Original Article

Methodology and Early Results of the First Surveillance Program on Prevention and Control of Antimicrobial Resistance in Isfahan, Iran: The IAS-I Study

Sayed Nasser Mostafavi, Soodabeh Rostami[1], Behrooz Ataei, Sina Mobasherizadeh[1], Azam Cheraghi[2], Somayeh Haghighipour, Samereh Nouri[3], Arezoo Pourdad[4], Parisa Ataabadi[4], Naser Almasi[5], Leila Heidary[5], Kourosh Naderi[5], Setareh Korangbeheshti[5], Shiva Navabi[6], Laleh Masssah[6], Zohreh Norouzi[6], Mehrnoush Bakhtiyaritabar[6], Saeed Moayednia[3], Dariush Shokri[1], Mahin Mikhak[5], Majid Rahmani[6], Mohammad Hashemi[7], Reza Etminani[2], Nasrin Ahmadi[8], Mahboubeh Akhlaghi[9], Roya Kelishadi[10]

Infectious Diseases and Tropical Medicine Research Center, Isfahan University

Abstract

Background: Isfahan Antibiotic Resistance Surveillance System-1 has been instituted in Isfahan, Iran to construct a project for surveillance of clinically significant bacteria, and to help raise a logic regional stewardship program for prevention and control of disseminating-resistant organisms. **Methods:** During March 2016 to March 2018, an antibiotic resistance surveillance system was designed and implemented by Isfahan Infectious Diseases and Tropical Medicine Research Center. The surveillance program was implemented in three general hospitals in Isfahan. In addition to the routine microbiology data, clinical data (differentiation between true infections and contamination, healthcare-associated infections (HCAI) and community-acquired infections (CAI), as well as determination of the infection site) were obtained and analyzed by WHONET software. **Results:** During a 2-year period, from 7056 samples that revealed growth of bacteria, 3632 (51.5%) isolates were detected as contamination and 3424 (48.5%) true bacterial isolates were identified. Of these, about 32% of isolates were recognized as HCAI. Totally, the most recognized infections were urinary tract infection, bloodstream infection and skin and soft tissue infections. In patients with HCAIs, 70% of isolates were gram negative and in patients with CAIs 73% isolates were gram negative bacteria. **Conclusions:** The strength of the project is gathering enough clinical information in addition to microbiologic data, which would increase application of the results for empiric treatment and prevention of the infectious diseases in clinical settings.

Keywords: *Bacteria, drug resistance, epidemiology, Iran, methods*

Introduction

Antimicrobial resistance (AMR) is one of the most important international problems.[1] World Health Organization (WHO) highlighted the significance of this statement by naming the 2011 World Health Day as "Antibiotic resistance: no action today, no cure tomorrow." This organization recognized surveillance programs on prevention of AMR as essential necessities to tackle this threat.[2] To date, several antimicrobial surveillance systems have been initiated; however in developing nations few surveillance programs have been established.[2,3]

Multiple studies have been conducted on AMR in different regions of Islamic republic of Iran. These researches showed extraordinary resistance among bacterial strains.[4-11] However, these investigations had been performed in limited area, sometimes in small number of the organisms, and with different methodologies that make the results unsuitable for decision about the best empiric treatments for infections in the country. Therefore, there is a need for an active surveillance of clinically significant bacteria for better recognition and prevention of antibiotic resistance.

The aim of present survey was to implement a regional surveillance program for determining antibiotic resistance in bacteria isolated from clinical samples. In addition, it targeted to differentiate true infections from contamination, healthcare-associated infections (HCAI) from community-acquired infections (CAI), as well as to determinate the infection site.

