Chapter

WASPSS: A Clinical Decision Support System for Antimicrobial Stewardship

Bernardo Cánovas Segura, Antonio Morales, Jose M. Juarez, Manuel Campos and Francisco Palacios

Abstract

The increase of infections caused by resistant bacteria has become one of the major health-care problems worldwide. The creation of multidisciplinary teams dedicated to the implementation of antimicrobial stewardship programmes (ASPs) is encouraged by all clinical institutions to cope with this problem. In this chapter, we describe the Wise Antimicrobial Stewardship Program Support System (WASPSS), a CDSS focused on providing support for ASP teams. WASPSS gathers the required information from other hospital systems in order to provide decision support in antimicrobial stewardship from both patient-centered and global perspectives. To achieve this, it combines business intelligence techniques with a rule-based inference engine to integrate the data and knowledge required in this scenario. The system provides functions such as alerts, recommendations, antimicrobial prescription support and global surveillance. Furthermore, it includes experimental modules for improving the adoption of clinical guidelines and applying prediction models related with antimicrobial resistance. All these functionalities are provided through a multi-user web interface, personalized for each role of the ASP team.

Keywords: antimicrobial stewardship, antimicrobial resistance, infection management, rule-based systems, data and knowledge integration, clinical practice guidelines

1. Introduction

Antibiotics have been one of the most significant discoveries in medicine, to the point that some researches talk about pre-antibiotic and post-antibiotic eras in clinical practice due to their repercussion in the treatment of infectious diseases [1]. However, bacteria are able to develop resistance against antibiotics when they are exposed to them for a long period of time. Indeed, in a short time after the widespread usage of a novel antibiotic, new strains of bacteria resistant to it have appeared [2]. The problem is so severe that international health organizations claim that "… a post-antibiotic era -in which common infections and minor injures can kill- is a very real possibility for the 21st century" [3].

It has been recognized by global health organizations that one of the main causes of this problem, also known as *antimicrobial resistance*, is the overuse of antibiotics. For this reason, they are encouraging the adoption of *antimicrobial stewardship* *programmes (ASPs)* [4–7], in order to develop specific actuations and protocols to improve the antimicrobial usage and limit the rise of antimicrobial resistance. These programs include recommendations about all the actions related to the use of antimicrobials in clinical practice, such as the appropriateness of a particular antibiotic for an infection, its dosage, the route of administration or the duration of the therapy [4].

Due to the complexity of this problem, one of the recommendations for the hospital setting is to constitute a multidisciplinary team, called the *antimicrobial stewardship programme team (ASP team)*. This team should be composed of specialists from different clinical areas such as physicians, epidemiologists, pharmacists, microbiologists and managers. The coordination of efforts obtained thanks to the diversity of the ASP team members is seen as fundamental in order to achieve an improvement in the rational use of antimicrobials within the institution.

First experiences in the implementation of ASP teams have obtained limited but satisfactory results regarding the usage of antimicrobials [8, 9]. A well-known disadvantage of the ASP methodology is the amount of time required by ASP members to review alerts and documentation [10]. Therefore, these studies also state the need for computerized tools to help with these complex tasks. The use of clinical decision support systems (CDSSs) can be a key factor in improving the results of ASP teams, taking into account the multi-user perspective of the problem, the need for data and knowledge integration from different sources, and the requirement to provide support both for a particular patient and for the whole institution in a coordinated manner. In this chapter, we perform an overview of different studies related with decision support in antimicrobial resistance and perform a detailed description of the *Wise Antimicrobial Stewardship Program Support System (WASPSS)*, a CDSS focused on ASP teams.

2. Decision support in the context of antimicrobial resistance

Infectious diseases were one of first clinical topics related with decision support systems. One of these first systems was MYCIN [11], which relied on production rules derived from discussions with clinical experts to provide suggestions about the diagnosis and appropriate management of infected patients. Although the system was never used clinically, it was a relevant reference for the research and development of CDSSs during the 1980s [12].

Another relevant work was the HELP system [13], which provided alerts, reports and suggestions obtained from the data available in clinical records. With additional epidemiologic data and expert knowledge, it was used to provide recommendations about antibiotic treatments and therapies [14].

The infections acquired within clinical institutions (i.e., nosocomial infections) are commonly caused by bacteria resistant to antibiotics and, therefore, harder to treat. The relevance of these infections led researchers to focus on this problem. The GermWatcher expert system [15, 16] is capable of evaluating the results of cultures with the aim of detecting nosocomial infections. GermWatcher uses a rule engine whose knowledge base is based on the guidelines of the Nosocomial Infection Surveillance System from the Centers for Disease Control. Thanks to them, it is capable of classifying the alert level of a microorganism and deciding whether or not to report it as a nosocomial infection.

The Mercurio system [17] is also focused on the detection and monitoring of nosocomial infections. It was intended for different kinds of users, such as laboratory physicians, clinicians and epidemiologists, and included knowledge from several sources, such as antibiotic hierarchical definitions and international guidelines for microbiological laboratories. It is capable of checking the susceptibility tests in order to ensure that they have been performed according to the guidelines, differentiating among possible strains of bacteria, and warning about possible outbreaks of a particular strain. Furthermore, association rules are used to identify local resistance patterns that are not covered by the standard guidelines.

Another example focused on this problem is the HASIS information system [18] that implements the guidelines for hospital-acquired infections published by the Centers for Disease Control and Prevention and includes algorithms for the detection of suspicious cases. It employs a service-oriented architecture as a basis on which to integrate the surveillance data required for this task.

However, the rise and spread of multidrug-resistant bacteria has forced the research community to tackle the problem of nosocomial infections from the broader perspective of antimicrobial stewardship.

The DebugIT (Detecting and Eliminating Bacteria UsinG Information Technology) European project [19] was developed to gather information about antimicrobial resistance from heterogeneous sources [20]. It uses semantic web technologies to structure data and is capable of performing data analysis on it in order to provide decision support [21].

From yet another point of view, the TREAT system [22] uses causal probabilistic networks to propose an antibiotic treatment when the infectious agent is still unknown, based on the local epidemiological data and clinical observations such as the site of infection, symptoms and background disorders. This signifies that the spectrum of the treatments can be narrower, and less antimicrobial resistance is, therefore, developed.

