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Shahnaz Rimaz[1], Parastoo Tajzadeh[2], Milad Bahrami[3,4], Mehdi Nooghabi[5], Babak Eshrati[6], Sohrab Effati
7
, Maryam Yaghoobi
8,9

[1]Radiation Biology Research Center, Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran. [2]Department of Medical Laboratory Sciences, School of Nursing, Kashmar, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.
3
Department of Laboratory Sciences, Faculty of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.
4
Student Research Committee, Faculty of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.
5
Department of Statistics, Ferdowsi University of Mashhad, Mashhad, Islamic Republic of Iran.
6
Preventive Medicine and Public Health Research Center, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran.
7
Department of Mathematics, Ferdowsi University of Mashhad, Mashhad, Islamic Republic of Iran.
8
Department of Epidemiology, Faculty of Public Health, Iran University of Medical Sciences, Tehran, Iran (Correspondence to M. Yaghoobi: Myaghooobi@yahoo.com).
9
Clinical Research Development Unit, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.

Abstract

Background: Healthcare-associated infections are a major cause of mortality worldwide, especially in intensive care units where severely ill patients have limited physical space.

Aims: To investigate the incidence, microbial aetiology, antimicrobial resistance profile, and mortality rate of healthcare-associated infections in intensive care units in the Islamic Republic of Iran.

Methods: This observational study retrospectively reviewed the medical records of 1722 intensive care units patients with confirmed healthcare-associated infections at hospitals affiliated with Mashhad University of Medical Sciences in 2017–2019. Data was analysed using SPSS for Windows version 11. Categorical variables were described using frequency and percentage, whereas continuous variables were defined using mean (standard deviation) with 95% confidence interval (CI) for precision. Logistic regression analysis was used to estimate crude odds ratio (OR) and adjusted OR (AOR) with 95% CI, and to identify univariate and multivariate predictors of healthcare-associated infection mortality.

Results: In total, 4077 pathogens were isolated, yielding a healthcare-associated infection incidence rate of 22.1%. The most common microorganisms were Acinetobacter spp. (25.0%), Klebsiella spp. (15.1%), Staphylococcus spp. (14.0%), and Candida spp. (12.3%). Ventilator-associated events (39.5%), urinary tract infections (22.7%), and bloodstream infections (14.8%) were the main types of infection. Comorbidities, skin and soft tissue infections, and infections with Acinetobacter spp., Klebsiella spp., Pseudomonas spp., and Candida spp. were significantly associated with higher mortality among intensive care unit patients. Gram-positive bacteria were most resistant to ciprofloxacin (49.2%), clindamycin (38.0%), and erythromycin (37.1%). Gram-negative bacteria were most resistant to ceftazidime (71.0%), ciprofloxacin (65.2%), and cefotaxime (60.5%). The overall mortality rate was 45.2%.

Conclusion: Healthcare-associated infections in nearly half of intensive care unit patients were fatal, especially when caused by Acinetobacter spp., Klebsiella spp., Pseudomonas spp., or Candida spp. Therefore, effective strategies must be implemented to combat antibiotic-resistant bacteria, along with stricter adherence to infection control programmes.

Keywords: healthcare-associated infection, intensive care unit, drug resistance, microorganism, antimicrobial resistance, mortality, Iran

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Introduction

Healthcare-associated infections can occur 48 hours after hospital admission, and are a major cause of morbidity and mortality worldwide, accounting for ~2 million infections and 100 000 deaths annually (1, 2). In addition to prolonging hospital stay, healthcare-associated infections carry a huge financial burden, estimated at US$4.5 billion annually(3, 4). According to a WHO report, out of every 100 patients, 7 in high-income countries and 15 in low- and middle-income countries develop healthcare-associated infections during their stay in acute-care hospitals (5). The intensive care units (ICUs), in particular, are hotbeds for contracting infections (5). Even though they account for

The prevention of healthcare-associated infections in ICUs requires rigorous control measures. To achieve infection control, WHO recommends a multimodal hand hygiene improvement strategy consisting of 5 critical elements: (1) providing clinical staff with the materials and equipment they need to perform hand hygiene at the point of care, such as alcohol-based hand rub, clean water, soap, and single-use towels; (2) training and education of health workers, patients, and visitors on the importance of hand hygiene; (3) regular evaluation of hand hygiene infrastructure, and monitoring compliance with hand hygiene programmes; (4) continually reminding health workers about the importance of maintaining hand hygiene, verbally or by visual prompts such as posters, stickers, or banners; and (5) prioritizing compliance with hand hygiene at institutional and individual levels to achieve patient and health worker safety (8). The WHO multimodal hand hygiene improvement strategy targets to prevent up to 50% of healthcare-associated infections and save 16 times the cost of implementation (8).