Methods

Initial research development and design

In May 2015, to design a local AMR surveillance system a work group organized in Isfahan Infectious Diseases and Tropical Medicine Research Center (IDRC). This group established a program entitled "Isfahan Antibiotic resistance Surveillance

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of Medical Sciences, Isfahan, Iran, [1]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Hospitals Supervision and Accreditation, Vice-Chancellery for Clinical Affairs, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Microbiology, Clinical Laboratory of Alzahra Medical Center, Isfahan, Iran, [4]Alzahra Medical Center, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Microbiology, Clinical Laboratory of Dr. Shariati Hospital, Isfahan Social Security Organization, Isfahan, Iran, [6]Department of Microbiology, Clinical Laboratory of Dr. Gharazi Hospital, Isfahan Social Security Organization, Isfahan, Iran, [7]Cardiovascular Department, Interventional Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [8]Vice-Chancellery for Clinical Affairs, Isfahan Social Security Organization, Isfahan, Iran, [9]Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran, [10]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Address for correspondence: *Dr. Soodabeh Rostami,*
Soffeh Street, Alzahra Hospital, Research Comprehensive Laboratory, Infectious Diseases and Tropical Medicine Research Center, Isfahan, Iran.
E-mail: srostami1876@gmail.com

system-1 (IAS-1)" and subsequently considered as surveillance system executive committee. Chairman of the research center was the head of committee. Committee members included: a representative of Research and technology, Food and Drug, Clinical affairs and Health vice-chancelleries of Isfahan University of Medical Sciences (MUI) and four faculty members of infectious diseases department. The main function of executive committee was to plan, implement, facilitate, and debug performance of the project. After the third meeting, the executive committee decisions were as follow: establishment of two main operational committees including: performing and scientific committee, and performance of the project in three major general hospitals of the Isfahan city during March 2016 to March 2018 as the first phase of surveillance program (Ethical approval and Project No: 194042). Performing committee was composed of three infection control physicians, four infection control nurses, three microbiologists, and one chief coordinator. The main function of the performing committee was to collect and report microbiologic and clinical data. Scientific committee was consisting of three infectious disease specialists, one pediatric infectious disease subspecialist, and two medical bacteriology PhDs. The scientific committee was responsible for preparing guidelines and interpretation of final results.

Procedure and measurements

Place of the surveillance

Geographically, the area under surveillance was the city of Isfahan, as the capital of Isfahan Province, located in center of Islamic Republic of Iran. The population under surveillance included the peoples who live in Isfahan (according to the census in 2016, 2,243,249 peoples).

In 2016, Isfahan has five general hospitals including: three educational general hospitals under the supervision of Isfahan University of Medical Sciences and two general hospitals under the supervision of Iranian Social Security Organization. In this survey, three hospitals (Alzahra hospital, Dr. Shariati hospital, and Dr. Gharazi hospital) were candidate to participate. Clinical microbiology laboratories of these referral medical centers achieved an approved Quality Credit from the Vice-Chancellor of Iranian Ministry of Health, Treatment, and Medical Education and were also two of them (Alzahra and Dr. Shariati hospitals) collaborators of WHO in reporting of susceptibility of microorganisms in Global AMR Surveillance System (GLASS)[12] program.

The Al-zahra hospital, which was the only tertiary care referral hospital in the Isfahan, included 318 medical, 300 surgical, 10 kidney transplant, and 115 intensive care unit (ICU) beds. The laboratory of the hospital received approximately 8000 specimens for bacterial culture per year. Dr. Shariati and Dr. Gharazi hospitals totally included 236 medical, 215 surgical and 19 ICU beds. The laboratories of these hospitals received approximately 6000 specimens for bacterial culture per year.

Data collection and reporting

During March 2016 to March 2018, all bacteria isolated from all clinical samples submitted to three hospital microbiology laboratories were enrolled to survey. Clinical sampling procedures were accomplished by experienced nurses in medical wards and sometimes by surgeons in operational rooms. National guidelines were applied for collecting and handling of the specimens. Respiratory samples that were collected with methods other than bronchoalveolar lavage and biopsy were excluded. Basic demographic information including: hospital record number, age, sex, and admission ward were collected on each patient.

Bacterial isolation, identification, and antibiotic susceptibility testing were performed using conventional methods and recommendations of Clinical Laboratory and Standards Institute (CLSI) guidelines 2016 through 2018.[13] In all participated hospitals, the same dehydrated antibiotic discs (Mast, UK) and if necessary minimum inhibitory concentration (MIC) test strip (Liofilchem, Italy) were applied.

For data collection, we used the WHONET software which has multifunctional analysis ability and was produced by WHO for routine microbiology laboratory data management. For accumulation of clinical results, we added three items for determination of contaminated samples, source of the infection (healthcare-associated versus community-acquired), and site of the infection (urinary tract, sepsis, blood stream …).