Other proposals are focused on intensive care units (ICUs), since they are the hospital wards with the highest number of nosocomial infections and multi-resistant bacteria.

For example, the objective of the MoniICU system [23] is to identify and monitor nosocomial infections in ICUs. It uses production rules defined by using ARDEN syntax, an HL7 standard oriented toward sharing medical knowledge. Furthermore, it includes a fuzzy abstraction module for the definition of nosocomial infections.

Another example is the COSARA platform [24], which is focused on infection surveillance in ICUs. It provides functionalities for the automatic integration of clinical data and clinical decision support and alerts to alarming trends, among others.

Recently, some relevant works have been finally focused on supporting ASP teams in order to assess in the use of antibiotics by hospitals. The Antimicrobial Prescription Surveillance System [25] is focused on identifying potentially inappropriate antimicrobial prescriptions and reporting them to pharmacists. It has a knowledge base with contraindications regarding drug–drug interactions, drug-bug mismatches and maximum daily dose, among others. Furthermore, the system includes a learning algorithm with which to evaluate the feedback regarding the launched alerts and reduce the number of those that are erroneous or clinically irrelevant.

In Evans et al. [26], a framework of medical informatics tools is proposed in order to provide ASP teams with support. It automatically generates spreadsheets containing the antibiotics that are used daily and the parameters available to decide the antimicrobial therapy for specific patients. It additionally sends e-mail and SMS alerts to ASP members when timely-critical laboratory results are available, such as positive blood or cerebrospinal fluid cultures. Finally, it generates different reports based on the National Healthcare Safety Network specifications.

The HAITooL system [27] is also focused on ASP teams. It monitors antibiotic usage, rates antibiotic-resistant bacteria and allows early identification of outbreaks. It integrates evidence-based algorithms with which to support proper antibiotic prescription.

And a final example is the Wise Antimicrobial Stewardship Program Support System (WASPSS) [10]. WASPSS is focused on ASP team support and gathers information for multiple hospital information systems in order to provide a unified decision support for typical ASP tasks. It is the CDSS explained in detail in this chapter.

3. The WASPSS project

The University Hospital of Getafe (UHG) is a medium-size hospital (approximately 450 beds), which is located in Madrid, Spain. It has units covering most medical specialities, including a burns unit, although there are no cardiac surgery or transplant units. In 2014, the UHG set up an antibiotic stewardship programme denominated as "program for the multidisciplinary care in the assessment and control of the antimicrobial therapy" (PAMACTA) [10]. The PAMACTA team is composed of members from different specialities, including pharmacists, microbiologists, surgeons, internists, intensivists and infection preventionists. This team has been formed to address two organizational proposals: (a) to include a representative of each hospital service, or at least those services with a higher use of antibiotics, and (b) to involve all the physicians as part of the ASP. The intention of these two proposals is to reduce the time spent on distributing the task among departments and the integration of individual clinical expertise with the best available external clinical evidence, a basic principle of evidence-based medicine [28].

The *Wise Antibiotic Stewardship Program Support System* (WASPSS) platform [10, 29] is a CDSS focused on ASPs and infectious disease management. It was developed by the University of Murcia in collaboration with UHG at the same time as the PAMACTA team was created, which provided the opportunity to focus on the current needs of an ASP team starting from scratch. WASPSS is currently in the production stage and it is used daily by the PAMACTA team. Furthermore, it is being piloted in other seven public hospitals in Spain.

4. System architecture overview

An overview of the WASPSS software architecture is shown in **Figure 1**. The system is capable of obtaining information from multiple hospital information systems, which is a key factor to provide a proper support to the ASP team. The hospital systems and some examples of data collected by WASPSS are the following:

- Pharmacy systems: the dispensations or administrations of antimicrobials
- Microbiology laboratory: the results of cultures, the microorganisms found, and the resistances or susceptibilities found in the laboratory
- Clinical tests laboratory: white-cell count, creatinine levels and other infection-related tests
- Electronic health records (EHR): data related to patient, such as previous stays, current ward, and stays at ICU.

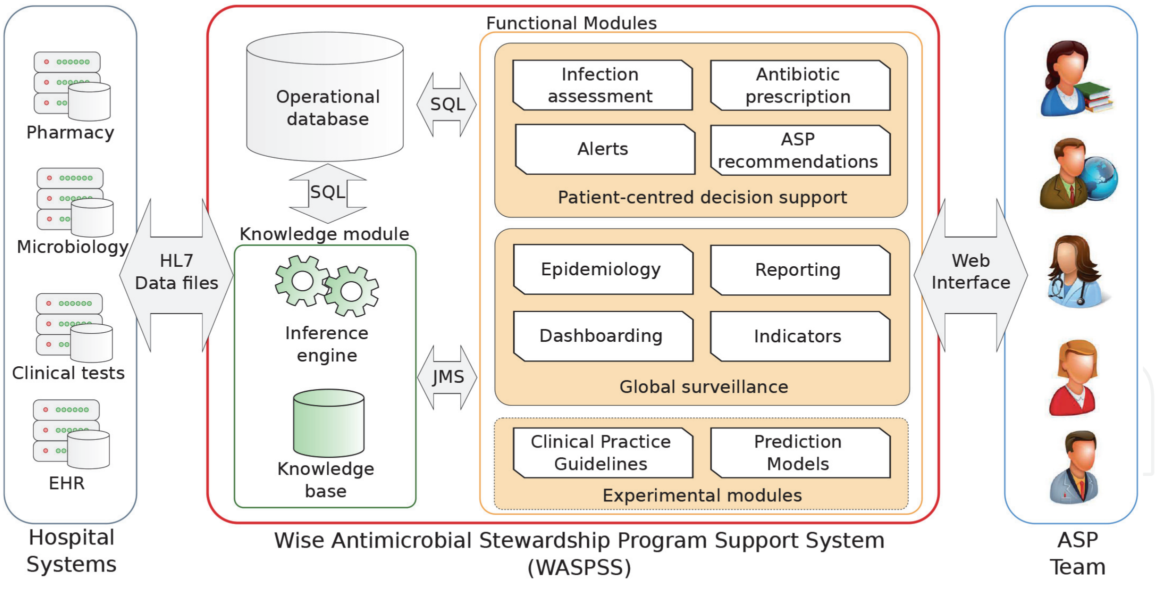


Figure 1.
Overview of the WASPSS platform and its different modules.

