential. J Infect. 2020;80:1-7.
216. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2017;10(10):CD007498.
217. Ito A, Ishida T. Diagnostic markers for community-acquired pneumonia. Ann Transl Med. 2020;8(9):609.
218. Flores-Mireles AL, Walker JN, Caparon, M. Hultgren, S. J. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat. Rev. Microbiol. 2015;13:269–84.
219. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68:1611-5.
220. Tandoğdu Z, Bartoletti R, Cai T, Çek M, Grabe M, Kulchavenya E, et al. Antimicrobial resistance in urosepsis: outcomes from the multinational, multicenter global prevalence of infections in urology (GPIU) study 2003-2013. World J Urol. 2016;34:1193-200.
221. De Cueto M, Aliaga L, Alós JI, Canut A, Los-Arcos I, Martínez JA, et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2017;35:314-20.

222. Esteve-Palau E, Grau S, Herrera S, Sorlí L, Montero M, Segura C, et al. Impact of an antimicrobial stewardship program on urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. Rev Esp Quimioter. 2018;31:110-7.
223. Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, et al. Guidelines of the European Association of Urology: Urological Infections 2019. Available at: https://uroweb.org/guideline/urological-infections.[Accessed December 9, 2021].
224. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20.
225. Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary tract infection in male veterans: treatment patterns and outcomes. JAMA Intern Med. 2013;173:62-8.
226. Germanos GJ, Trautner BW, Zoorob RJ, Salemi JL, Drekonja D, Gupta K, et al. No clinical benefit to treating male urinary tract infection longer than seven days: an outpatient database study. Open Forum Infect Dis. 2019;6(6):ofz216.
227. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection– 7 days or less *versus* longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2013;68:2183-91.
228. Erba L, Furlan L, Monti A, Marsala E, Cernuschi G, Solbiati M, et al. Short *vs* long-course antibiotic therapy in pyelonephritis: a comparison of systematic reviews and guidelines for the SIMI choosing wisely campaign. Intern Emerg Med. 2021;16:313-23.
229. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Executive summary: Diagnosis and treatment of catheter-related bloodstream infection: Clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology and (SEIMC)and the Spanish Society of Spanish Society of Intensive and Critical Care Medicine and CoronaryUnits (SEMICYUC). Enferm Infecc Microbiol Clin (Engl Ed). 2018;36:112-9.
230. Hebeisen, U, Babouee Flury B, Atkinson A, Marschall J, Buetti N. Catheter-related bloodstream infections due to coagulase-negative staphylococci managed with catheter removal: recurrences are rare. Am J Infect Control. 2020;48:837-9.
231. Jiménez-Aguilar P, López-Cortés LE, Rodríguez-Baño J. (2019). Impact of infectious diseases consultation on the outcome of patients with bacteraemia. Ther Adv Infect Dis. 2019;6:2049936119893576.
232. Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al. Association of 30-day mortality with oral step-down vs continued intravenous therapy in patients hospitalized with *Enterobacteriaceae* bacteremia. JAMA Intern Med. 2019;179:316-23.
233. Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven *versus* 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis. 2019; 69:1091-8.
234. López-Cortés LE, Del Toro MD, Gálvez-Acebal J, Bereciartua-Bastarrica E, Fariñas MC, Sanz-Franco M, et al. Impact of an evidence-based bundle intervention in the quality-of-care

management and outcome of Staphylococcus aureus bacteremia. Clin Infect Dis. 2013;57:1225-33.

235. Pérez-Rodríguez MT, Sousa A, López-Cortés LE, Martínez-Lamas L, Val N, Baroja A, et al. Moving beyond unsolicited consultation: additional impact of a structured intervention on mortality in *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother. 2019;74:1101-7.
236. European Centre for Disease Prevention and European Centre for Disease Prevention and Control. Healthcare-associated infections: surgical site infections. In: ECDC. Annual epidemiological report for 2017. Stockholm, ECDC; October 2019. https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-surgical-site-infections-annual-1
237. Del Toro López MD, Arias Díaz J, Balibrea JM, Benito N, Canut Blasco A, Esteve E, et al. Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Association of Surgeons (AEC) in antibiotic prophylaxis in surgery. Enferm Infecc Microbiol Clin (Engl Ed). 2021;39:29-40.
238. Sartelli M, Labricciosa FM, Barbadoro P, Pagani L, Ansaloni L, Brink AJ, et al. The global alliance for infections in surgery: defining a model for antimicrobial stewardship-results from an international cross-sectional survey. World J Emerg Surg. 2017;12:1–11.
239. Bowater RJ, Stirling SA, Lilford RJ. Is antibiotic prophylaxis in surgery a generally effective intervention?: testing a generic hypothesis over a set of meta-analyses. Ann Surg. 2009;249:55-6.
240. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;14:73-156.
241. European Centre for Disease Prevention and Control (ECDC). Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis. Stockholm, ECDC; June 2013. https://www.ecdc.europa.eu/en/publications-data/systematic-review-and-evidence-based-guidance-peri-operative-antibiotic
242. Ierano C, Thursky K, Marshall C, Koning S, James R, Johnson S, et al. Appropriateness of surgical antimicrobial prophylaxis practices in Australia. JAMA Netw Open. 2019;2(11):e1915003.
243. Plachouras D, Kärki T, Hansen S, Hopkins S, Lyytikäinen O, Moro ML, et al. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. Euro Surveill. 2018;23:1800393.
244. Koek MBG, Hopmans TEM, Soetens LC, Wille JC, Geerlings SE, Vos MC, et al. Adhering to a national surgical care bundle reduces the risk of surgical site infections. PLoS One. 2017;12(9):e0184200.
245. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of duration and type of surgical prophylaxis with antimicrobial-associated adverse events. JAMA Surg. 2019;154:590-8.
246. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e288–303.
247. Mohamed R, Wall J, Arumainathan R, Fink D, Sandhu T, Garg S, et al. Assessing antibiotic stewardship using the surgical site infection prevention bundle. Br J Hosp Med (Lond). 2018;79:643–7.