Even though many healthcare-associated infections can be avoided with proper infection control, it is impossible to eradicate them entirely, and antibiotics are still frequently prescribed for ICU patients (9). With abundant use of antibiotics in a limited space, ICUs are an ideal setting for the emergence and transmission of antibiotic-resistant bacteria (10). In this situation, clinicians may lack effective treatment options as bacteria withstand the effects of antibiotics, leading to the emergence of multidrug-resistant, extensively drug-resistant, and pandrug-resistant strains (11). In 2019, antimicrobial resistance was estimated to be responsible for 1.27 million deaths worldwide (12). If we do not take prompt action now, antimicrobial

resistance is estimated to cause 10 million deaths annually by 2050 (13).

The distribution of nosocomial infections and antibiotic resistance patterns vary geographically; therefore, each medical centre should devise its own specific antimicrobial treatment policy (14). This is the only way to reduce the incidence, mortality rate, and treatment cost of healthcare-associated infections. In this study, we attempted to investigate the incidence, microbial aetiology, antimicrobial resistance profile, and clinical outcomes of healthcare-associated infections in ICUs in north-eastern Islamic Republic of Iran.

Methods

Study design

This observational study retrospectively reviewed the medical records of patients who acquired healthcare-associated infections in ICUs at 4 hospitals affiliated with Mashhad University of Medical Sciences, Islamic

Republic of Iran between April 2017 and September 2019. Inclusion was restricted to patients who had been in an ICU for ≥ 48 hours and had developed healthcare-associated infections. Those with incomplete medical records were excluded from the data analysis. The infections were diagnosed according to criteria established by the US Centers for Disease Control and Prevention and the Iranian National Nosocomial Infections Surveillance Guideline (15, 16). Apart from clinical manifestations and physical examination, microbiological tests were undertaken to confirm the diagnoses of healthcare-associated infections. Antibiotic therapy was initiated in all patients after the antimicrobial sensitivity of bacterial isolates was determined.

Definitions

Healthcare-associated infection was defined as an adverse reaction to an infectious agent or its toxins 48 hours after hospital admission. Bloodstream infection was diagnosed if a pathogen was identified in 1 or more blood culture samples from a patient who had accompanying symptoms such as fever, chills, or hypotension. Pneumonia was diagnosed when a patient showed newly developed or progressive infiltrates, cavitation, consolidation, or pleural effusion; had new onset of purulent sputum or a change in the character of the sputum; or a pathogen was cultured from blood, tracheal aspirate, bronchoalveolar lavage, bronchial brushing, or biopsy. If pneumonia was caused by mechanical ventilation, the patient was diagnosed with ventilator-associated infection. Skin and soft tissue infection was defined as purulent pustules, vesicles, or boils, or having at least 2 of the following symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat. Surgical site infection was defined as an infection arising 30 days after surgery, from which a microorganism was isolated, or the site had a purulent discharge. Urinary tract infection was diagnosed when a patient had a urinary

catheter placed for ≥ 2 consecutive days and showed 1 or more of the following symptoms: fever, urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain/tenderness.

Data collection

We obtained details of hospitalized patients with healthcare-associated infection from their medical records in the Iranian Nosocomial Infection Surveillance System. The data collected included age, sex, comorbidities, invasive device use, type of infection, causative agents, antimicrobial resistance profile, length of stay, and mortality. Patients who experienced multiple healthcare-associated infections during their stay in hospital were counted separately for analysis of the type of microorganisms and site of infection.

Ethical considerations

The protocol complied with the ethical principles specified in the 1964 Helsinki Declaration and was approved by the Ethics Committee of Mashhad University of Medical Sciences (registration number IR.MUMS.REC.1399.331)and Iran University of Medical Sciences (registration number IR.IUMS.REC.1398.1219)

Statistical analysis

SPSS for Windows version 11 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The categorical variables were described using frequency and percentage, whereas continuous variables were defined by mean (standard deviation) with 95% confidence interval (CI) for precision. Logistic regression analysis using the stepwise forward method was applied to estimate crude odds ratio (OR) and adjusted OR (AOR) with 95% CI, and to identify univariate and multivariate predictors of healthcare-associated infection mortality. All statistics were subjected to an effect size analysis. Statistical significance was defined as P

Results

Clinical and demographic characteristics

Over the course of the study, 18 382 patients were admitted to ICUs and 1722 contracted healthcare-associated infections: 901 male (52.3%) and 821 female (47.7%), with a mean age of 57.30 (24.24) years (Table 1). Most (55.2%) patients with healthcare-associated infections were aged > 60 years. Children aged Figure 1). The median length of hospital stay was 20 days (interquartile range, 11–33 days). During their stay, patients developed healthcare-associated infections at a median of 5 days from admission (interquartile range, 2–12 days). Unfortunately, 45.2% of patients eventually died from infections acquired in the ICU (
Table 1
).

