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# Arden Syntax Clinical Foundation Framework for Event Monitoring in Intensive Care Units: Report on a Pilot Study

**Jeroen S. de Bruin[a,b], Julia Zeckl[a,c], Katharina Adlassnig[a], Alexander Blacky[d], Walter Koller[e], Andrea Rappelsberger[b], Klaus-Peter Adlassnig[a,b]**

[a] *Medexter Healthcare GmbH, Borschkegasse 7/5, A-1090 Vienna, Austria*
[b] *Section for Artificial Intelligence and Decision Support, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria*
[c] *University of Applied Sciences Technikum Wien, Höchstädtplatz 6, A-1200 Vienna*
[d] *VAMED-KMB Hospital Management and Operation GmbH, Spitalgasse 23, A-1090 Vienna, Austria*
[e] *University Clinic for Hospital Hygiene and Infection Control, Medical University of Vienna and Vienna General Hospital, Währinger Gürtel 18–20, A-1090 Vienna, Austria*

**Abstract**

The creation of clinical decision support systems has received a strong impulse over the last years, but their integration into a *clinical* routine has lagged behind, partly due to a lack of interoperability and trust by physicians. We report on the implementation of a clinical foundation framework in Arden Syntax, comprising knowledge units for (a) preprocessing raw clinical data, (b) the determination of single clinical concepts, and (c) more complex medical knowledge, which can be modeled through the composition and configuration of knowledge units in this framework. Thus, it can be tailored to clinical institutions or patients' caregivers. In the present version, we integrated knowledge units for several infection-related clinical concepts into the framework and developed a clinical event monitoring system over the framework that employs three different scenarios for monitoring clinical signs of bloodstream infection. The clinical event monitoring system was tested using data from intensive care units at Vienna General Hospital, Austria.

***Keywords:***

Expert Systems, Knowledge Bases, Infection Control.

## Introduction

Recognition of the benefits and potentialities of information and communication technology in healthcare (eHealth) [1-3] led to political support for healthcare digitization; healthcare institutions were given financial incentives to adopt and make "meaningful use" of electronic health records (EHRs) [4]. Although the term "meaningful use" is quite expansive, it does include the development and use of clinical decision support systems (CDSSs). CDSSs are eHealth systems designed to assist health professionals in clinical decision-making tasks at the point of care.

Clinical event monitors are CDSSs specialized in the delivery of information. A clinical event monitor delivers information to healthcare providers where and when they need it [5]. Generally, a clinical event monitor performs one or more of the following tasks [5]: (a) it issues warnings about adverse events such as potentially harmful drug–drug interactions or complications of treatment, (b) it interprets medical findings, such as laboratory test results, (c) it provides reminders for immediate or future diagnostic or therapeutic steps, (d) it proposes (alternative) diagnoses or treatment options, and (e) it coordinates complex clinical protocols or workflows.

A substantial number of clinical event monitoring systems have effectively addressed one or more of the aforementioned tasks for a variety of healthcare settings. In the field of infection control, there have been many studies on (semi-) automated systems for the detection and monitoring of healthcare- associated infections [6-8]. Similarly, computerized adverse drug event detection and computerized physician order entry have also been widely researched [9, 10]. The performance of the large majority of systems has been good or excellent. The systems, when measured, proved to be an improvement over traditional or manual methods.

Despite the success of these systems, their use and integration have been limited to their local setting. This is a multifactorial problem. In the present report, we focus on technical and psychological aspects. From a technical point of view, most systems were developed for a specific hospital information system and specific EHRs. Furthermore, they might not always be implemented with established communication standards. As a result, the systems lack interoperability. The effort of porting or recreating the systems outweigh their potential benefits. From a psychological point of view, many systems have only been verified internally. In other words, they have been tested with data from a single healthcare institution. Lacking external validation, the general applicability of the results remains unproven. Moreover, even if a system is verified externally its acceptance by third parties is not guaranteed because the adoption of the system might be perceived as a loss of autonomy [11]. This is especially true of illnesses and adverse events that are not yet fully understood, or which lack consensus regarding their definition or method of detection.