248. Kamarudin G, Penm J, Chaar B, Moles R. Educational interventions to improve prescribing competency: a systematic review. BMJ Open. 2013;3(8):e003291.
249. Mouwen AMA, Dijkstra JA, Jong E, Buijtels PCAM, Pasker-de Jong PCM, Nagtegaal JE. Early switching of antibiotic therapy from intravenous to oral using a combination of education, pocket-sized cards and switch advice: a practical intervention resulting in reduced length of hospital stay. Int J Antimicrob Agents. 2020;55(1):105769.
250. Bupha-Intr O, Blackmore T, Bloomfield M. Efficacy of early oral swich with beta-lactams for low-risk *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother. 2020;64(7):e02345-19.
251. Gasparetto J, Tuon FF, Dos Santos Oliveira D, Zequinao T, Rammert-Pipolo G, Velloso-Ribeiro G, et al. Intravenous-to-oral antibiotic switch therapy: a cross-sectional study in critical care units. BMC Infect Dis. 2019;19(1):650.
252. Beyene Beerha A, Molla Kassie G. Current practice and barriers to an early antimicrobial conversion from intravenous to oral among hospitalized patients at Jimma University Specialized Hospital: prospective observational study. Interdiscip Perspect Infect Dis. 2019;2019:7847354.
253. Zhang L, Huang Y, Zhou Y, Buckley T, Wang HH. Antibiotic administration routes significantly influence the levels of antibiotic resistance in gut microbiota. Antimicrob Agents Chemother. 2013;57:3659-66.
254. Catry B, Latour K, Bruyndonckx, R, Diba C, Geerdens C, Coenen S. Characteristics of the antibiotic regimen that affect antimicrobial resistance in urinary pathogens. Antimicrob Resist Infect Control. 2018;7:76.
255. Sullivan O, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis. 2001;1:101-14.
256. Edlund C, Nord CE. Effect of the human normal microflora of oral antibiotics for treatment of urinary tract infections. J Antimicrob Chemother. 2000;46(Suppl 1):41-8.
257. Bassetti M, Vena A, Castaldo N, Righi E, Peghin M. New antibiotics for ventilator-associated pneumonia. Curr Opin Infect Dis. 2018;31:177-86.
258. Benítez-Cano A, Luque S, Sorlí L, Carazo J, Ramos I, Campillo N, et al. Intrapulmonary concentrations of meropenem administered by continuous infusion in critically ill patients with nosocomial pneumonia: a randomized pharmacokinetic trial. Crit Care. 2020;24(1):55.
259. Shatsky M. Evidence for the use of intramuscular injections in outpatient practice. Am Fam Physician. 2009;79:297-300.
260. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009;23:791-815.
261. Khan SA, Waqas M, Siddiqui UT, Shamim MS, Nathani KR, Jooma R, et al. Intrathecal and intraventricular antibiotics for postoperative Gram-negative meningitis and ventriculitis. Surg Neurol Int. 2017;8:226.
262. Chusri S, Sakarunchai I, Kositpantawong N, Panthuwong S, Santimaleeworagun W, Pattharachayakul S, et al. Outcomes of adjunctive therapy with intrathecal or intraventricular administration of colistin for post-neurosurgical meningitis and ventriculitis due to carbapenem-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents. 2018;51:646-50.

263. Khawcharoenpom T, Apisarnthanarak A, Mundy LM. Intrathecal colistin for drug-resistant *Acinetobacter baumannii* central nervous system infection: a case series and systematic review. Clin Microbiol Infect. 2010;16:888-94.
264. Collin E, Baldolli A, Verdon R, Saint-Lorant G. Subcutaneously administered antibiotics. Med Mal Infect. 2020;50:231-42.
265. Roberts JA, Webb S, Paterson D, Ho KM, Lipman J. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med. 2009;37:2071-8.
266. van Zanten AR. The jury is still out on continuous infusion of beta-lactam antibiotics in intensive care patients. Crit Care Med. 2009;37:2137-8.
267. Shiu_J, Wang E, Tejani AM, Wasdell M. Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev. 2013;(3):CD008481.
268. Kuti JL, Dandekar PK, Nightingale CH, Nicolau DP. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J Clin Pharmacol. 2003;43:1116-23.
269. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipaman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother. 2009;64:142-50.
270. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis. 2013;56:272-82.
271. Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, et al. Continuous versus intermittent β-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med. 2016;194:681-91.
272. Yu Z, Pang X, Wu X, Shan C, Jiang S. Clinical outcomes of prolonged infusion (extended infusion or continuous infusion) versus intermittent bolus of meropenem in severe infection: A meta-analysis. PLoS ONE 2018;13(7):e0201667.
273. Adembri C, Fallani S, Cassetta MI, Arrigucci S, Ottaviano A, Pecile P, et al. Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. Int J Antimicrob Agents. 2008;31:122-9.
274. De Pascale G, Fortuna S, Tumbarello M, Cutuli SL, Vallecoccia M, Spanu T, et al. Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator- associated pneumonia: intermittent *vs* continuous administration. Intensive Care Med. 2015;41:103-10.
275. Vu DH, Nguyen DA, Delaltre IK, Ho TT, Do HG, Pham HN, et al. Determination of optimal loading and maintenance doses for continuous infusion of vancomycin in critically ill patients: population pharmacokinetic modelling and simulations for improved dosing schemes. Int J Antimicrob Agents. 2019;54:702-8.
276. Chu Y, Luo Y, Quan X, Jiang M, Zhou B. Intermittent *vs*. continuous vancomycin infusion for Gram-positive infections: a systematic review and meta-analysis. J Infect Public Health. 2020;13:591-7.