Device use, infection sites and nosocomial pathogens

During the study period, 4077 pathogens were isolated from 1722 patients: 981 (24.0%) Gram-positive bacteria, 2591 (63.6%) Gram-negative bacteria, and 505 (12.4%) fungi, yielding a healthcare-associated infection incidence rate of 22.1% (Table 2). The most common microorganisms were Acinetobacter spp. (25.0%), Klebsiella spp. (15.1%), Staphylococcus spp. (14.0%), and Candida spp. (12.3%). Among Gram-negative strains, Acinetobacter spp. (39.3%) were the most frequently isolated, followed by Klebsiella spp. (23.9%), Pseudomonas spp. (15.5%), and Escherichia coli (14.1%). Among Gram-positive strains, Staphylococcus spp. (58.4%), especially Staphylococcus aureus (25.0%), and Enterococcus spp. (32.8%) were responsible for most healthcare-associated infections among ICU patients. Endotracheal tubes (39.5%), urinary catheters (19.9%), central venous catheters (12.9%), and arterial catheters (0.3%) were the invasive devices mostly associated with healthcare-associated infections, and other devices were responsible for 31.0%. Ventilator-associated infection (39.5%), urinary tract infection (22.7%), and bloodstream infection (14.8%) were the 3 main types of infection among ICU patients (Table 2).

Independent predictors of mortality

Multivariate logistic regression analysis identified 6 independent predictors of mortality among ICU patients (Table 3). Patients with comorbidity had a significantly increased risk of death (P

Antimicrobial resistance profile

Gram-positive and Gram-negative bacteria demonstrated varying levels of antimicrobial resistance. Gram-positive bacteria were most resistant to ciprofloxacin (49.2%), clindamycin (38.0%), erythromycin (37.1%), and cefoxitin (27.1%) (Table 4). S. aureus, Staphylococcus epidermidis, and other coagulase-negative staphylococci exhibited considerable resistance to ciprofloxacin (44.4%, 37.0%, and 50.2%), clindamycin (52.8%, 62.0%, and 56.8%), erythromycin (51.2%, 62.0%, and 53.3%), and cefoxitin (41.4%, 52.0%, and 42.2%). Enterococcus spp. were highly resistant to ciprofloxacin (63.0%), vancomycin (63.0%), and ampicillin (47.2%). However, Streptococcus spp. was susceptible to most antibiotics, except for erythromycin and clindamycin, which recorded resistance of 36.9% and 30.7%, respectively.

Gram-negative bacteria exhibited strong resistance to ceftazidime (71.0%), ciprofloxacin (65.2%), cefotaxime (60.5%), gentamicin (55.2%), trimethoprim–sulfamethoxazole (51.2%), amikacin (46.6%), and imipenem (35.2%). Infections with Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. were best treated with amoxicillin/clavulanic acid (99.4%, 99.4%, and 99.6% susceptibility), ampicillin (98.0%, 96.4%, and 97.1% susceptibility), levofloxacin (96.8%, 98.3%, and 98.6% susceptibility), and cefepime (81.7%, 81.7%, and 80.7% susceptibility). However, treatment with ceftazidime and ciprofloxacin was relatively ineffective because Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. were resistant to ceftazidime

(74.9%, 79.8%, and 62.0%) and ciprofloxacin (70.1%, 61.4%, and 69.6%). E. coli demonstrated resistance to ceftazidime (50.1%), ciprofloxacin (47.9%), cefotaxime (43.8%), and trimethoprim–sulfamethoxazole (36.7%), although to a lesser extent than the other Gram-negative bacteria.

