Semantic Approach for Rational Use of Antibiotics: A Perspective from Clinical Research

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Abstract. Antibiotic abuse has potentially serious effects on health. Rational use of antibiotics has become a basic principle in medical practice. In this paper we propose a semantic approach for rational use of antibiotics, by introducing the semantic technology into the monitoring on the use of antibiotic agents. In particular, we investigate the problem from the perspective of clinical research. The proposed approach has been implemented in a prototype system named SeSRUA, a Semantically-enabled System for Rational Use of Antibiotics. This semantic system with the support of data interoperability provides a basic infrastructure for the intelligent monitoring on the use of antibiotics.

Keywords: semantic technology, antibiotics, rational use, intelligent monitoring

1 Introduction

In recent years, antibiotics abuse leads to the high-rate of bacterial resistance to antibiotics and the world widespread of "super bacteria" [1]. The development of new antibiotics requires longer cycle and higher cost. All these will threaten the human health, and even the survival. Antibiotics abuse in China has been increasingly fierce. Faced with severe situation, the Chinese Ministry of Health with other four healthcare authorities jointly launched a national campaign against the antibiotics abuse in 2011.

Using the semantic technology to solve the problem in biomedical area is a hot topic in recent years. The semantic technology provides a common framework for network data sharing, reuse and interoperability. Linked Life Data (LLD)

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and Bio-medical data in Linked Open Data (LOD)[2], such as Drugbank[3] and SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms)[4], provide rich data resources for the data interoperability to solve the problem of heterogeneous medical data in the existing medical information systems.

In this paper, we will investigate the problem of the development of a system for rational use of antibiotics from the perspective of clinical research. Furthermore, we will propose a semantic approach for rational use of antibiotics, by introducing the semantic technology into the monitoring on the use of antibiotics. We have implemented a prototype named SeSRUA (Semantically-enabled System for Rational Use of Antibiotics). This semantic system with the support of data interoperability provides a basic infrastructure for the intelligent monitoring on the use of antibiotics.

The contributions of this paper are:

– We analyze the present situation of the information management for antibiotics. The key points for antibiotics management and the difficulties of its hospital management are also discussed.
– We propose a semantic approach for rational use of antibiotics by introducing the semantic technology, which has been widely used in the Semantic Web and Ontology Engineering.
– We present the system of SeSRUA and discuss the initial implementation of the system.

2 Rational Use of Antibiotics and Semantic Technology

2.1 Research Problem and Analysis

The health authorities have published the guidelines for rational use of antibiotics. It aims at further strengthening the management of clinical rational use of antibiotics, effectively controlling antibiotic resistance and ensuring medical quality and safety.

However, the status of antibiotics application in China is still not optimistic. The irrational use of antibiotics is still a serious problem[5, 6]. All the data suggested that the use of antibiotics in China is still far away from the rational level. Due to the limit time and heavy task caused by domestic strained medical resources, along with all kinds of medical information exploding and long-term drug habit, medication errors maybe easily occurred.

Antibiotics have the following characteristics:

1. *Particularity.* Antibiotics acts on pathogen, rather than the human tissues and organs. The relationship among infected body, antibiotics and pathogens, as shown in Figure 1, which requires multiple knowledge containing not only clinical pharmacy but also microbiology and diagnosis on infectious diseases
2. *Universality.* Infectious diseases, especially the bacterial infections are the most common diseases in clinical, so that the antibiotics is one of the drugs most widely applied in clinical.

3. *Complexity.* As shown in Figure 2, there are so many factors effecting rational use of antibiotics in all aspects of clinical.

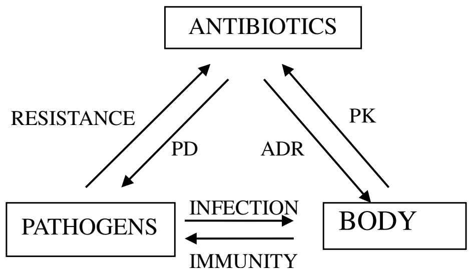

Fig. 1. Schematic diagram of antibiotics- pathogens - body relationship.PD:pharmacodynamics ;PK:pharmacokinetic; ADR:adverse drug reaction