From the above discussion, it follows that the acceptance and dissemination of the system could be improved by providing an interoperable, configurable system. Such a system would use established standards of communication and knowledge representation, thus enhancing its interoperability. A widely known standard for computerized knowledge representation and processing is Arden Syntax [12]. The latter is a programming language for the collection, description, and exchange of medical knowledge in a machine-executable format. Indeed, many of

the tasks performed by clinical monitoring systems have already been modeled in Arden Syntax [13-16]. Improving its acceptance among clinicians would require a knowledge base that could be configured to fit the user's clinical knowledge and experience.

In our view, clinical event monitors are systems that can be composed of standardized configurable building blocks. As such, a limited set of standardized medical knowledge units, which we refer to as the clinical foundation framework, should be available. Based on these, event systems may be constructed and configured according to the wishes of clinical institutions or patient caregivers. These basic blocks of knowledge would be used for preprocessing raw clinical data and determining less complex, clearly defined clinical concepts that are directly measured from objective data and laboratory results. Based on this clinical foundation framework, more complex medical knowledge can then be modeled through the composition and configuration of these basic knowledge blocks.

In the present study, we report preliminary results following the implementation of a clinical foundation framework. We created a clinical event monitoring system that monitors several infection-related clinical concepts based on definitions from internationally respected institutions, such as Centers for Disease Control and Prevention (CDC), Atlanta, USA, and the European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden. For each of these concepts, we constructed rules in Arden Syntax and integrated them into the clinical foundation framework. Based on a retrospective data analysis with data from intensive care units (ICUs) we show that using knowledge units in the clinical foundation framework as building blocks, we can provide multiple definitions for higher- level clinical concepts.

## Methods

### Clinical background

We discuss six infection-related clinical concepts included in the clinical foundation framework. These clinical concepts are well-known signs of infection and are used in existing surveillance definitions for infections from the CDC and ECDC. These concepts are fever, leukopenia, leukocytosis, elevated C-reactive protein (CRP), shock, and drop in blood pressure. Definitions of fever, leukopenia and leukocytosis were taken from the "ECDC European surveillance of healthcare-associated infections for intensive care units" protocol, version 1.02 [17]. The definition of elevated CRP was obtained from the CDC National Healthcare Safety Network surveillance definitions for specific types of infection [18]. Definitions of the remaining concepts were constructed by clinical experts. The definitions are listed in Table 1.

### Study design, setting, and participants

We conducted a retrospective single-center cohort study on prospectively collected and validated data. The investigation was performed at the Vienna General Hospital (VGH), Austria, which is a 1,933-bed tertiary-care and teaching hospital. Data were collected from patients admitted to one or more of the ICU's at the hospital between 1 January and 31 March 2013. All adult patients (age ≥ 18 years) admitted for at least 24 hours were eligible for the study.

*Table 1 – Definitions of clinical concepts modeled in the clinical foundation framework.*

| Clinical concept | Definition |
|---|---|
| *Fever* | Body temperature > 38 °C |
| *Leukopenia* | < 4,000 WBC/mm$^3$ blood |
| *Leukocytosis* | ≥ 12,000 WBC/mm$^3$ blood |
| *Elevated CRP* | CRP >10 mg/dl blood |
| *Shock* | $\frac{\text{Systolic blood pressure}}{\text{Heart rate}} < 1$ |
| *Drop in BP* | BP value in the 37.5% percentile of all averages between systolic and diastolic BP over the last 3 days |

*Note: WBC, white blood cell; CRP, C-reactive protein; BP, blood pressure.*

### Data management and sample size

Demographic patient data, as well as clinical and laboratory values, were obtained through systematic interrogation of the Philips IntelliSpace Critical Care and Anesthesia (ICCA) information system, which is in operation at ICUs in the VGH. Interrogation of the data sources using the selection criteria mentioned earlier yielded a total of 984 patient stays.