277. Gómez-Baraza C, Agustín-Fernández MJ, Palomo-Jiménez PI, Real-Campaña JM, Abad-Sazatornil R. Intravenous drugs infusion safety through smart pumps. Farm Hosp. 2014;38:276-82.
278. Voumard R, Gardiol C, André P, Arensdorff L, Cochet C, Boillat-Blanco N, et al. Efficacy and safety of continuous infusions with elastomerics pumps for outpatient parenteral antimicrobial therapy (OPAT). J Antimicrob Chemother. 2018;73:2540-5.
279. Candel FJ, Julián-Jiménez A, González-Del Castillo J. Current status in outpatient parenteral antimicrobial therapy: a practical view. Rev Esp Quimioter. 2016;29:55-68.
280. Rout J, Essack S, Brysiewicz P. Are nursing infusion pratices delivering full-dose antimicrobial treatment? J Antimicrob Chemother. 2019;74:3418-22.
281. Pani A, Colombo F, Agnelli F, Frantellizzi V, Baratta F, Pastori D, et al. Off-label use of ceftaroline fosamil: a systematic review. Int J Antimicrob Agents. 2019; 54:562-71.
282. Lupia T, Pallotto C, Corcione S, Boglione L, De Rosa FG. Ceftobiprole perspective: current and potential future indications. Antibiotics (Basel). 2021;10(2):170.
283. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018;18:285-95.
284. Kollef MH, Nováček M, Kivistik Ü, Réa-Neto Á, Shime N, Martin-Loeches I, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2019;19:1299-1311.
285. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, et al. Imipenem-relebactam and meropenem-vaborbactam: two novel carbapenem-β-lactamase inhibitor combinations. Drugs. 2018;78:65-98.
286. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and *in vivo* profiles of a novel siderophore cephalosporin. Clin Infect Dis. 2019;69(Suppl 7):S538-S543.
287. Tulkens PM, Van Bambeke F, Zinner SH. Profile of a novel anionic fluoroquinolone-delafloxacin. Clin Infect Dis. 2019;68(Suppl 3):S213-S222.
288. Kaasch AJ, Seifert H. Oritavancin: a long-acting antibacterial lipoglycopeptide. Future Microbiol. 2016;11:843-55.
289. Van Hise N, Petrak RM, Skorodin NC, Fliegelman RM, Anderson M, Didwania V, et al. A real-world assessment of clinical outcomes and safety of eravacycline: a novel fluorocycline. Infect Dis Ther. 2020;9:1017-28.
290. Papadimitriou-Olivgeris M, Bartzavali C, Lambropoulou A, Solomou A, Tsiata E, Anastassiou ED, et al. Reversal of carbapenemase-producing *Klebsiella pneumoniae* epidemiology from blaKPC- to blaVIM-harbouring isolates in a Greek ICU after introduction of ceftazidime/avibactam. Antimicrob Chemother. 2019;74:2051-4.
291. Fraile-Ribot PA, Cabot G, Mulet X, Periañez L, Martín-Pena ML, Juan C, et al. Mechanisms leading to *in vivo* ceftolozane/tazobactam resistance development during the treatment of infections caused by MDR *Pseudomonas aeruginosa*. J Antimicrob Chemother. 2018;73:658-66.
292. Rodríguez-Núñez O, Periañez-Parraga L, Oliver A, Munita JM, Boté A, Gasch O, et al. Higher MICs (>2 mg/L) predict 30-day mortality in patients with lower respiratory tract infections caused

by multidrug- and extensively drug-resistant *Pseudomonas aeruginosa* treated with ceftolozane/tazobactam. Open Forum Infect Dis. 2019;6(10):ofz416.

293. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, et al. Emergence of ceftazidime-avibactam resistance due to plasmid-borne bla(KPC-3) mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother. 2017;61(3):e02097-16.
294. Escolà-Vergé L, Pigrau C, Los-Arcos I, Arévalo Á, Viñado B, Campany D, et al. Ceftolozane/tazobactam for the treatment of XDR *Pseudomonas aeruginosa* infections. Infection. 2018;46:461-8.
295. Tyler LS, Coler SW, May JR, Millares M, Valentino MA, Vermeulen Jr, LC, et al. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. Am J Health Syst Pharm. 2008;65:1272-83.
296. Durán-García E, Santos-Ramos B, Puigventós-Latorre F, Ortega A. Literature review on the structure and operation of pharmacy and therapeutics Committees. Int J Clin Pharm. 2011;33:475-83.
297. World Health Organization. The WHO essential medicines and health products information portal. Drug and therapeutics committees 2003. https://apps.who.int/medicinedocs/en/d/Js4882e/6.html (Accessed December 9, 2021).
298. Sofat R, Cremers S, Ferner RE. Drug and therapeutics committees as guardians of safe and rational medicines use. Br J Clin Pharmacol. 2020;86:10-12.
299. European Commission. EU Guidelines for the prudent use of antimicrobials in human health (2017/C 212/01) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52017XC0701(01)&from=ET (Accessed December 9, 2021).
300. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18:318-27.
301. Palacios-Baena Z, Valiente de Santis L, Maldonado N, Rosso-Fernández C, Borreguero I, Herrero-Rodríguez C, et al. Quasiexperimental intervention study protocol to optimise the use of new antibiotics in Spain: the NEW_SAFE Project. BMJ Open. 2020;10(7):e035460.
302. Lorencatto F, Charani E, Sevdalis N, Tarrant C, Davey P. Driving sustainable change in antimicrobial prescribing practice: How can social and behavioural sciences help? J Antimicrob Chemother. 2018;73:2613-24.
303. Davey P, Marwick C, Scott C, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2(2):CD003543.
304. Davey P, Peden C, Charani E, Marwick C, Michie S. Time for action - Improving the design and reporting of behaviour change interventions for antimicrobial stewardship in hospitals: Early findings from a systematic review. Int J Antimicrob Agents. 2015;45:203-12.
305. Donisi V, Sibani M, Carrara E, Del Piccolo L, Rimondini M, Mazzaferri F, et al. Emotional, cognitive and social factors of antimicrobial prescribing: can antimicrobial stewardship

intervention be effective without addressing psycho-social factors? J Antimicrob Chemother. 2019;74:2844-7.

306. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.
307. Steinmo S, Fuller C, Stone SP, Michie S. Characterising an implementation intervention in terms of behaviour change techniques and theory: The "Sepsis Six" clinical care bundle. Implement Sci. 2015;10:111.
308. Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, et al. A checklist for identifying determinants of practice: A systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Implement Sci. 201;8:35.
309. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46:81-95.
310. Nudge theory - Wikipedia. Available from: https://en.wikipedia.org/wiki/Nudge_theory (Accessed December 9, 2021).
311. Spellberg B. Antibiotic judo: working gently with prescriber psychology to overcome inappropriate use. JAMA Intern Med. 2014;174:432-3.
312. Thaler R, Sunstein C. Nudge: improving decisions about health, wealth, and happiness. New Haven, CT: Yale University Press; 2008. Available from: https://books.google.com/books?id=dSJQn8egXvUC (Accessed December 9, 2021).
313. Leis JA, Rebick GW, Daneman N, Gold WL, Poutanen SM, Lo P, et al. Reducing antimicrobial therapy for asymptomatic bacteriuria among noncatheterized inpatients: A proof-of-concept study. Clin Infect Dis. 2014;58:980–3.
314. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350:h1258.
315. Boyles TH, Whitelaw A, Bamford C, Moodley M, Bonorchis K, Morris V, et al. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. PLoS One. 2013;8(12):e79747.
316. Molina J, Peñalva G, Gil-Navarro MV., Praena J, Lepe JA, Pérez-Moreno MA, et al. Long-term impact of an educational antimicrobial stewardship program on hospital-acquired candidemia and multidrug-resistant bloodstream infections: a quasi-experimental study of interrupted time-series analysis. Clin Infect Dis. 2017;65:1992-9.
317. So M, Morris AM, Nelson S, Bell CM, Husain S. Antimicrobial stewardship by academic detailing improves antimicrobial prescribing in solid organ transplant patients. Eur J Clin Microbiol Infect Dis. 2019;38:1915-23.
318. Dull D, Baird SK, Dulac J, Fox L. Improving prophylactic perioperative antibiotic utilization in a hospital system. J Healthc Qual. 2008;30:48-56.

319. Hulgan T, Rosenbloom ST, Hargrove F, Talbert DA, Arbogast PG, Bansal P, et al. Oral quinolones in hospitalized patients: an evaluation of a computerized decision support intervention. J Intern Med. 2004;256:349-57.
320. Peto Z, Benko R, Matuz M, Csullog E, Molnar A, Hajdu E. Results of a local antibiotic management program on antibiotic use in a tertiary intensive care unit in Hungary. Infection. 2008;36:560-4.
321. Bremmer DN, Trienski TL, Walsh TL, Moffa MA. Role of technology in antimicrobial stewardship. Med Clin North Am. 2018;102:955-63.
322. Carracedo-Martinez E, Gonzalez-Gonzalez C, Teixeira-Rodrigues A, Prego-Dominguez J, Takkouche B, Herdeiro MT, et al. Computerized clinical decision support systems and antibiotic prescribing: a systematic review and meta-analysis. Clin Ther. 2019;41:552-581.
323. Baysari MT, Lehnbom EC, Li L, Hargreaves A, Day RO, Westbrook JI. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: a systematic review and meta-analysis. Int J Med Inform. 2016;92:15-34.
324. Curtis CE, Al Bahar F, Marriott JF. The effectiveness of computerised decision support on antibiotic use in hospitals: a systematic review. PLoS One. 2017;12(8):e0183062.
325. Micallef C, Chaudhry NT, Holmes AH, Hopkins S, Benn J, Franklin BD. Secondary use of data from hospital electronic prescribing and pharmacy systems to support the quality and safety of antimicrobial use: a systematic review. J Antimicrob Chemother. 2017;72:1880-5.
326. Doukas FF, Cheong E, McKew G, Gray T, McLachlan AJ, Gottlieb T. Antimicrobial stewardship audit and feedback rounds: moving beyond the restricted antibiotic list and the impact of electronic systems. Intern Med J. 2021;51:1876-83.
327. López-Medrano F, Moreno-Ramos F, de Cueto M, Mora-Rillo M, Salavert M. How to assist clinicians in improving antimicrobial prescribing: tools and interventions provided by stewardship programs. Enferm Infecc Microbiol Clin. 2013;31(Suppl 4):38-44.
328. Kirkendall ES, Kouril M, Dexheimer JW, Courter JD, Hagedorn P, Szczesniak R, et al. Automated identification of antibiotic overdoses and adverse drug events via analysis of prescribing alerts and medication administration records. J Am Med Inform Assoc. 2017;24:295-302.
329. Cresswell K, Mozaffar H, Shah S, Sheikh A. Approaches to promoting the appropriate use of antibiotics through hospital electronic prescribing systems: a scoping review. Int J Pharm Pract. 2017;25:5-17.
330. Lee F, Kuper KM. Informatics and stewardship. In: Practical implementation of an antibiotic stewardship program. 1st ed. Cambridge University Press; 2018. pp. 206-19.
331. Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, et al. A computer-assisted management program for antibiotics and other antiinfective agents. N Engl J Med. 1998;338:232-8.
332. Rhoads DD, Sintchenko V, Rauch CA, Pantanowitz L. Clinical microbiology informatics. Clin Microbiol Rev. 2014;27:1025-47.
333. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the microbiology laboratory can right the ship. Clin Microbiol Rev. 2016;30:381-407.