For example, it is necessary to exercise caution for the risk of kidney damage from antibiotics as shown in Figure 2. According to dispensatory, when using antibiotics, it should be paid more attention for dose and renal function monitoring, such as renal insufficiency patients, children (renal function not yet mature), senile patients (renal function decline) and other special groups. There are different kinds of damage for kidney:

1. Basic diseases such as hypertension, diabetes, hyperlipidemia and systemic lupus erythematosus often complicated with nephropathy;
2. Some drugs have renal toxicity themselves, such as cyclosporine, tacrolimus, aminoglycosides, vancomycin, non-steroidal anti-inflammatory drugs;
3. Some drugs cleared by the kidney. While taking these drugs combined with kidney-harmful drugs, then the probability of renal injury will increased along with the higher blood concentration in kidney.

Some laboratory parameters are closely related to the renal function and valuable to determine whether renal injury. Once the parameters fluctuating abnormally, the clinician should adjust the dosage regimen in time.

Common laboratory parameters for renal impairment are as follows:

1. *Blood uric acid*: uric acid is an independent risk factor for renal dysfunction. The risk is even higher than the urine protein volume. Rise of serum uric acid is closely related to renal disease, which involve acute uric acid nephropathy, uric acid nephrolithiasis and chronic uric acid nephropathy, etc. Normal serum uric acid values are 149∼417μmol/L (male) and 89∼357μmol/L (female) for the adults; 250∼476μmol/L (male), 190∼434μmol/L (female) for elderly (>60 years old). The value above 420μmol/L(7.0 mg/dl)for male or 360μmol/L(6.0 mg/dl) for female are diagnosed as hyperuricemia.
2. *Proteinuria*: normal urine protein is <40mg/24h, adult ceiling 150mg/24h. Pathological proteinuria is common in all types of kidney diseases, such

Fig. 2. Schematic diagram of factors affecting the rational use of antibiotics in clinical

as primary and secondary glomerular disease, renal disease and interstitial nephritis, etc.

3. *Hematuria*: It is common in acute or chronic glomerulonephritis, acute cystitis, pyelonephritis and renal calculi, etc.
4. *Blood urea nitrogen* (BUN): BUN is mainly filtrated through glomerular with urine. When the kidney function is impaired, glomerular filtration rate will reduced along with serum urea nitrogen increased. BUN has a certain reference value in reflecting the filtration function of glomerular. Normal reference value is 3.2∼7.5mmol/L for adult; 1.8∼6.5mmol/L for infants and children.
5. *Serum phosphorus* (Pi): normal reference value is 0.97∼1.62mmol/L for adult, 1.29∼1.94mmol/L for children. Elevated Pi is common in chronic kidney disease, multiple myeloma.
6. *Serum creatinine* (Scr): Normal reference value is 53∼106 μmol/L for male, 44∼97 μmol/L for female, and 44∼70μmol/L for the elderly (>60 years old). Reduced glomerular filtration function caused by kinds of factors can lead to a rise in Scr, which is more sensitive than BUN to reflect the situation of the renal function. Endogenous creatinine clearance rate (Ccr) is a sensitive parameter for glomerular damage. The normal value is 90pm10 ml/min. The clinical significance of Ccr as follows:
   - below the reference value of 80% or less implies glomerular filtration hypofunction;
   - 50∼70 ml/min value means mild renal function damage;
   - 31∼50 ml/min value implies moderate renal damage;
   - below 30 ml/min value means severe renal damage;
   - 11∼20 ml/min value means early renal inadequacy;
   - 6∼10 ml/min value means advanced renal inadequacy;
   - below 5 ml/min value means end-stage renal failure.

In addition, imageological examination is another common method for the diagnosis of renal function, including:

1. Ultrasound imaging of the urinary tract, which is helpful to rule out possibilities of urinary tract obstruction and chronic renal inadequacy;
2. CT examination, which shows the existence of stress-related expansion. If there is sufficient reason to doubt the obstruction, then retrograde or descending pyelography could discover some recurrent urinary tract infection factors such as urinary tract stones, obstruction, reflux or deformities;
3. CT angiography, MRI or radionuclide examination, which are helpful to determine the presence of occlusive vascular disease;
4. Renal angiography, which help make a definitive diagnosis of renal inadequacy.