### Knowledge base and data processing

For this project, we reimplemented a part of the knowledge base of Moni (Monitoring of Nosocomial Infections), a fully automated knowledge-based surveillance tool for the identification, monitoring, and reporting of nosocomial (hospital-acquired) infections in ICUs [19].

We used Arden Syntax to implement rules for the clinical infection-related concepts listed in Table 1, as well as rules for data preprocessing and feature extraction. Arden Syntax is a programming language used for representing, processing, and sharing medical knowledge, employed in an executable format by CDSSs to generate alerts, reminders, interpretations, as well as manage messages to clinicians [20]. In an Arden Syntax knowledge base, medical knowledge is divided into medical logic modules (MLMs) [13]; each MLM contains instructions and logic to support at least a single medical decision.

In the clinical foundation framework, MLMs perform one of three types of processing tasks:

- Raw data processing, which deals with importing and processing raw data directly from the structured data source, here the Philips ICCA system.
- Data-to-symbol conversion, which deals with data preprocessing (such as handling missing or contradictory values), and feature extraction (such as calculating mean values or intermediate scores).
- Symbol calculation, which deals with the calculation of basic clinical concepts (e.g., medical symptoms and signs).

In all 17 MLMs were created; seven for raw data import and processing, four for preprocessing and feature extraction, and six for symbol calculation. Table 2 lists these MLMs with a brief description of their task(s).

We used the ARDENSUITE integrated development and test environment (IDE) for the implementation, management, and testing of MLMs in the clinical foundation framework. For the execution of MLMs, we used the ARDENSUITE server [21], to be executed through service-oriented access for client applications.

*Table 2 – Medical logic modules part of the clinical foundation framework*

| MLM name | Task description |
|---|---|
| **Raw data processing** | |
| *Temp* | Imports body temperature in centigrade over the last 24 hours |
| *ThermoReg* | Imports explicit indications of thermoregulation in the last 24 hours, which is performed to cool the patient |
| *Leuko* | Imports leukocyte concentrations in G/l |
| *CRP* | Imports CRP values in mg/dl |
| *SystBP* | Imports systolic blood pressure measurements over the last 24 hours |
| *DiastBP* | Imports diastolic blood pressure measurements over the last 24 hours |
| *HeartRate* | Imports heart rate measurements over the last 24 hours |
| **Data-to-symbol conversion** | |
| *TempMax* | Determines the daily maximum body temperature in centigrade |
| *LeukoMax* | Determines the daily maximum leukocyte concentration in G/l |
| *CRPMax* | Determines the daily maximum CRP in mg/dl |
| *BPProfile* | Determines the blood pressure profile with data over the last 6 hours |
| **Symbol calculation** | |
| *TempElev* | Determines the presence of fever based on a patient's body temperature |
| *Leukopenia* | Determines the presence of leukopenia based on a patient's leukocyte count |
| *Leukocytosis* | Determines the presence of leukocytosis based on a patient's leukocyte count |
| *CRPElev* | Determines the presence of elevated CRP based on a patient's CRP value |
| *Shock* | Determines the presence of (septic) shock based on a patient's systolic BP and heart rate |
| *DropInBP* | Determines the presence of a drop in BP based on BP profiles over the last 72 hours |

*Note: MLM, medical logic module; CRP, C-reactive protein; BP, blood pressure.*

**Presentation of results**

We show how different versions of a system for the detection of clinical signs of infection can be constructed and configured, using basic building blocks from the clinical foundation framework. Based on the data collected from the ICUs at VGH, we show how different setups yield different results.