Operational procedures

In each participated hospital, after obtaining microbial culture results, the infection control team made difference between true infection and contamination, HAI and CAI and recognized the infection site. This was made by practical guidelines which prepared by scientific committee with regard to previous literature [Boxes 1, 2 and Supplement Table 1].[14-16] Finally, all microbiology and clinical data were recorded in WHONET software by the laboratory staff that was responsible for data record. At the end of each month, the WHONET files were sent to IDRC. There, all WHONET files from participated hospitals were merged and analyzed.

Ethical consideration

The study protocol was approved by the Institutional Review Board of Isfahan University of Medical Sciences (Approval number: 194042). As the subject of the surveillance was the bacteria, it was not necessary to obtain the patients' consent.

Results

From March 2016 to March 2018, 24 WHONET files (1 file/per month) were received from Dr. Shariati and Dr. Gharazi hospitals and 17 WHONET files (1 file/per month) from Alzahra hospital. Urine culture information was reviewed and analyzed only in the first year due to the large number of samples. Totally, data from 29,176 clinical samples were analyzed. Of these, about 21654 (74%) samples showed negative results and 466 (2%) samples revealed growth of fungi. In 7056 samples that revealed growth of bacteria, 3632 (51.5%) isolates were detected as contamination and excluded from the study. From 3424 remaining isolates that included in the study, 2327 (68%) isolates were isolated from CAIs and the remaining ones (1097; 32%) from HCAIs. In patients with confirmed CAIs and HCAIs, 1193 (51%) and 589 (54%) were males, 286 (12%) and 118 (10%) were ≤20 years, respectively.

In patients with CAI, most samples were received from emergency room (55%), internal medicine (17%), surgery (8%), ICU (4%), and other wards (17%), whereas in the HCAIs, most infections occurred in ICU (34%), internal medicine (26%), surgery (12%), emergency room (10%), and other wards (18%).

The most recognized infections in CAIs were urinary tract infection (50%), bloodstream infections (31%), and skin and soft tissue infections (10%). In patients with HCAIs bloodstream infections (36%) and urinary tract infections (26%) were the most diagnosis followed by surgical site infections (18%), pneumonia (6%), and meningitis (6%).

In patients with CAIs, 1707 (73%) isolates were gram negative bacteria and the most common gram negative strains were *Escherichia coli* (62%) [Table 1]. Overall, they were more susceptible to colistin (100%), imipenem (93.2%), amikacin (86.3%), meropenem (85.6%), and nitrofurantoin (83%) [Table 2]. The most common gram positive isolates from CAIs were *Staphylococcus aureus* (37%) [Table 1]. The more sensitivity of gram positives was to amikacin (96.9%), teicoplanin (89.9%), vancomycin (89.9%), nitrofurantoin (88.9%), linezolid (88.5%), rifampin (88.3), and gentamicin (72.6%) [Table 3].

In patients with HCAIs, 766 (69.8%) isolates were gram negative. The most common gram negative strains were *Klebsiella pneumoniae* (30%) [Table 1]. In total, gram negatives were more susceptible to colistin (100%), nitrofurantoin (67.3%), imipenem (66.2%), and amikacin (55.7%) [Table 2]. The most common gram positive isolates from HCAIs were *enterococcus spp* (43%) [Table 1]. Higher sensitivity of gram positive organisms was to linezolid (97%), rifampin (86.7%), amikacin (81.8%), nitrofurantoin (75%), and vancomycin (69.5%), respectively [Table 3].

Discussion

In this paper, we presented design, methodology, and early results of IAS-1 program. This AMR surveillance program seems to be the first project in which combined clinical data to microbiologic results. To date, many AMR surveillance programs have been implemented around the world. They are different in various factors including:

Box 1: Differentiation of contamination from true infection in isolated bacteria

1. If the bacterium is a common pathogen in accordance to the site of isolation and patient has clinical or laboratory findings of inflammation at that site it is considered as a true pathogen
2. If the bacterium is an inhabitant skin flora* and the strain cultivated only once from the patient, it is considered as contaminate organism
3. If inhabitant skin flora or an uncommon pathogen in accordance to the site of isolation is cultivated for more than one time with identical serotype and susceptibility profile and the patient has clinical or laboratory findings of inflammation at that site it is considered as a true infection
4. If an uncommon pathogen in accordance to the site of isolation is cultivated only once from a sterile site, and the patient has clinical or laboratory findings of inflammation at that site and the patient's physician agrees about the reality of the organism as a pathogen, it is expected as a true pathogen