334. Passerini R, Biffi R, Riggio D, Pozzi S, Sandri M. Laboratory-based management of microbiological alerts: effects of an automated system on the surveillance and treatment of nosocomial infections in an oncology hospital. Ecancermedicalscience. 2009;3:137.
335. Young HL, Shihadeh KC, Skinner AA, Knepper BC, Sankoff J, Voros J, et al. Implementation of an institution-specific antimicrobial stewardship smartphone application. Infect Control Hosp Epidemiol. 2018;39:986-8.
336. Morales A, Campos M, Juarez JM, Canovas-Segura B, Palacios F, Marin R. A decision support system for antibiotic prescription based on local cumulative antibiograms. J Biomed Inform. 2018;84:114-22.
337. Kuper KM, Hamilton KW. Collaborative antimicrobial stewardship: working with information technology. Infect Dis Clin North Am. 2020;34:31-49.
338. Fernández-Urrusuno R, Meseguer CM, Benavente RS, Hevia E, Martino CS, Aldasoro AI, et al. Successful improvement of antibiotic prescribing at primary care in Andalusia following the implementation of an antimicrobial guide through multifaceted interventions: An interrupted time-series analysis. PLoS One. 2020;15(5):e0233062.
339. Fleet E, Rao GG, Patel B, Cookson B, Charlett A, Bowman C, et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing homes: a prospective cluster randomized control pilot study. J Antimicrob Chemother. 2014;69:2265-73.
340. Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA. 2013;309:2345-52.
341. Pasay DK, Guirguis MS, Shkrobot RC, Slobodan JP, Wagg AS, Sadowski CA, et al. Antimicrobial stewardship in rural nursing homes: impact of interprofessional education and clinical decision tool implementation on urinary tract infection treatment in a cluster randomized trial. Infect Control Hosp Epidemiol. 2019;40:432-7.
342. Gulliford MC, Juszczyk D, Prevost AT, Soames J, McDermott L, Sultana K, et al. Electronically delivered interventions to reduce antibiotic prescribing for respiratory infections in primary care: cluster RCT using electronic health records and cohort study. Health Technol Assess. 2019;23:1-70.
343. Carvalho É, Estrela M, Zapata-Cachafeiro M, Figueiras A, Roque F, Herdeiro MT. E-health tools to improve antibiotic use and resistances: a systematic review. Antibiotics (Basel). 2020;9(8):505.
344. Pisano J, Pettit N, Bartlett A, Bhagat P, Han Z, Liao C, et al. (2016). Social media as a tool for antimicrobial stewardship. Am J Infect Control. 2016;44:1231-6.
345. Messacar K, Parker SK, Todd JK, Dominguez SR. Implementation of rapid molecular infectious disease diagnostics: the role of diagnostic and antimicrobial stewardship. J Clin Microbiol. 2017;55:715-23.
346. Dyar OJ, Moran-Gilad J, Greub G, Pulcini C. Diagnostic stewardship: are we using the right term? Clin Microbiol Infect. 2019;25:272–3.
347. Bou G, Cantón R, Martínez-Martínez L, Navarro D, Vila J. Fundamentals and implementation of microbiological diagnostic stewardship programs. Enferm Infecc Microbiol Clin (Engl Ed). 2021;39:248-51.

348. Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gilligan PH, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67(6):e1-e94.
349. Kim J, Craft DW, Katzman M. Building an antimicrobial stewardship program: cooperative roles for pharmacists, infectious diseases specialists, and clinical microbiologists. Lab Med. 2015;46(3):e65–71.
350. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis. 2014;59(Suppl 3):S134-45.
351. Gimeno Cardona C, Gómez E, Leiva J, Navarro D. Evaluación económica de las pruebas diagnósticas en Microbiología Clínica. 2018. 64. Navarro D (coordinador). Procedimientos en Microbiología Clínica. Cercenado Mansilla E, Cantón Moreno R (editores). Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), 2018.
352. Patel R, Fang FC. Diagnostic stewardship: opportunity for a laboratory-infectious diseases partnership. Clin Infect Dis. 2018;67:799-801.
353. Pulcini C. Antibiotic stewardship: update and perspectives. Clin Microbiol Infect. 2017;23:791–2.
354. Malcolmson C, Ng K, Hughes S, Kissoon N, Schina J, Tilley PA, et al. Impact of matrix-assisted laser desorption and ionization time-of-flight and antimicrobial stewardship intervention on treatment of bloodstream infections in hospitalized children. J Pediatric Infect Dis Soc. 2017;6:178-86.
355. She RC, Bender JM. Advances in rapid molecular blood culture diagnostics: healthcare impact, laboratory implications, and multiplex technologies. J Appl Lab Med. 2019;3:617-30.
356. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis. 2017;64:15–23.
357. Monard C, Pehlivan J, Auger G, Alviset S, Tran Dinh A, Duquaire P, et al. Multicenter evaluation of a syndromic rapid multiplex PCR test for early adaptation of antimicrobial therapy in adult patients with pneumonia. Crit Care. 2020;24(1):434.
358. Beganovic M, McCreary EK, Mahoney MV, Dionne B, Green DA, Timbrook TT. Interplay between rapid diagnostic tests and antimicrobial stewardship programs among patients with bloodstream and other severe infections. J Appl Lab Med. 2019;3:601-16.
359. Bouza E, Muñoz P, Burillo A. Role of the clinical microbiology laboratory in antimicrobial stewardship. Med Clin North Am. 2018;102:883-98.
360. Bouza E, Sousa D, Munoz P, Rodriguez-Creixems M, Fron C, Lechuz JG. Bloodstream infections: a trial of the impact of different methods of reporting positive blood culture results. Clin Infect Dis. 2004;39:1161-9.
361. Kjærsgaard M, Leth RA, Udupi A, Ank N. Antibiotic stewardship based on education: minor impact on knowledge, perception and attitude. Infect Dis (Lond). 2019;51:753-63.
362. European Centre for Disease Prevention and Control. Proposals for EU guidelines on the prudent use of antimicrobials in humans. EU: Publications Office; 2017. Available from: https://data.europa.eu/doi/10.2900/9621 [Accessed Dec 9, 2021].