In summary, in the application of antibiotics treatment, when faced with complex disease, just for renal function, there are many things need for caution. Doctors must make a thoughtful therapeutic schedule considering all information, such as contraindication, drug interaction, various laboratory parameters and examination reports etc. In addition to this, close monitoring of kidney function and real-time adjust regimen are necessary. Doctors exercise extreme caution as mild negligence may cause serious consequences, for which the doctor and the patient have to pay a terrible price. In clinical, far more than antibiotics or renal function should be cautious about. All these brought great pressure for doctors. So it is urgent to effectively reduce the professional burden on doctors and avoid medication risk.

Compared with general drugs, the supervision of antibiotics is more difficult and the situation is more urgent as its irrational use may do greater harm to humans. So it is not enough for clinical antibiotics management only depending on rules, regulations and manual intervention of Medical Management[7, 8]. Network management based on advanced information technology becomes the inevitable choice for rational use of antibiotics. The information technology which able to integrate and interoperate all kinds of information flow will enable monitoring of antibiotics more intelligent and more suitable for clinical practice requirements.

To reduce the risk of the patient's medication and make up the lack of professional knowledge structure, both clinicians and clinical pharmacists are in urgent need of specialized system solutions for technical and resource support[9, 10]. Foreign software for the rational use of drugs has many restrictions in the domestic large-scale hospital application due to the difference of language habits, number of patients and medical model. In nearly a decade, the rational drug use system embedded in HIS system is developing rapidly in China. With the application in some hospitals, the software achieved good clinical effect in rational drug use and provided valuable experience and ideas for the use of information means to control the clinical medication.

But the existing system of rational drug use still has some drawbacks:

1. The collected information is poor, which only covered drug information but no the important clinical information, such as "medical indications", "diagnosis" and so on (see the gray part of Figure 2).
2. What the system checked and warned real time mainly covered the irrational use between drug and drug, such as interaction, incompatibility, repeated use, etc.But the irrational use between drug and disease are omitted.
3. Some systems can warn for some irrational drug use such as allergies, Pathophysiology changes, but require doctors filling out online, which cost lots of time but obtain limited information.

This situation brought problems for the management of rational drug use:

1. We can only rely on software to realize partial but not overall control for clinical rational drug use.
2. To judge whether clinical factors like medication indications was reasonable or not, we couldnt obtain the real-time warning results by linkage analysis from massive information, but need input the medical record number for inquiries in different information systems, such as PACS (medical image storage and transmission system), LIS (inspection information system), EMR (electronic medical record system), etc.

Seen from Figure 3, when the irrational drug use occurred, current domestic antibiotics supervision software unable automatically extract patients clinical information or provide optional dosage regimen for physician, but only requiring physician's manual input (left) or artificial distinction(right), which may increase the burden on doctors.

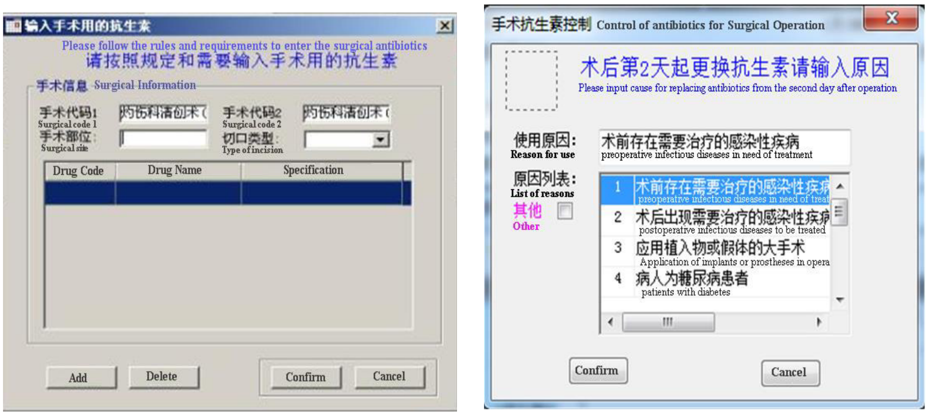

Fig. 3. Common interface diagram of current domestic antibiotics supervision software

In short, there are many areas in need of improvement to achieve efficient and intelligent network management. Confront the complex clinical condition, current system failed to achieve real time monitoring of rational drug use for actual individuals.