To perform data integration, a *Health Level 7* (*HL7*) interface engine has been included. HL7 is a widely accepted set of standards for interoperability between health care organizations. HL7 provides messaging for exchanging, sharing and retrieving electronic health information between medical applications in near real time. Most HIS vendors adhere to these standards when developing application interfaces to exchange patient data. Additionally, WASPSS also supports the batch-loading of data files for those cases in which the HL7 interface is not available. Furthermore, a *Java Message Service* server is also used for the communication between WASPSS modules.

The data collected from hospital systems are filtered, structured and stored into an operational database by using extract-transform-load processes. This database acts as a centralized data hub for all the WASPSS modules.

WASPSS uses artificial intelligence techniques to provide proper support for ASP teams. In particular, WASPSS includes a knowledge module to incorporate clinical literature and daily practice knowledge [30–32]. To this end, the module implements a rule-based reasoning architecture composed of a knowledge base and a rule-based engine. The knowledge base contains production rules, ontologies and other business process models related with antimicrobial stewardship. The rule-based engine can make use of both the knowledge base and the data collected from the hospital to perform abstractions, raise alerts or evaluate processes, and its results can be stored back into the database or communicated through JMS to the other WASPSS modules.

Finally, the system includes a web-based interface that offers a different front-end for each user role of the ASP team, facilitating its usage for each clinician involved with antimicrobial stewardship within the institution. In the next sections, we describe in detail the capabilities of WASPSS to provide decision support for tasks related with both particular patients and the whole clinical organization.

5. Patient-centered decision support

The capability of WASPSS to aggregate information from different hospital systems allows to provide comprehensive decision support for a particular patient. This is especially useful in antibiotic prescription and patient-related alerts, as explained next.

5.1 Antibiotic prescription

The selection of the most appropriate antibiotic treatment is a key decision both to improve the patient's health and to reduce the risk of antimicrobial resistance for the community. However, it usually occurs that the microorganism responsible for the infection has not yet been determined when the clinician must decide the antibiotic therapy to use. In these situations, clinicians must use all the available information about the patient and the infection (possible focus, previous infections, etc.) along with the information regarding the common pathogens found in the hospital and their resistance patterns, which is called the *local cumulative antibiogram*. After deciding this initial therapy, known as *empiric therapy*, clinicians can adjust, suspend or incorporate antibiotics when the infecting microorganism is found and analyzed, starting then a *targeted therapy*. However, the development of a local cumulative antibiogram is a time-consuming task that requires gathering information about the microorganisms found within the institution, and therefore, it is usually generated yearly.

The *antibiotic prescription module* of WASPSS assists physicians in the prescription of appropriate empiric or targeted antibiotic treatments (**Figure 2**). Thanks to the data collected from the microbiology system, WASPSS can calculate the cumulative antibiograms instantly. Furthermore, it can use data from any period and stratify them attending to different criteria in order to obtain, for example, the most effective antibiotic for blood infections in the ICU ward during the last year.

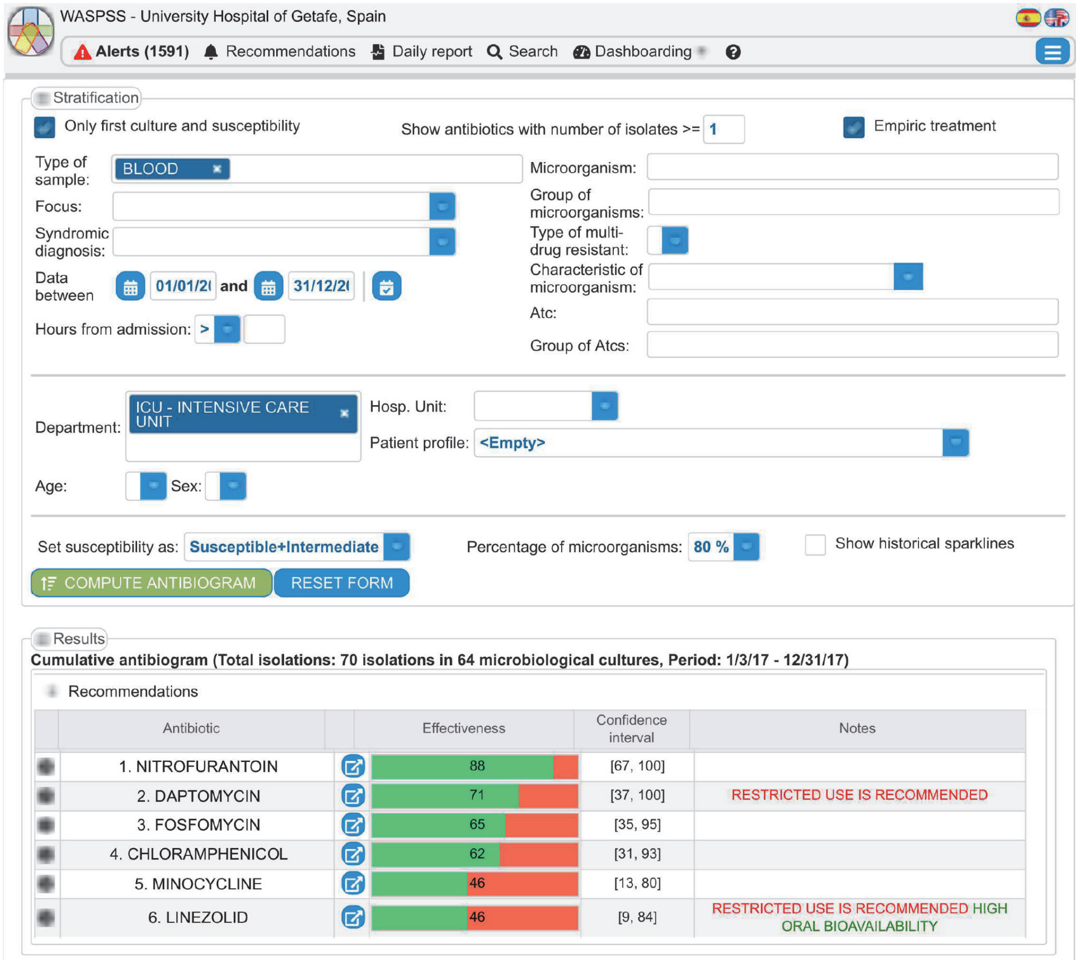
The efficacy of each antibiotic is computed under those criteria, from 1 (less effective) to 100 (fully effective), based on the number needed to fail measure [33]. Finally, a list with the available antibiotics ranked by efficacy and confidence interval is proposed to the physician. The tool shows additional notes about each option, such as whether a restricted use of the antibiotic is recommended or if it can be administered orally. Furthermore, the tool can present the list of most common microorganisms found under the search criteria, along with their susceptibilities to antimicrobials. A graphical view of the results is also available through a bipartite model, which represents the relationships between microorganisms and antibiotics by means of channels of different width [34]. With these tools, physicians can take a more informed decision related with both empiric and targeted antimicrobial therapies.