*Inhabitant skin flora: Diphtheroid (Corynebacterium) spp., Bacillus (not B. anthracis) spp, Propionibacterium spp, Coagulase-negative staphylococci (including S. epidermidis), Viridans group streptococci spp., Aerococcus spp., and Micrococcus spp.

Box 2: Differentiation of healthcare associated from CAIs in isolated organisms

In patients in whom the sample for culture is obtained after 48th h of the admission and the specimen is sent for a new symptom of the infection (such as fever, erythema/swelling of the surgical site, or any change in the general condition of the patient), the infection is considered as a HAI.

In other cases, the infection is assumed as CAI.

Table 1: The list of bacteria isolated from CAIs and HCAIs

	Organism	Number of isolates (%)
CAIs		
Gram negative bacteria	*Escherichia coli*	1066 (62)
	Klebsiella pneumoniae	207 (12)
	Pseudomonas aeruginosa	120 (7)
	Klebsiella aerogenes	108 (6)
	Acinetobacter baumannii	82 (5)
	Other Enterobacteriaceae	81 (5)
	Other gram negatives	43 (3)
	Total	1707
Gram positive bacteria	*Staphylococcus aureus*	232 (37)
	Enterococcus sp.	160 (26)
	Staphylococcus epidermidis	133 (21)
	Other *Streptococci*	50 (8)
	Streptococcus pneumoniae	17 (3)
	Coagulase-negative Staphylococci	16 (3)
	Streptococcus pyogenes	12 (2)
	Total	620
HCAIs		
Gram negative bacteria	*Klebsiella pneumoniae*	230 (30)
	Escherichia coli	182 (24)
	Acinetobacter baumannii	172 (22)
	Pseudomonas aeruginosa	88 (11)
	Klebsiella aerogenes	40 (5)
	Proteus mirabilis	22 (3)
	Other gram negatives	19 (3)
	Other Enterobacteriaceae	13 (2)
	Total	766
Gram positive bacteria	Enterococcus sp.	141 (43)
	Staphylococcus aureus	98 (30)
	Staphylococcus epidermidis	71 (21)
	Streptococcus pyogenes	8 (2)
	Streptococcus pneumoniae	4 (1)
	Other Streptococcus sp.	7 (2)
	Coagulase-negative Staphylococcus	2 (1)
	Total	331

geographic location, priority pathogens and specimens, type of information, and source of infection (nosocomial/outpatient).[2,3,17,18]

One of the most comprehensive programs is SENTRY program which includes 30 medical centers in the United States, 8 in Canada, 10 in South America, and 24 in Europe.[19] The most important advantages of the program are multinational coverage, low workload for participating laboratory, and testing of isolates in a central reference laboratory. The most notable disadvantage is delay in reporting of data.[17,18]

European AMR Surveillance System is another multinational surveillance that was organized in 375 centers in 15 European countries on *Streptococcus pneumoniae* and *Staphylococcus aureus* isolates. The advantages of the program are good external quality and timeliness in reporting of information. The disadvantage is relatively great workload for participating laboratory.[17]

Despite these relatively high qualities surveillance programs that were established in high income countries, few high quality surveillance programs were implemented in middle or low income countries[1-3] The most prominent limitation in these areas is the low yield of isolation of significant bacteria in microbiological laboratories.[2] In addition, the rates of antibiotic pretreatment in these communities are high which will decrease the yield of positive blood cultures.[3] Funding source is another concern in these countries.[3]

However, many surveillance programs have been initiated in these areas. Some of these systems include: Central Asian and Eastern European Surveillance (CAESAR) in 17 middle income and 3 high income countries, and AMR national surveillance systems in Viet Nam, Nepal, and China.[2]

In 2015, WHO launched Global AMR Surveillance System (GLASS). AMR data for nine microorganisms are registered in the surveillance. The data are collected from specimens that have been sent routinely to laboratories for clinical purposes. For data entry, an automated computer software (WHONET) was developed and adapted.[12] Laboratories in more than 90 countries including Islamic Republic of Iran are included in GLASS.