363. Coupat C, Pradier C, Degand N, Hofliger P, Pulcini C. Selective reporting of antibiotic susceptibility data improves the appropriateness of intended antibiotic prescriptions in urinary tract infections: a case-vignette randomised study. Eur J Clin Microbiol Infect Dis. 2013;32:627-36.
364. Graham M, Walker DA, Haremza E, Morris AJ. RCPAQAP audit of antimicrobial reporting in Australian and New Zealand laboratories: opportunities for laboratory contribution to antimicrobial stewardship. J Antimicrob Chemother. 2019;74:251-5.
365. Hughes SJ, Moore LS. Antimicrobial stewardship. Br J Hosp Med (Lond). 2019;80(3):C42-C45.
366. Okumura LM, da Silva MMG, Veroneze I. Effects of a bundled antimicrobial stewardship program on mortality: a cohort study. Braz J Infect Dis. 2015;19:246-52.
367. Akhloufi H, Verhaegh SJC, Jaspers MWM, Melles DC, van der Sijs H, Verbon A. A usability study to improve a clinical decision support system for the prescription of antibiotic drugs. PLoS One. 2019;14(9):e0223073.
368. Oteo-Iglesias J. Vigilancia activa de la resistencia a antibióticos. Enferm Infec Microbiol Clin. 2019;37:26-31.
369. Levy Hara G, Kanj SS, Pagani L, Abbo L, Endimiani A, Wertheim HFL, et al. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. Int J Antimicrob Agents. 2016;48:239-46.

Table 1. Studies reporting results of antimicrobial stewardship interventions in Critical Care Units.

Reference	Type of ICU, no. of beds	No. of patients and population characteristics	Study design and intervention	Duration of intervention	Outcomes	Results and comments
34	Medical 24-beds	282 prescriptions; 182 patients Patients receiving antibiotics	Before (retrospective) - after (prospective) PAIF[a]	2 years	Antimicrobial consumption Patient´s safety Rate of multidrug-resistant organisms Healthcare costs	Decrease of antimicrobial consumption including broad-spectrum antibiotics No patient safety events Decrease of MDR *A baumannii* and MRSA rates. No effect on multidrug-resistant *K. pneumoniae* (concomitant outbreak)
39	Cardio-thoracic 11 beds	37 patients Bloodstream infection	Before-after. Rounds with a clinical microbiologist (5 days per week)	4-year period	Length of mechanical ventilation and ICU stay Occurrence of acute kidney injury 30-day mortality	Significant improvement of appropriate empirical treatments, compliance with guidelines, number of de-escalations; decrease in time to optimization of antimicrobial therapy
40	Medical 10 beds	81 prescriptions Empiric antibiotic therapy courses	Interrupted time series analysis. 3-weekly rounds with an infectious diseases specialist, interactive teaching courses, daily contact with microbiologist	5-month	Changes in the level and/or linear trend of the prevalence of appropriate antibiotic therapies around day 3	The intervention triggered a more frequent reassessment of the diagnosis between day 2 and day 4 and slightly improved the adaptation of antibiotic therapies to

						positive microbiology
41	Medical, surgical	196 patients Patients receiving imipenem or piperacillin-tazobactam	Before-after. PAIF[a]; [e]valuation by an Infectious Diseases physician; a pharmacist communicated the recommendations	Feb- May 2006 Oct 2006-Jul-2008 Sep-2008 Feb-2009	Mortality Emergence of resistance Appropriate antimicrobial selection Length of stay	Improvement of appropriate antimicrobial selection and prevention of resistance
42	Medical, surgical, burns, cardiovascular, surgery 48 beds	4697 patients on day 3 or 10 of broad-spectrum antibiotics	Interrupted time series analysis. PAIF; reviewed by the senior Infectious Diseases pharmacist for optimization	1 year	Broad-spectrum and overall antibiotic use Gram-negative susceptibility *C. difficile* rate Length of stay, mortality	Reduction in the use of broad-spectrum antimicrobial agents Decrease in incidence of nosocomial *C. difficile* infections Increase in gram negative susceptibility to meropenem
43	Surgical 12 beds	2,422 patients (all admissions)	Before-after Antimicrobial stewardship programme with a procalcitonin guided protocol	2010-2012	Antibiotic use density Changes in antibiotic classes	Decrease in total antibiotic use density Change in the spectrum of antibiotics No impact on clinical variables
44	Medical and surgical 16-beds	269 patients. Positive microbial cultures, and receiving antimicrobials	Before-after Education, expert consultation, PAIF[a]	4 months	Decision to treat cultures from sterile sites compared with nonsterile sites Documentation of antimicrobial use	A significant increase in the treatment of sterile-site cultures and reduction in the treatment of nonsterile-site cultures. Increased explicit antimicrobial regimen documentation in formally documented stop dates and regimen de-escalation

45	Medical, surgical 12 beds	142 prescriptions Patients receiving antibiotics	Before-after PAIF[a]	3 months	The cost and utilization of antimicrobials Hospital-acquired *C. difficile* rates	Reduction in the cost of antimicrobial drugs. Decrease in the use of broad-spectrum antipseudomonal antimicrobial agents No differences in hospital-acquired *C. difficile*, mortality rates or severity of illness.
46	Medical 24 beds	246 patients. Patients receiving antibiotics	Before (retrospective) - after (prospective) PAIF[a]	6 months	Guidelines compliance Antimicrobial expenditure Healthcare costs	Higher guideline compliance; decrease in antibiotic use (included broad-spectrum) Reduction in mechanical ventilation duration, length of stay and hospital mortality Reduction in healthcare costs
47	18 neds Medical and surgical	5002 patients All admitted patients	Before (retrospective) - after (prospective) PAIF[a]	*9 years*	Antimicrobial consumption Antimicrobial costs	Decrease of antimicrobial consumption Cost savings (up to one million euros)
48	25 beds Medical and surgical, surgical and trauma	2717 patients All admitted patients	Before (retrospective) - after (prospective) PAIF[a]	2 years	Antimicrobial consumption Patient´s safety Rate of multidrug-resistant *E coli* and *P aeruginosa*	Decrease in antimicrobial consumption No patient safety events No effect on *E coli* and *P aeruginosa* resistance patterns

[a]PAIF: prospective audit with intervention and feedback

TABLE 2. Effective minimum total antibiotic duration for frequent uncomplicated pediatric infectious diseases.