5.2 Alerts, recommendations and assessment of infections

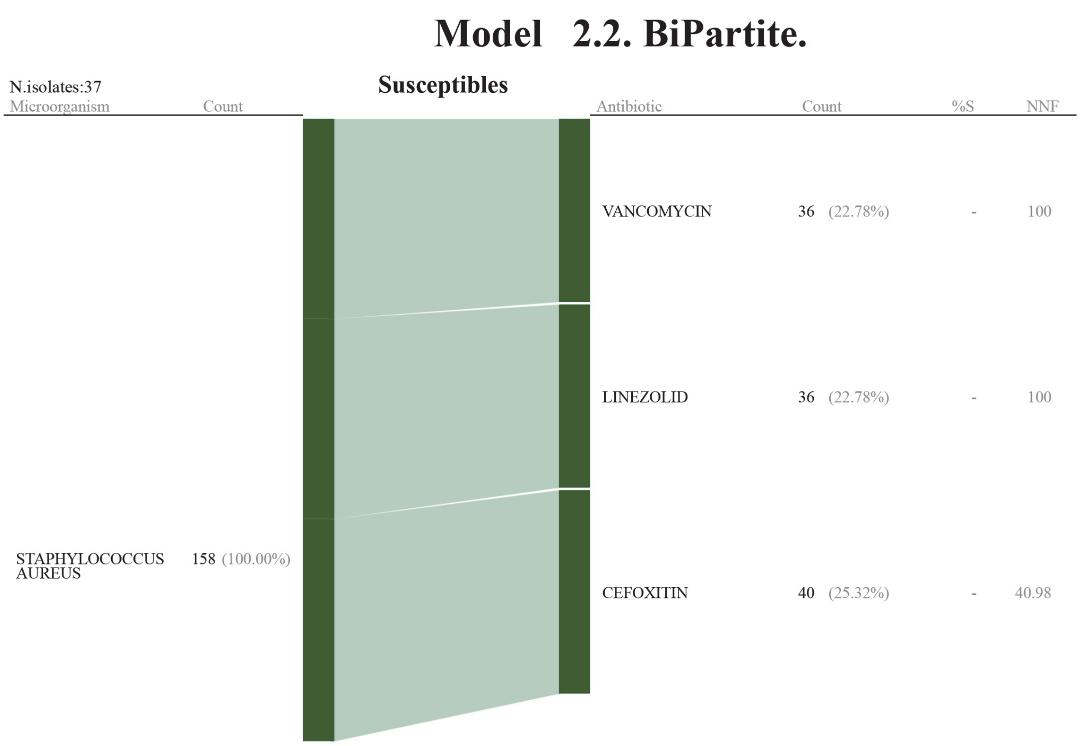
One of the common decision support tasks from CDSSs is to alert clinicians when certain events occur. In case of the antimicrobial stewardship scenario, typical alerts are related with the detection of bacteria resistant to multiple antibiotics, the results of tests that indicate severe infections, the prescription of restricted antibiotics or the opportunities to change the route of administration of an antibiotic to a less aggressive route for a patient.

WASPSS includes a pre-defined set of these alerts in the form of production rules within its knowledge base. Furthermore, as shown in **Figure 3**, clinicians may use the web-based interface to perform detailed queries that can also be stored as new alerts. If that is the case, the query is translated into production rules, stored in the knowledge base and executed daily. Each new case found will be notified then as any other alert automatically.

One recurrent problem is CDSSs is the *alarm fatigue*, that is, users tend to ignore all alerts when too many of them are launched [35]. In order to cope with this problem, WASPSS allows to define alerts with three different levels of severity. Furthermore, alerts can be restricted to specific user profiles. By this way, each user