Our surveillance was performed in three laboratories in Isfahan, Iran which two of them are collaborated with GLASS and have qualification certificate from Iranian government for performing standard microbiologic tests. In our surveillance, to optimize the use of information in prevention and control of antibiotic resistance in pathogen bacteria, we added more clinical data to microbiologic data. Added clinical data included: differentiation between contamination from true infection, determination of site of infection, and clarification of nosocomial from CAIs. It could be a good model of combining antibiotic resistant surveillance results and patient's clinical information for planning preventive measures in clinical settings.

The project was the first AMR surveillance experience in the area and had some limitations. First, we collected antibiotic resistance data of pathogens which isolated from patients admitted in three major hospitals and these results could not be representative of the total antibiotic resistance

Table 2: Susceptibility pattern of gram negative bacteria isolated from CAIs and HCAIs

Antibacterial class	Antibiotic agents that may be used for AST	Type of infections	
		CAIs (%)*	HCAIs (%)*
Cephalosporins	Ceftazidime	47.4	23.8
	Ceftriaxone	41.3	20.4
	Cefotaxime	41	32.3
	Cefepime	51.1	23.8
Carbapenems	Meropenem	85.6	42.8
	Imipenem	93.2	66.2
Aminoglycosides	Amikacin	51.1	55.7
	Gentamicin	66.7	50.5
Fluoroquinolones	Ciprofloxacin	47	29.1
	Levofloxacin	69.4	18.6
Polymyxins	Colistin	100	100
Penicillin-Penicillinase Inhibitors	Ampicillin-sulbactam	25.3	15.7
Folate Pathway Antagonists	Trimethoprim-sulfamethoxazole	34.8	27.6
Nitrofurans	Nitrofurantoin	82.3	67.3

*Susceptible percentage, AST=Antibiotic susceptibility testing, CAIs=Community-acquired infections, HCAIs=Healthcare-associated infections

Table 3: Susceptibility pattern of gram positive bacteria isolated from CAIs and HCAIs

Antibacterial class	Antibiotic agents that may be used for AST	Type of infections	
		CAIs (%)*	HCAIs (%)*
Penicillinase-Labile Penicillins	Penicillin G	14.1	14.1
Penicillinase-Stable Penicillins	Cefoxitin	52.7	31.9
Aminoglycosides	Gentamicin	71.8	62
	Amikacin	96.9	81.8
Fluoroquinolones	Ciprofloxacin	48	23
	Levofloxacin	90	46.7
Glycopeptides	Vancomycin	76.9	33.8
	Vancomycin (MIC)	95.2	69.5
Macrolides	Erythromycin	36.1	21.9
Lincosamides	Clindamycin	42.3	27
Folate Pathway Antagonists	Trimethoprim-sulfamethoxazole	58.3	44.8
Nitrofurans	Nitrofurantoin	88.9	75
Oxazolidinones	Linezolid	88.5	97
Ansamycins	Rifampin	88.3	86.7

*Susceptible percentage, AST=Antibiotic susceptibility testing, CAIs=Community-acquired infections, HCAIs=Healthcare association infections

in area can lead to high estimation of the antibiotic resistance rates. In addition, we relied on data which obtained from routine medical microbiology tasks without external quality control in a reference laboratory. However, it should be acknowledged that all these laboratories have received quality certificate from Iranian Ministry of Health and the methods of microbiological tests were the same and frequently checked by supervisor of the surveillance. The third limitation was delay in reporting data. The results were sent to the IDRC at the end of each month. However, some laboratories send their data with delay. Using the Web-based systems could be helpful in second phase of the project to achieve on time distribution of data.

The forth limitation was inadequate project budget. Our surveillance was funded through a research project planned for 2 years. For the second phase of surveillance a sustainable source of funding will be required. Finally, the fifth limitation was the high workload for laboratory personnel, which would increase the cost of the surveillance program and decrease timeliness of reporting of information.