Diagnosis*	**Days**	**Comments**
Acute bacterial pharyngitis	10	5-7 days might be sufficient if eradication of *S. pyogenes* is not mandatory
Acute bacterial sinusitis	10	
Community-acquired pneumonia	5	
Ventilator-associated pneumonia	7-8	10 days if *Pseudomonas* spp. or *Acinetobacter* spp.
Pyelonephritis	7-10	10 days for children < 6 months old
Cellulitis	5-7	7-10 days if preseptal cellulitis
Septic arthritis	14-21	
Acute osteomyelitis	21-28	
Staphylococcus epidermidis bacteraemia	5-7	
Gram-negative bacteraemia	7-10	

*Otitis media is not included as antibiotics are not systematically needed

TABLE 3. Quality indicators in surgical antimicrobial prophylaxis (SAP).

Indicator	**Formula**
Proportion of adherence to appropriate indication of SAP, selection and dosage of SAP according to protocol	No. of interventions in which SAP was administered among those with indication /No. of all surgeries in which SAP was indicated x100 No. of interventions in which SAP was administered among those without indication/ No. of all surgeries in which SAP was not indicated x100
Proportion of adherence to drug and dosing in SAP	No. of surgeries with appropriate choice of drug and dose for SAP/No. of surgeries in which SAP was administered x 100
Proportion of adherence to the appropriate timing for administration of SAP	No. of intervention with SAP administered within 60 minutes before incision/No. of interventions in which SAP was administered x 100
Proportion of adherence to appropriate duration of SAP	No. of interventions in which SAP had ana appropriate duration according to local protocol/ No. of interventions in which SAP was administered X 100

In all cases, a selected representative sample of interventions can be used.

TABLE 4. Recently approved antimicrobials in Europe

Drug Name	Spectrum	Dose	Approved Indications*	Comments
Ceftaroline	Gram-positives (including multidrug-resistant *S. pneumoniae,* MRSA), Gram-negative species (*Haemophilus* spp., *Moraxella catarrhalis,* Enterobacterales)	600 mg/12 h	SSTI CAP	For off-label use in MRSA bacteremia and VAP, 600 mg iv/8 h is recommended Not active against Enterobacterales producing ESBL, AmpC or carbapenemases
Ceftobiprole	Gram-positives (including multidrug-resistant *S. pneumoniae*, MRSA) Gram-negative species (*Haemophilus* spp., *Moraxella catarrhalis*, Enterobacterales, *Pseudomonas aeruginosa*)	500 mg/8 h 0.5 g x 3 iv over 2 hours	CAP HAP (excluding VAP)	Not active against Enterobacterales and *P. aeruginosa* producing ESBL, AmpC and carbapenemases
Ceftolozane + tazobactam	Gram-negatives (Enterobacterales including ESBL- and AmpC producers, *Pseudomonas aeruginosa)* Limited activity against anaerobes, Gram-positive cocci, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, Enterobacterales producing AmpC, carbapenemases, or metallo-β-lactamases.	1.5 g IV/8h (1 g ceftolozane /500 mg tazobactam) for UTI, IAI 3 g IV/8h (2 g ceftolozane/1 g tazobactam) for HAP/VAP	Complicated UTI Complicated IAI Pyelonephritis HAP/VAP	Active against *P. aeruginosa* expresing efflux pumps
Ceftazidime + avibactam	Gram-negatives including Enterobacterales producing ESBL, KPC, AmpC, and several class D β-lactamases, and *Pseudomonas aeruginosa* Limited activity against anaerobes, Gram-positives cocci, *Acinetobacter* spp., *Stenotrophomonas*	2.5 g IV/8 (2 g ceftazidime/ 1 g avibactam)	Complicated UTI Complicated IAI Pyelonephritis HAP/VAP	

	maltophilia, Enterobacterales producing AmpC, carbapenemases, or metallo-β-lactamases.			
Meropenem-vaborbactam	Same activity as meropenem plus KPC producing Enterobacterales. Not active against OXA-48 or metallo-beta-lactamase producing Enterobacterales	4 g IV/8h (2 g meropenem/ 2 g vaborbactam)	Complicated UTI Complicated IAI Pyelonephritis HAP/VAP Infections due to aerobic Gram-negatives with limited treatment options	
Imipenem-relebactam	Same activity as imipenem plus KPC producing Enterobacterales, and 80% of carbapemen-resistant *P.aeruginosa.* Non active against OXA-48 or metallo-beta-lactamase-producing Enterobacterales	500 mg of imipenem/ 250 mg of relebactam every 6 hours	HAP/VAP including bacteremic infections Infections due to aerobic Gram-negatives with limited treatment options	
Cefiderocol	Gram-negative bacilli including ESBL-, Amp-C-, carbapenemase-metallo-beta-lactamase- producing Enterobacterales Carbapenem resistant *Pseudomonas aeruginosa* *Acinetobacter* spp., *S. maltophilia.* No activity against *Staphylococcus* spp. *Enterococcus* spp., and anaerobes	2 g iv/8 h	Infections due to aerobic Gram-negative bacteria with limited treatment options	New mechanism of action (siderophore). Not affected by porin mutations
Eravacycline	Gram-positive and Gram-negative organisms expressing tetracycline resistance mechanisms. No activity against *P. aeruginosa*	1 mg/kg / 12 h	Complicated IAI	IV and oral formulations
Tedizolid	Gram-positive pathogens including MRSA, enterococci, and coagulase-negative staphylococci	200 mg once daily iv or by oral route	SSTI	Demonstrated activity against linezolid-resistant staphylococci (only active if resistance is mediated by the *cfr* gene, not active if