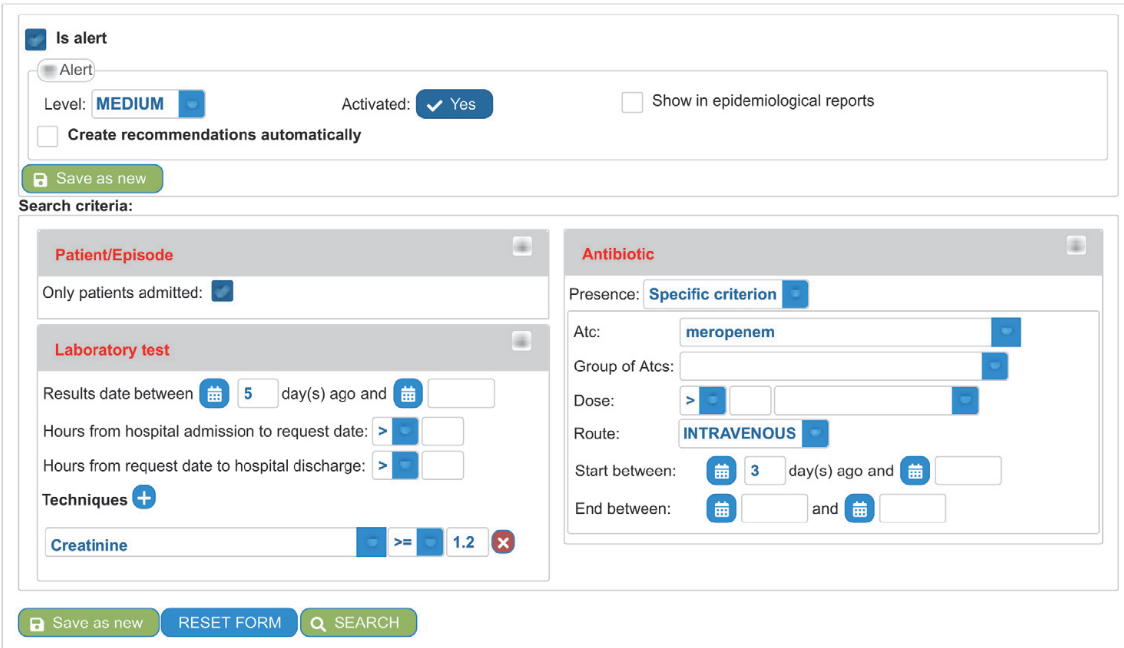


a)



b)

Figure 2.
Screenshot of the antibiotic prescription module. Given a search criteria, a rank of most effective antimicrobials is provided based on the local cumulative antibiogram (a). A graphical bipartite model is also available in order to show relationships between antibiotics and microorganisms (b). The antimicrobial efficacy data shown in this picture are fictitious.