## Results

Of the 984 patients included in this study, 417 were female (42.4%). The youngest was 18 years old, the oldest 92 years; the median age was 61 years, with an interquartile range (IQR) of 24 years. In all 7,573 patient days were recorded during the study period. The length of the hospital stay ranged between two and 93 days, median 4 days, and an IQR of 6 days.

We developed three scenarios, which we model with the clinical foundation framework:

1. *ClinSignsV1*: A straightforward definition of the concept "clinical signs of bloodstream infection" as specified by the ECDC in [17], involving only the clinical concepts *elevated body temperature*, *leukopenia,* and *leukocytosis*.
2. *ClinSignsV2:* A more complex definition that employs a more comprehensive modeling of the clinical concept of *fever*. In this case, the presence of fever is not only derived from the patient's body temperature, but also from clinical interventions that indirectly indicate the presence of fever, such as the use of cooling packs or blankets (cf., ThermoReg in Table 2).
3. *ClinSignsV3:* A definition that extends the *ClinSignsV2* definition by including known markers of infection such as *elevated CRP* and *hypotension*. In this scenario, hypotension is modeled with the clinical concepts of *shock* and *drop in blood pressure*.

Table 3 shows the logical definitions of the clinical concepts used in each scenario. Table 4 shows the number of registered events for relevant clinical concepts and infection symptoms in the clinical foundation framework, and for the clinical concepts listed in Table 3.

*Table 3 – Medical logic modules created for various definitions of "clinical signs of bloodstream infection" and their respective logical rules.*

| MLM name | Definition |
|---|---|
| **Scenario 1** | |
| *ClinSignsV1* | *TempElev* ∨ *Leukopenia* ∨ *Leukocytosis* |
| **Scenario 2** | |
| *Fever* | *TempElev* ∨ *ThermoReg* |
| *ClinSignsV2* | *Fever* ∨ *Leukopenia* ∨ *Leukocytosis* |
| **Scenario 3** | |
| *Hypotension* | *Shock* ∨ *DropInBP* |
| *ClinSignsV3* | *Fever* ∨ *Leukopenia* ∨ *Leukocytosis* ∨ *Hypotension* ∨ *CRPElev* |

*Note: MLM, medical logic module; BP, blood pressure; CRP, C-reactive protein.*

*Table 4 – Symbolic calculation and the resulting number of symptom and scenario events.*

| MLM name | #Events |
|---|---|
| **Clinical foundation framework** | |
| *TempElev* | 1,394 |
| *ThermoReg* | 4,527 |
| *Leukopenia* | 270 |
| *Leukocytosis* | 2,214 |
| *CRPElev* | 3,606 |
| *Shock* | 2,968 |
| *DropInBP* | 3,217 |
| **Scenario 1** | |
| *ClinSignsV1* | 3,268 |
| **Scenario 2** | |
| *Fever* | 5,154 |
| *ClinSignsV2* | 5,760 |
| **Scenario 3** | |
| *Hypotension* | 4,656 |
| *ClinSignsV3* | 6,835 |