One reason is that the process monitoring methods of existing rational drug use systems are based on the structured document. But lots of important clinical information is a semi-structured or non-structured data form, such as electronic medical records (text), imaging results like X ray (picture). In result, clinical data among different disciplines, such as clinical medicine, pharmacy, laboratory science and medical imaging, could not be combined analysis. For example, any name of drug or dis-ease should only be input or query in a unique code, even if their names are synonymous. So it is necessary to introduce semantic technologies to change the current situation.

2.2 Semantic Approach

In fact, all experience of antibiotics use should be shared. In the Semantic Web, web content can not only be understood, but also be easily processed or inferred by machines. Due to the application of antibiotics has accumulated huge amount of information and valuable empirical data which distributed in kinds of systems, it is impossible to fully grasp for practitioners. Only by recombining and processing upon the computer technology, can these scattered, isomeric, numerous, inconsistent and dynamic resources be understood by computer. This exceeds the traditional information-process systems function and must rely on the new semantic technology.

The community of the semantic technology has developed several international standards for data representation language based on semantics, such as resource description framework (RDF) and the Web Ontology Language (OWL), so that data can be independent from the specific system. Pharmaceutical knowledge was described with the technology of ontology. The rational use of antibiotics related management documents and application guidelines are converted from natural language to semantic description, which has more clear relationship mapped to the corresponding ontology graph in order to realize intelligent monitoring and knowledge management. With the help of semantic web technology, knowledge management for the large amounts of data generated by traditional information system will become easy, while redundancy or incomplete knowledge would be effectively overcome. As a result, quality and effectiveness of rational use system for antibiotics would be further improved.

3 Implementation of SeSRUA

Based on the analysis above, we propose the approach of semantic technology to realize intelligent monitoring on rational use of antibiotics. We have implemented SeSRUA, a Semantically-enabled System for Rational Use of Antibiotics. The architecture of SeSRUA is shown in Figure 4. SeSRUA is built on the top of LarKC[11], a platform for scalable semantic data processing[5]. OWLIM is used to be the basic data layer of LarKC. The platform has a pluggable architecture in which it is possible to exploit techniques and heuristics from diverse areas such as databases, machine learning, cognitive science, the Semantic Web, and others. LarKC provides a number of pluggable components: retrieval, abstraction, selection, reasoning and deciding. In LarKC, massive, distributed and necessarily incomplete reasoning is performed over Web-scale knowledge sources.

3.1 Knowledge and Semantic Patient Data

At present, there exist several pharmaceutical data sets, such as DrugBank[3],which is developed by University of Alberta, and RxNorm[12], which is developed by US National Library of Medicine. Those data sets provide the basic knowledge of drugs and become basic data sources for the application of semantic technology in medical pharmacy. However, many of drug properties have still not yet been refined to meet comprehensive needs of knowledge for applications. For example,in Drugbank, multiple indications of a drug are described in a natural language text, which is not easy to be processed directly in a medical information system, because they are not structured data. So we should make the design of semantic data, so that they are suitable for the practice for monitoring antibiotic use.