In spite of these limitations, our study is the first surveillance in the region that can provide valuable information on the antibiotic resistance of a wide range of pathogens along with patient's clinical data and it can be a proper guide for clinicians, microbiologists, infection control practitioners and public-health authorities.

Conclusion

We described design and methodology of IAS-1 surveillance project in this paper. The strength of the project is gathering enough clinical information in addition to microbiologic data that would increase the application of the results for empiric treatment of the infectious diseases and planning of infection control programs in clinical

settings. However, our program faces some limitations in representativeness of samples, external quality assessment of data, timeliness of reporting, sustained funds, and additional workload for health professionals, and will be improved in further phase.

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Conflicts of interest

There are no conflicts of interest.

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Supplement Table 1: Definition of the site of infection

Type of Infections in accordance to involved organ	Recommended case definitions	Common Pathogens
Urinary Tract Infection (UTI)	Clinical: Each of these symptoms: dysuria, frequent urination, hematuria, lower abdominal pain, flank pain Or Para Clinic: Pyuria in urine analysis (≥10 WBC/ml of urine)+ positive bacterial culture with at least 10^5colony count	*Escherichia coli*, Proteus spp, Klebsiella spp, Enterobacter spp, Enterococcus spp, *Pseudomonas aeruginosa*, Acinetobacter spp, *Staphylococcus saprophyticus*, *Staphylococcus* epidermidis
Meningitis	Clinical: Fever in addition to any of these symptoms: decreased alertness, stiff neck, positive kerning test, positive Brudzinski's sign Or Para Clinic(each of the following): ≥100 WBC in the CSF analysis report 10-100 WBC in the CSF analysis report and Protein ≥100 or sugar ≤40 mg/deciliter in the CSF analysis report Meningeal inflammation in the Brain MRI	*Streptococcus pneumonia, Haemophilus influenza, Neisseria meningitides*, group A streptococci, *Listeria monocytogenes*, *Escherichia coli, Klebsiella pneumonia, Enterobacter, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter*
Subdural Empyema, Epidural Empyema and Brain Abscess	Para Clinic: Empyema or abscess manifestations in the MRI or brain CT scan report	Gram-negative bacteria, *Pseudomonas aeruginosa, Staphylococcus aureus*, Streptococcus spp
Osteomyelitis	Clinical(each of the following): Pain and tenderness, local inflammation, warmth and drainage of the bone area Or Para clinic: Meeting at least one of the following criteria: Signs of infection in the bone biopsy in the Pathology report MRI report indicating bone infection	*Staphylococcus aureus,* group A streptococci, *Haemophilus influenzae* type B, *Streptococcus pneumonia*, *Kingella kingae*, Brucella spp., Salmonella spp., *Pseudomonas aeruginosa*
Septic Arthritis	Clinical: Fever in addition to one of the following symptoms (if present in one of the body's joints): Pain and tenderness, local inflammation, warmth, limited movement, discharges or observing cloudy fluid during joint surgery Or Para clinic(each of the following): WBC ≥10,000 with a domination of neutrophils in the synovial joint analysis The presence of a significant fluid in the joint ultrasound or MRI reports	*Staphylococcus aureus*, group A streptococci, *Haemophilus influenzae* type B, *Streptococcus pneumonia*, *Kingella kingae*, Brucella spp., Salmonella spp
Occult Bacteremia	Clinical: A fever higher than 38°C without any focus of infection and reason based on the clinical symptoms and para-clinical findings	*Streptococcus pneumonia*, *Haemophilus influenzae* type B, *Neisseria meningitides*, *Staphylococcus aureus*, Gram-negative bacteria (*Escherichia coli*, Proteus spp, Enterobacter spp, Salmonella *spp*), *Pseudomonas aeruginosa*, Acinetobacter spp
Sepsis	Clinical: The presence of at least two of the following criteria (except for symptoms 1 and 2): A fever higher than 38°C WBC ≥15,000/µl in children and ≥12,000/µl in adults Unexpected tachypnea Unexpected tachycardia Hypotension	*Streptococcus pneumonia, Haemophilus influenzae* type b, *Neisseria meningitides spp*., *Staphylococcus aureus*, Gram-negative bacteria (*Escherichia coli*, Klebsiella spp, Proteus spp, Enterobacter spp, Salmonella spp), *Pseudomonas aeruginosa*, Acinetobacter spp, group A *Streptococci*, Enterococcus spp

Contd...