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rule "Meropenem-Indication␣of␣dose␣adjustment␣based␣on␣renal␣function"
when
  $c: Clock()
  $p: Patient(isAdmitted == true)
  $a: Antibiotic(patient==$p, atcCode == "J01DH05", // Meropenem
      route == "IV", startDate >= substract_days($c.now, 3, "days"))
  $l: LaboratoryTest(patient == $p,
      requestDate >= substract_days($c.now, 5, "days"))
  and exists (
    TechniqueResult(labTest == $l, tech == "Creatinine", result >= 1.2)
  )
then
  insert (new Alert(drools.getRule(), "MEDIUM", $p, $a, $l))
end
```

Figure 3.
Screenshot of the alerts module. Clinicians can build detailed queries with a user-friendly interface. Those queries considered as relevant can be automatically translated into production rules and stored as new alerts in the knowledge base.

receives only those alerts relevant to their role in the ASP team, and they can decide whether to revise only those with higher severity or all of them.

To manage each particular alert, WASPSS displays a patient-centered timeline view (**Figure 4**). This view provides a temporal perspective of all the data recovered from hospital systems that are related with antimicrobial stewardship, such as treatments, cultures, clinical tests and stays in wards. When an alert is fired, it is linked with the clinical events that caused it and they are highlighted in this view. By this way, the ASP team can evaluate all the relevant data regarding a patient when deciding which clinical action must be made in response to each alert.

Most of the clinical actions undertaken by the ASP team consist of performing recommendations to the physician staff related to changes in the antibiotic therapy of a particular patient, or to suggest cultures or other clinical tests whose results can improve the treatment of an infection. WASPSS allows the ASP team to create those recommendations for a specific patient, attaching their reasons and the suggested actions. Physicians can then access these recommendations by using the WASPSS platform. Optionally, these recommendations can be sent through the HL7 interface to other systems in order to facilitate the daily hospital workflow.

Alerts can also generate automatically informed recommendations that only need to be validated by the ASP team in order to be communicated. For example, WASPSS can detect that an antibiotic that is being administered by the intravenous route for many days can also be administered orally, which is less aggressive for the

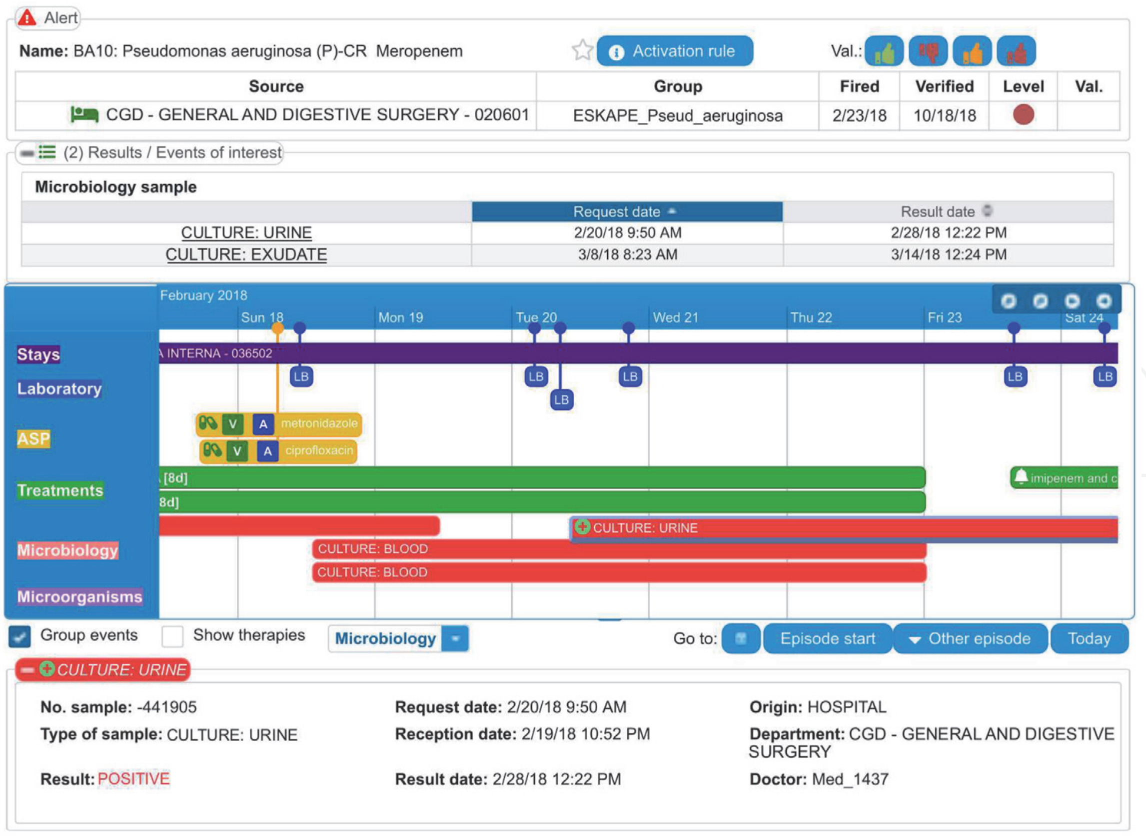

Figure 4.
Screenshot of the timeline view with the details of the alert and all the patient's clinical events. The patient's data shown in this picture are fictitious.

patient. Then, an alert is raised with a recommendation completed by the system, which includes the antibiotic, the suggestion of changing its administration route, and also the conditions that must be checked before undertaking this action, such as that the patient has no digestive problems that contraindicate the ingest of antibiotics.

WASPSS also facilitates the assessment of the infection for a particular patient. The patient-centered view includes the relevant data obtained from the EHR, along with the results from the microbiology tests and the rest of the clinical tests performed to the patient. The visualization of all these data in a clear and organized way facilitates the evaluation of the patient's infection by clinicians.

6. Institutional decision support

Along with the patient-centered perspective, a broader vision is required in order to perform a proper antimicrobial stewardship within the institution. The monitoring of both clinical and process outcomes is important for proposing new strategic actions, and also for removing measures or policies that are not having any real impact on patient safety, economy or antibiotic resistance.

Global surveillance and monitoring in WASPSS is achieved by four modules. First, the epidemiology module (**Figure 5a**) visualizes the evolution of statistical measures such as prevalence and incidence of microorganisms, antibiotics, microbiological sample types and alerts.