				other mechanisms of resistance are present)
Dalbavancin	Gram-positives including MRSA, *Enterococcus* spp. Enterococci (except *vanA*- VRE), and coagulase-negative staphylococci	1000 mg iv over 30 min followed by 500 mg one week later, or a single dose of 1500 mg	SSTI	Long half-life (14 days) Activity against linezolid-resistant staphylococci
Oritavancine	Gram-positives including MRSA, enterococci and coagulase-negative staphylococci	1200 mg iv over 30 min only one dose If multiple dose: 800 mg weekly, or 1200 mg every 10-15 days	SSTI	Long half-life (14 days) Activity against linezolid-resistant staphylococci Activity against VRE including VanA isolates
Delafloxacin	Gram-positives including MRSA, coagulase-negative staphylococci, *S. pneumoniae, S. pyogenes, S. agalactiae* and *Enterococcus faecalis*. Quinolone-susceptible Gram-negatives Anaerobes *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae*	300 mg iv/12h 450 mg po/12h	SSTI CAP	First anti-MRSA fluoroquinolone

*SSTI: skin and soft-tissue infections; CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; UTI: urinary tract infection; IAI: intraabdominal infection.

TABLE 5. Intervention functions matched to behavioural determinants (filled boxed). Adopted from Michie et al.[321]

	Intervention functions								
COM-B components	**Education**	**Persuasion**	**Incentivisation**	**Coercion**	**Training**	**Restriction**	**Environmental restructuring**	**Modelling**	**Enablement**
Physical capability									
Psychological capability									
Physical opportunity									
Social opportunity									
Automatic motivation									
Reflective motivation									

Table 6. Mapping and definition of intervention functions, behavioural change techniques and their incorporation to antimicrobial stewardship interventions.[317, 322] The most frequent are highlighted in bold**.**

Intervention function	Aim	Behaviour change techniques (BCT)*	Intervention component
Education	Increase knowledge or understanding	• **Information about health, social and environmental consequences** • **Feedback on behaviour and on** • **outcome(s) of the behaviour** • Prompts/cues • Self-monitoring of behaviour • Behavioural experiments • Information about emotional consequences • Information about others' approval	• Educational meetings or sessions • Antibiotic rounds[330] • Academic detailing (one-to-one encounters)[331, 332] • Educational contents (infographics) • Reminders [333, 334]
Persuasion	Use communication to induce positive or negative feelings to stimulate action	• **Credible source** • **Information about health social and environmental consequences** • **Feedback on behaviour and on outcome(s) of the behaviour** • Information about others' approval • Framing/reframing • Identity associated with changed behaviour • Identification of self as role model • Salience of consequences • Social comparison	
Incentivisation	Create an expectation of reward	• **Feedback on behaviour and on outcome(s) of behaviour**	• Academic detailing (one-to-one encounters) [324, 325]

		• **Monitoring of behaviour and outcome of behaviour by others without evidence of feedback** • **Self-monitoring of behaviour** • Paradoxical instructions • Remove aversive stimulus • Reward approximation • Rewarding completion • Situation-specify reward • Social rewarding • Behavioural contract • Commitment • Discrepancy between current behaviour and goal • Imaginary reward	• Audit and feedback of results over time [331]
Coercion	Create an expectation of punishment or cost	• **Feedback on behaviour and on outcome(s) of behaviour** • **Monitoring of behaviour and on outcome(s) of behaviour by others without evidence of feedback** • **Self-monitoring of behaviour** • Punishment • Behaviour cost • Remove reward • Future punishment • Behavioural contract • Commitment • Imaginary punishment	
Training	Impart skills	• **Instruction on how to perform a behaviour** • **Feedback on the behaviour and on outcome(s) of behaviour**	

		• **Self-monitoring of behaviour** • **Behavioural practice/rehearsal** • Habit formation • Habit reversal • Graded tasks • Behavioural experiments • Mental rehearsal of successful performance • Self-talk • Self-reward	
Enablement	Increase means or reduce barriers to increase capability (beyond education or training) or opportunity (beyond environmental restructuring)	• Social support • Goal setting (behaviour / outcome) • Adding objects to the environment • Problem solving • Action planning • Self-monitoring of behaviour • Restructuring the physical environment • Review behaviour and outcome goal(s) • Social support (emotional) • Reduce negative emotions • Conserve mental resources • Pharmacological support • Self-monitoring of outcome(s) of behaviour • Behaviour substitution • Overcorrection • Generalisation of a target behaviour • Graded tasks • Avoidance/reducing exposure to cues for the behaviour • Restructuring the social environment • Distraction • Body changes	• Academic detailing (one-to-one encounters) [331, 332]

		• Behavioural experiments • Mental rehearsal of successful performance • Focus on past success • Self-talk • Verbal persuasion about capability • Self-reward • Behavioural contract • Commitment • Discrepancy between current behaviour and goal	
Modelling	Provide an example for people to aspire to or emulate	• **Demonstration of the behaviour**	
Environmental restructuring	Change the physical or social context	• **Adding objects to the environment** • **Prompts/cues** • **Restructuring the physical environment** • Cue signalling reward • Remove access to the reward • Remove aversive stimulus • Satiation • Exposure Associative learning • Reduce prompt/cue • Restructuring the social environment	• Reminders [333, 334]
Restrictions	Use rules to reduce the opportunity to engage in the behaviour (or to increase behaviour by reducing opportunity to engage in competing behaviours)		• Expert approval [335]