Supplement Table 1: Contd...

Type of Infections in accordance to involved organ	Recommended case definitions	Common Pathogens
Endocarditis	Clinical: The presence of at least two of the following symptoms Two positive blood culture Vascular phenomena (arterial embolism, pulmonary embolism, brain hemorrhage, conjunctival hemorrhage, subungual hematoma) Predisposing conditions of endocarditis including drug injection or valvular abnormalities or having a permanent catheter Temperature higher than 38°C Immunologic phenomena (glomerulonephritis, subcutaneous nodules) Presence of vegetation in the echocardiography report	Common Pathogens: Viridans Group Streptococci, *Streptococcus bovis*, Other strains of Streptococci, *Staphylococcus aureus*, Enterococcus spp. Common pathogens in artificial heart valve infection: in addition to the common pathogens: Staphylococcus spp.and Gram-negative bacteria
Pericarditis	Para clinical(each of the following): Purulent drainage or cloudy discharge in pericardial fluid aspiration Predominance of polymorphonuclear leukocytes in aspiration of pericardial fluid aspiration	*Streptococcus pneumonia*, other species of Streptococcus, different types of *Haemophilus influenzae*, Brucella spp, Salmonella spp, *Staphylococcus aureus, Listeria monocytogenes*
Mediastinitis	Para clinical: Evidence of the presence of air, inflammation or abscess in the mediastinum according to radiographic or chest CT scan reports	Common Pathogens: Staphylococcus aureus, Coagulase-negative Staphylococci, Streptococcus spp, different types of Corynebacterium, Enterobacteriaceae, Pseudomonas spp Less Common Pathogens: Salmonella, Brucella, anthrax bacterium, *Streptococcus pneumoniae*
Pneumonia	Clinical: Fever in addition to one of the following two symptoms: Cough and dyspnea and tachypnea Presence of localized rales in the examination Or Para Clinic: Evidence of pneumonia in chest graph, CT scan or MRI report	*Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis, Staphylococcus aureus*, Group A Streptococcus, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterobacter spp
Pulmonary empyema	Para Clinic(each of the following): Positive gram stain in aspirated fluid PH <7.2 in aspirated fluid analysis WBC >100,000 in aspirated fluid analysis	*Streptococcus pneumonia,* Haemophilus influenza, Staphylococcus aureus, Group A Streptococcus and other Streptococcus spp
Lymphadenitis	Clinical: Fever in addition to inflammation and tenderness of the lymph nodes	*Staphylococcus aureus*, Group A Streptococcus
Gastroenteritis	Clinical: Fever in addition to mucoid or bloody diarrhea Or Para Clinic: ≥10 WBC in analyzing stool sample	Salmonella spp, Shigella spp, *Escherichia coli* (Enteropathogenic, Enterohemorrhagic, Enterotoxigenic, Enteroinvasive, Enteroaggregative)
Peritonitis	Clinical(each of the following): Fever and significant fluid accumulation in the peritoneal spaces Purulent or cloudy discharges in the peritoneal fluid aspiration Or Para Clinic: PMN ≥250/µl in peritoneal fluid analysis	*Streptococcus pneumoniae*, Gram-negative bacteria (Escherichia, Klebsiella, Proteus, Enterobacter, Salmonella), Pseudomonas spp, Acinetobacter spp, Streptococcus spp

Contd...

Supplement Table 1: Contd...

Type of Infections in accordance to involved organ	Recommended case definitions	Common Pathogens
Abscess	Para Clinic: Thick-walled lesion with a low density center in ultrasonography/CT- scan/MRI in an organ	*Staphylococcus aureus*, Gram-negative bacteria (Escherichia, Klebsiella, Proteus, Enterobacter, Salmonella)
Skin Infection	Clinical(each of the following): Erythema of the skin Warmth of the skin Discharge from a wound	*Staphylococcus aureus*, gram-negative bacteria (escherichia, klebsiella, proteus, enterobacter, salmonella), *Pseudomonas aeruginosa*, Group A streptococcus, *Streptococcus pneumonia, Haemophilus influenza* type B