Second, the dashboarding module (**Figure 5b**) provides interactive charts that summarize global measures related to antibiograms, alerts and ASP recommendations over a specified time interval.

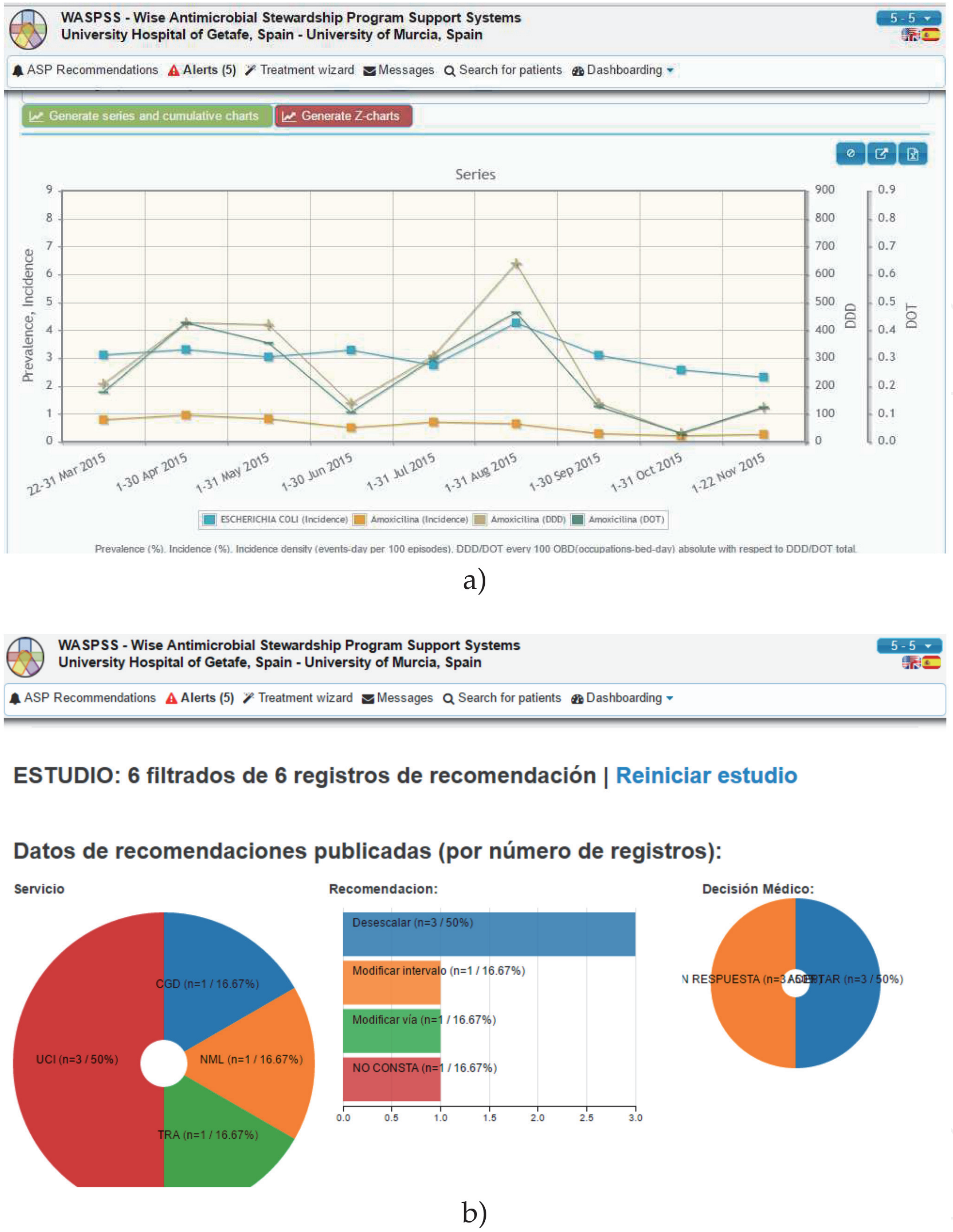

Figure 5.
Global surveillance support in WASPSS: (a) epidemiology and (b) dashboarding modules. The data shown in this picture are fictitious.

Third, actionable reports are generated using the reporting module (**Figure 6a**). Currently, two kinds of parameterized reports are available: the first one lists all the antibiotics and microbiological tests of hospitalized patients during a specified period of time, grouped by department and sorted by bed number; the second one includes statistical information (prevalence, incidence, etc.) about all the microorganisms, antibiotics, sample types and alerts occurred over a specified time interval.

Last, the ASP indicator module computes several process indicators (**Figure 6b**) whose results are presented in two forms: (i) as a run chart showing the evolution of

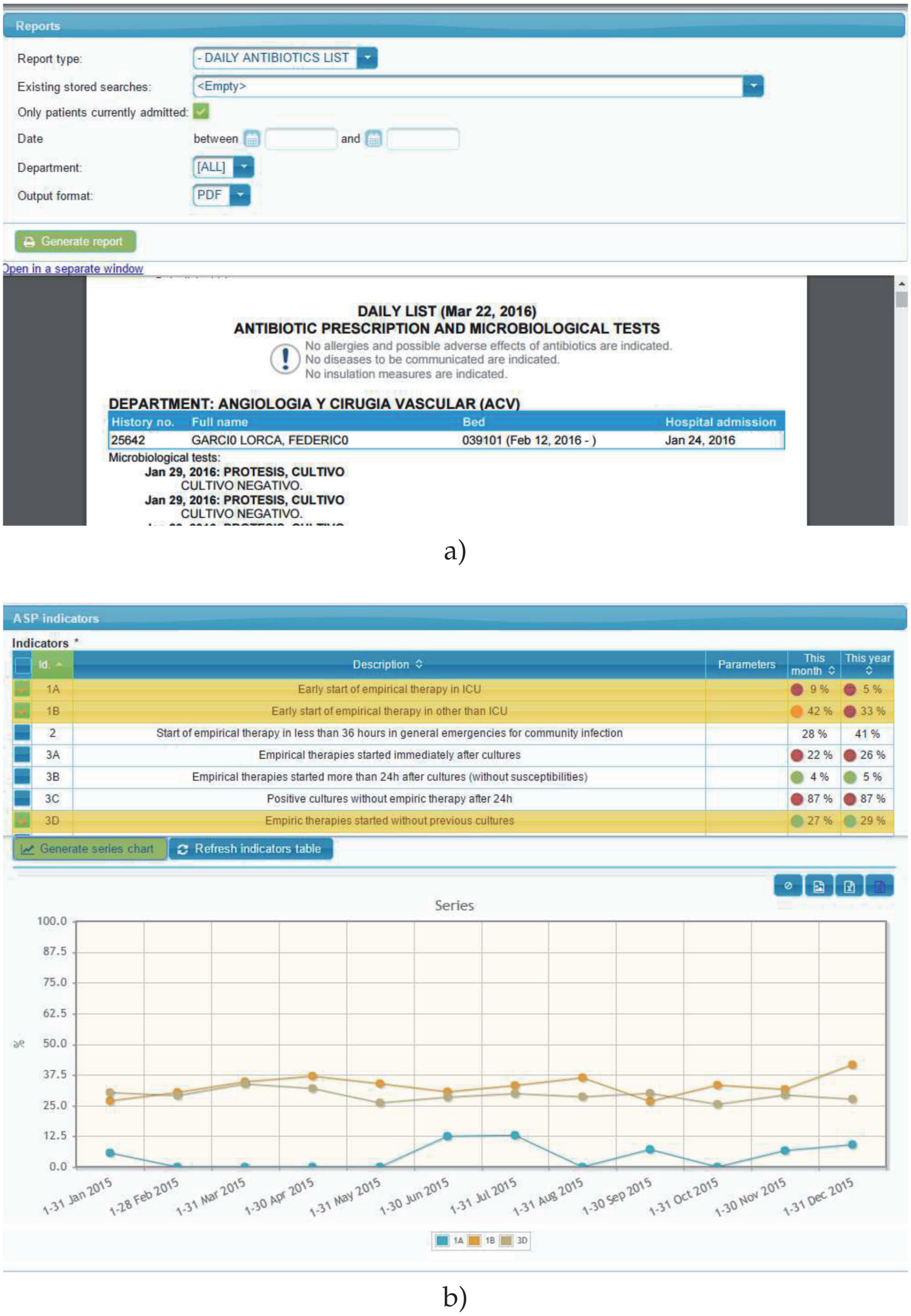

Figure 6.
Global surveillance support in WASPSS: (a) reporting and (b) ASP indicator modules. The data shown in this picture are fictitious.

the indicator over time and (ii) as a control table showing results of the current month and year, labeled with color codes indicating the goodness of the result.

7. Incorporation of clinical knowledge

WASPSS is also designed to incorporate different kinds of knowledge related with antimicrobial resistance [30].

The main source for the knowledge included is the expert rules from the EUropean Committee on Antimicrobial Susceptibility Testing (EUCAST) [36, 37]. These rules include the antibiotics to which each bacterial species is intrinsically resistant, those resistant patterns that are considered as exceptional and that should be re-checked to discard any problem on the laboratory tests, and resistance patterns that can be inferred from others found in laboratory.

WASPSS combines production rules with ontologies in order to incorporate the EUCAST rules in its knowledge base. Production rules are used to model most of the EUCAST knowledge, while ontologies are needed to model the hierarchical relationships of antibiotics and bacteria [31, 38].

This knowledge can be useful for many tasks such as the detection of incoherencies in laboratory results (e.g., bacteria that are found susceptible to an antibiotic to which they should be intrinsically resistant according to the EUCAST rules) and the detection of possible therapy failure because the infecting agent is found as resistant to all the antibiotics currently administered to the patient. In this last example, this knowledge has proved to be useful for increasing the number of cases detected and their clinical relevance [39].

8. Experimental features

The knowledge base and the inference engine provide opportunities for further knowledge-based expansions, incorporating knowledge from different sources. One of these sources can be the *Clinical Practice Guidelines* (*CPGs*), that is, widely accepted recommendations, processes and decision steps based on clinical evidence focused on improving the assistance of patients [40, 41]. Despite the fact that the use of CPGs has proved to improve clinical outcomes, they must be adapted to the particularities of each individual patient, which sometimes present a cumbersome problem for they use in daily practice [42].

WASPSS includes an experimental module to facilitate the visualization, adoption and evaluation of guidelines related with antimicrobial stewardship, focusing on the processes and decisions included in the guideline and those tasks that can be monitored thanks to the information gathered by the system [32]. An example of the graphical interface of this module is shown in **Figure 7**. The processes included in the guideline must be modeled by using the Business Process Model Notation (BPMN) and the decision-related recommendations by using the Decision Model Notation (DMN). These models are stored within the knowledge base and can be used to graphically visualize the tasks and decisions contained in the guideline. Production rules are then used to evaluate the status of each relevant task of the guideline and provide an estimation of the tasks already finished, those on-going and also those that may have been omitted. Finally, in combination with the patient-centered timeline view, the next guideline tasks can be scheduled in a flexible way, allowing the adaptation of the guideline to the particularities of each patient.