*Note: MLM, medical logic module; CRP, C-reactive protein; BP, blood pressure.*

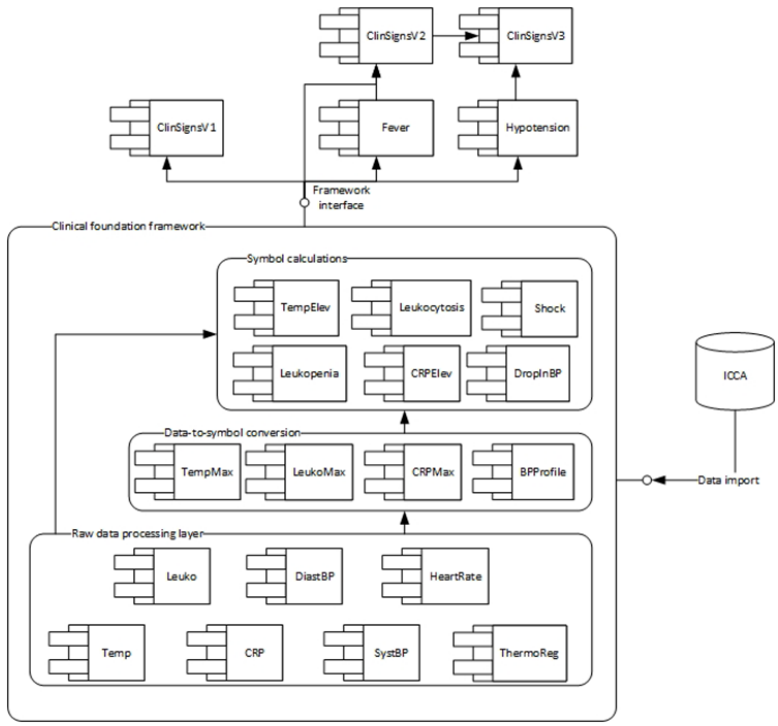


*Figure 1 – Graphical depiction of the clinical event monitoring system's architecture. The picture shows the medical logic modules (MLMs) integrated into the clinical foundation framework, and custom-built MLMs for the detection of additional symptoms and infection signs constructed above it. The arrows indicate data dependencies between MLMs or MLM collections. Note: CRP, C-reactive protein; BP, blood pressure.*

A graphical depiction of the knowledge base for these clinical concepts (including the clinical foundation framework) is shown in Figure 1.

## Discussion

We presented the implementation of a clinical foundation framework in Arden Syntax. The calculation of standardized lower-level clinical concepts directly related to raw clinical data is pre-implemented in a framework of this nature. Consequently, more complex and semantically richer concepts can be calculated by combining elements from the framework with custom implementations. This permits easier and more rapid construction of CDSSs.

The scenarios presented in the Results section all yielded different results. Using the clinical foundation framework, we were able to create different versions of the same clinical concept. This may be useful when the system needs to be implemented for different purposes or different stages of the problem. For example, ClinSignsV1 would be more suited for prospective clinical alerting due to its relatively low number of occurrences, while the more complex ClinSignsV2 would be more suited for retrospective detection of healthcare-associated infections.

The limitations of the study are worthy of mention. First, as the clinical foundation framework is still in its pilot phase, not many MLMs have been implemented so far. Second, we still need to reimplement the systems integrated at VGH in order to test the framework in a clinical routine. Finally, new systems need to be created and composed in order to assess the ease of construction and improve the performance of the framework and its interfaces.

Several CDSSs have been implemented with Arden Syntax and integrated into clinical routine at VGH, in a variety of clinical specialties, such as nephrology, oncology, and infection control [22]. Inspection of these systems revealed that most of the MLMs in these CDSSs have processing duties performed by the clinical foundation framework, such as raw data processing, data-to-symbol conversion, or symbol calculation. As such, the implementation and configuration of these and similar systems could be simplified by the clinical foundation framework. Furthermore, as the clinical foundation framework grows, an extension of these systems and more complex modeling of symptoms, signs, interpretations of laboratory test results, clinical findings, diseases, therapies, adverse events, quality measures, etc. will become easier.

## Conclusion

We created a clinical foundation framework, based on which clinical event monitoring systems can be constructed through combination and configuration. Using the framework, CDSSs can be created more rapidly and configured according to the specific needs of healthcare institutions and patients' caregivers.

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**Address for correspondence**

Univ.-Prof. DI Dr. Klaus-Peter Adlassnig, FACMI Section for Artificial Intelligence and Decision Support

Center for Medical Statistics, Informatics, and Intelligent Systems Medical University of Vienna

Spitalgasse 23, 1090 Vienna, Austria

E-mail: klaus-peter.adlassnig@meduniwien.ac.at and

Medexter Healthcare GmbH Borschkegasse 7/5, 1090 Vienna, Austria

E-mail: kpa@medexter.com