[5] `http://www.larkc.eu`

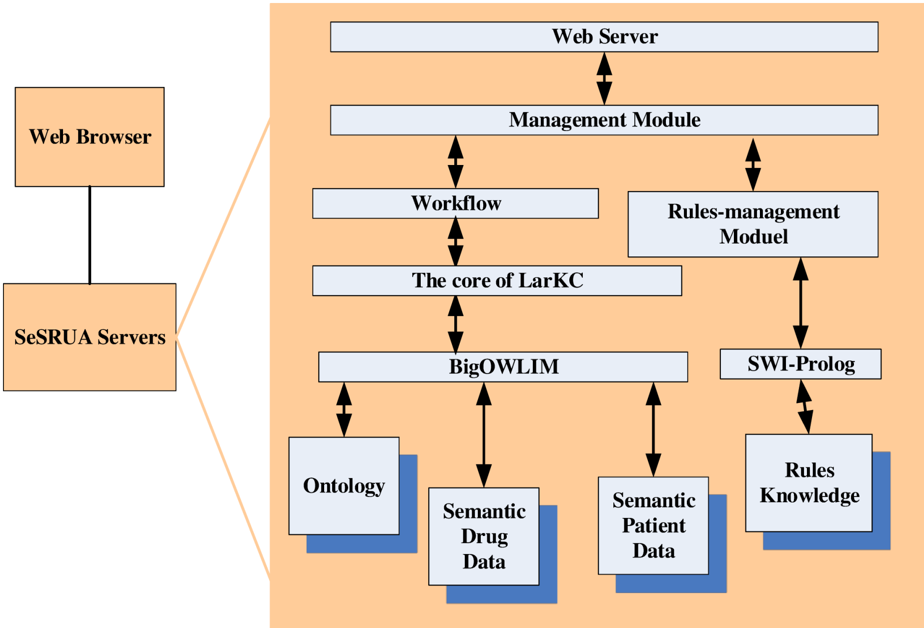

Fig. 4. The Architecture of SeSRUA

We use APDG (Advanced Patient Data Generator)[13], a knowledge-based patient data generator, to generate ten thousand of virtual patients of chronic bronchial in Hubei Province, China. Those virtual patient data are loaded into the SeSRUA system for the test. APDG uses domain knowledge to generate virtual patient data, so that the generated patient data look like real ones.

Table 1 shows the integrated data sets in SeSRUA, which include drug data sets, patient data, and generated data sets of the Chinese guidelines for rational use of antibiotics.

Table 1. The number of triples in the SeSRUA system

Group	Numbers	Triple number for each	Triple Numbe
Guidelines	247 rules	4	988
Patient Data	10,000 patients	350	3,500,000
Antibiotics	88 drugs	31	2,728
DrugBank	6,689 drugs	79	528,431
Total			4,032,147

3.2 Guidelines and Rules

Clinical guideline are one of the most useful knowledge resources for rational use of antibiotics. As the monitoring of rational use of antibiotics involves complex knowledge of guideline analysis and management process, traditional way of human intervention is not sufficient to monitor rational use of antibiotics effectively. Therefore, we introduce the semantic technology to semi-automatically transform the knowledge contained in the clinical guideline and get the semantic data with the following steps[14]:

1. Preprocessing of the guidelines. We transfer the guideline in natural language style to "if ..., then ..." style, we call these guidelines abstract rules.
2. Then we transfer the abstract rules to concrete rules with pattern based natural language processing technology. Concrete rules are relative to abstract rules. It means to make abstract rules in the guideline more concrete so that hyponymy, entailment and other logical relationship between the knowledge will become more clear.
3. Last, we use Prolog to convert some knowledge in the guidelines for rational use of antibiotics into the semantic data. The logic programming language Prolog is a rule-based language for knowledge representation. It is also convenient to be used to formalize the dynamic workflow, a distinguish feature to realize the automatic monitoring and dynamic management for the rational use of antibiotics.

3.3 User Interface

Figure 5 shows the graphic user interface of SeSRUA. The figure shows the result of monitoring over a patient on her routine blood test. Users can use web browser to visit the data in JSON form, which return from the SPARQL server. The user interface of SeSRUA transforms these JSON data into corresponding visual data and displays them in a user-friendly interface. Therefore, any SeSRUA user will be able to use it even if he/she has no any knowledge of the semantic technology. The SPARQL server returns the data in the JSON format, which can be accessed by the users. Because the JSON format data is accessed by the user through user-friendly interface of the SeSRUA system.

The SeSRUA system is expected to make effectively use of the mass clinical information. This semantic data interoperability platform can finely reduce clinical doctors?professional burden and finally realize the intelligent supervision of antibiotics.

4 Evaluation

Currently we have developed SeSRUA system framework for the initial study, and obtained preliminary results:

1. Integrated DrugBank and Chinese semantic data of nearly 100 kinds of present antibiotics used in China hospitals;

Fig. 5. The SeSRUA system frame diagram

2. Integrated semantic patient data of ten thousand virtual patients with chronic bronchitis;
3. Transformed the knowledge of the guidelines of clinical use of antibiotics, which are expressed in natural language, into one in a semantic language, namely, to generate the corresponding semantic data of the guidelines.
4. Evaluated the clinical application effects of the experimental system of SeSRUA.