Another experimental extension is the incorporation of prediction models within the knowledge base. WASPSS includes an experimental clinical prediction rules module that is capable of incorporating prediction models based on logistic regression and evaluating them for a particular patient. Logistic regression is one of the most used techniques for developing models in clinical practice and can be combined with other techniques to deal with common problems related with data mining in antimicrobial resistance, such as unbalanced datasets or concept drift [43].

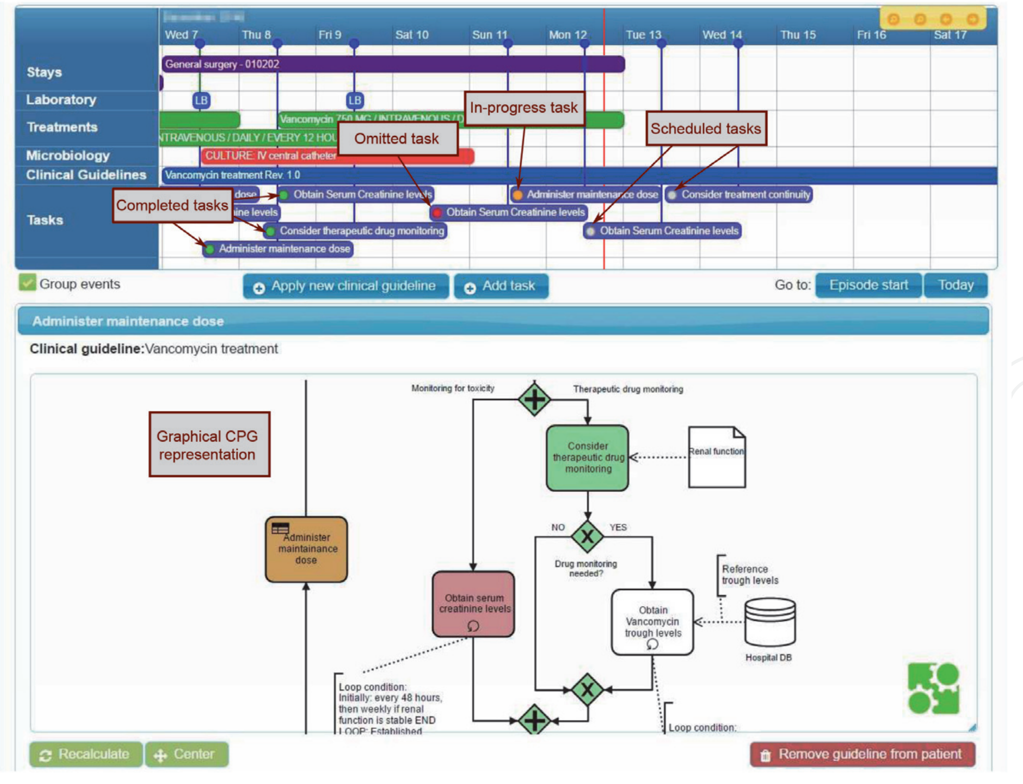

Figure 7.
Graphical interface for the CPG experimental module of WASPSS. The patient's data shown in this picture are fictitious.

9. Future work

When dealing with clinical data, it is usual to find uncertainties in test results, clinical guidelines or prediction models, especially due to missing patient data. As a future research line, we plan to detect these uncertainties as well as the data required to solve them when possible. Then, these data will be asked to the user and incorporated into the knowledge base to improve the results of the different WASPSS modules.

We consider that a grounded explanation of a recommendation is one of the key factors for the success of a CDSS. The methods and models used in WASPSS (production rules, ontologies, etc.) allow the traceability of any alert, decision or abstraction. Following this idea, we are studying the incorporation of explainable machine learning methods to improve the justifications of the results of the prediction models.

The use of WASPSS in several hospitals offers us the opportunity to combine efforts among different ASP teams to improve the global outcomes in antimicrobial stewardship. On the other hand, it raises the problems of the interchange of knowledge among hospitals [31] and the need for dealing with a huge amount of data, which may require the adaptation of WASPSS to a big data environment [44].

Other future changes may be taken into consideration as new technologies are adopted by the hospitals using WASPSS. For example, the Fast Healthcare Interoperability Resources (FHIR) protocol has become very popular in last years and its incorporation into WASPSS may be considered in the medium term.

10. Conclusions

CDSSs have been widely used to assist physicians when dealing with infectious diseases. However, the need for coordinated efforts against the rise of antimicrobial resistance urges them to provide new functionalities.

WASPSS is our proposal for a CDSS focused on the assistance of ASP teams in the hospital environment. It combines techniques from business intelligence and artificial intelligence to provide an integrated perspective for antimicrobial stewardship.

On the one hand, WASPSS collects data from multiple hospital information systems and incorporates knowledge in the form of alerts and expert EUCAST rules. It is also capable of incorporating knowledge from CPGs and prediction models related with antimicrobial resistance.

On the other hand, WASPSS provides alerts and functionalities for antibiotic prescription, ASP recommendations and infection assessment through a patient-centered view in order to assist physicians when taking decisions concerning a particular patient, and global surveillance modules to provide support for strategic decisions related with epidemiology, global clinical outcomes and reporting.

In conclusion and according to our experience with WASPSS, a multi-user perspective, capabilities to integrate data and knowledge from different sources, and both patient-centered and institutional perspectives are key requisites for any CDSS focused on antimicrobial stewardship.

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Conflict of interest

The authors declare no conflict of interest.

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