Table 2. Clinical Evaluation of Overall Results

Projects of evaluation	Correct Medical Records	Total Ratio
Whether to Use Antibiotics	93	93%
What Antibiotics to Use	55	55%
Total Evaluation	55	55%

Clinicians and clinical pharmacists together selected the first 100 copies of medical records and estimated the automatic results of SeSRUA which contain “Whether to use antibiotics” and “What antibiotics to use” (see Tab. 2). The medical records are divided into five groups based on their common character evaluated, the detailed results see Figure 6, which is also mentioned in Table 3.

Group	Number of Medical records	Indications of drug use	Whether to use antibiotics		What antibiotics to use		Overall evaluation	Main problems for improvement*
			Systematic Review	Whether correct	Systematic Review	Whether correct		
1	38	Fever, Abnormal blood test results	No enough reason to use	Yes	No, did not find any bacterial infection	No	No	2 (1,3)
2	24	None	No enough reason to use	Yes	No, did not find any bacterial infection	Yes	Yes	(1,3)
3	14	Fever, Abnormal blood test results, etiology check for bacterial infection	Probably should use	Yes	Bacterial test positive, recommend using certain types of antibiotics	Yes	Yes	4,5(1,3)
4	17	etiology check for bacterial infection	Probably should use	Yes	Bacterial test positive, recommend using certain types of antibiotics	Yes	Yes	5(1,3)
5	7	Fever	No enough reason to use	No	No, did not find any bacterial infection	No	No	2(1,3)
Total	100							

*The details see Table 3.

Fig. 6. Groups of Medical records

Table 3. Groups of SeSRUA for Improvement

Group	Main problems for improvement
1*	The present history description should be improved. It will be perfect if the content of diagnostic description be more accurate. For example, the outpatients' chest radiograph should include variety of situations such as chest infection and pulmonary thicker texture without infection etc. It is necessary to increase cases of chronic bronchitis in relieving stages besides acute stages appropriately.
2	For patients with acute exacerbation of chronic bronchitis (AECB), if there are any signs of infection, such as symptoms or examination results, then there is a possibility to choose antimicrobial drugs for prophylaxis based on experience. Even though the bacteriological examination report did not find any bacterial infection, as inspection reports may be false-negative results.
3*	Further expand the content to cover more medication indications, such as sputum color (yellow-green represents infection), antimicrobial susceptibility test results, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and other indicators.
4	The pathogens of acute exacerbation of chronic bronchitis (AECB) coverage should be: Haemophilus influenzae, Streptococcus pneumoniae, Moraxelle catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae and Klebsiella pneumoniae etc. The variety of Pathogens in SeSRUA should be increased.
5	The dose schedule provided should be more accurate and comprehensive. For example?What specific drugs is the third-generation cephalosporin? Is there any alternative medicine to choice in addition to the preferred drugs?

* Group 1 and 3 happens highly in all the medical records

5 Conclusion and Future Work

5.1 Conclusion

In this paper, the problems and necessities in antibiotics management were analyzed. A noted technical method using semantic technology to monitor rational use of antibiotics was put forward. We designed the system framework of the rational use of antibiotics of semantic technology system based on SeSRUA, introduces the basic technology of module of SeSRUA system, including the use of LarKC massive se-mantic data processing platform as the basis of the data processing core, and adopts the logic programming language Prolog as the rules for dynamic language data work-flow description language, the realization of the basic functions of SeSRUA system. Experimental system of SeSRUA realized linkage analysis of electronic medical records, routine blood tests and pathogens inspection reports. It directly search drug indications for doctors and offer dose regimen with a comprehensive analysis based on advanced semantic technology. It has solved the "Why" and "How" questions of using antibiotics, which is more intelligent than the existing other systems, which have been used in China hospitals. However, due to SeSRUA is still in its prototype, there is still much future work for improvement.

5.2 Future Work

1. Improvement of the system. Due to SeSRUA is still in its prototype, there are still lots of work needed for improvement. According to the existing evaluation results, Improvement for SeSRUA are expected to be done in five groups (see Tab.3).
2. Tests of SeSRUA in a medical practice. We will test the system in some small clinics in China for one year. After that, we will exploy SeSRUA in some medium-sized hospitals in China for further improvement.

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