Discussion

In this study, we found a high incidence (22.1%) of healthcare-associated infections in ICUs in north-eastern Islamic Republic of Iran. The most commonly isolated microorganisms were Acinetobacter spp., Klebsiella spp., Staphylococcus spp., and Candida spp. The main types of infection were ventilator-associated, urinary tract, and bloodstream infections. Comorbidities, skin and soft tissue infections, and infections with Acinetobacter spp., Klebsiella spp., Pseudomonas spp., and Candida spp. were associated with higher mortality among ICU patients. Gram-positive bacteria exhibited the strongest resistance to ciprofloxacin, clindamycin, and erythromycin, and Gram-negative bacteria were most resistant to ceftazidime, ciprofloxacin, and cefotaxime.

ICUs are breeding grounds for healthcare-associated infections (5). In ICUs, physicians and nurses can act as media for transmitting pathogens between wards (17). ICU patients undergo invasive medical procedures and are in a debilitated condition; therefore, they have a 5–10 times higher risk of developing healthcare-associated infections than patients in general medical wards (18). This is why despite representing

knowledge of hand hygiene (24). It is now evident that serious action is required to lower the incidence of healthcare-associated infections in Iranian hospitals. We hope to take a critical step toward helping hospitals optimize their infection control programmes and minimize cross-infection risk by identifying the causes of healthcare-associated infections as well as their microbial aetiology and patterns of antimicrobial resistance.

This study indicated that Acinetobacter spp. (25.0%), Klebsiella spp. (15.1%), Staphylococcus spp.(14.0%), and Candida spp. (12.3%) were the most common microorganisms responsible for healthcare-associated infections in ICUs in northeast Islamic Republic of Iran. Infections with Acinetobacter spp., Klebsiella spp., Pseudomonas spp., and Candida spp. were independently associated with higher in-hospital mortality among ICU patients. In a national study with a similar design, Etemad et al. discovered that Acinetobacter spp. (16.52%), E. coli (12.01%), and Klebsiella spp. (9.93%) were the major microorganisms isolated from ICU patients in the Islamic Republic of Iran. They also found that Acinetobacter spp., Enterococcus spp., Enterobacter spp., and Candida spp. were associated with an increased risk of in-hospital mortality (25). Similarly, in a multicentre study by Jahani-Sherafat et al., Acinetobacter baumannii (33.3%), S. aureus (14.4%), and Pseudomonas aeruginosa (14.4%) were the most prevalent pathogens causing healthcare-associated infections in ICUs, followed by Klebsiella pneumoniae (10.9%)

and Enterococcus spp. (8.7%) (26). The prevalence and distribution of microorganisms that cause healthcare-associated infections vary by hospital, geographic area, and patient status (27). It is, therefore, reasonable to expect differences from previous studies regarding microbial aetiology

In our study, endotracheal tubes, urinary catheters, and central venous catheters were the invasive devices most frequently associated with healthcare-associated infections. As demonstrated by the US National Nosocomial Infection Surveillance System, mechanical ventilators, urinary catheters, and central venous catheters contributed 83% of nosocomial pneumonia, 97% of urinary tract infections, and 87% of bloodstream infections in ICUs (28). The most common types of infection among our ICU patients were ventilator-associated, urinary tract, and bloodstream infections, in accordance with previous regional studies (29, 30). However, none of these infections was associated with an increased risk of death, as also found by Boncagni et al. (31). The only type of infection that was independently associated with increased mortality risk was skin and soft tissue infection. In contrast, Rosenthal et al. conducted a multicentre cohort study of 786 ICUs worldwide and found that ventilator-associated, urinary tract, and bloodstream infections were independent risk factors for mortality (32). This was supported by Bonnet et al. who reported that lung, urinary tract, and bloodstream infections were the most prevalent among ICU patients and were all closely associated with higher mortality (33). The currently available data are inconclusive; therefore, this issue warrants further research.

In our study, treatment of ICU patients was largely interrupted because the bacteria were resistant to the antibiotics. Ceftazidime, cefotaxime, and ciprofloxacin achieved little clinical success against Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. Isolates of Staphylococcus spp. showed resistance to ciprofloxacin, clindamycin, and erythromycin, and Enterococcus spp. was resistant to ciprofloxacin, vancomycin, and ampicillin. Similar patterns of resistance were observed in ICUs in Tehran, where Amimi et al. reported high resistance to ciprofloxacin, cefotaxime, ceftazidime, and ampicillin among A. baumannii, E. coli, P. aeruginosa, and K. pneumoniae isolates (34). Likewise, in Qazvin, Bagherian et al. demonstrated that most strains of Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. were markedly resistant to most prescribed antibiotics, especially ciprofloxacin, ceftazidime, cefotaxime, cefepime, and piperacillin (35). With such high resistance to a variety of antibiotics, infections that were once curable with a short course of antibiotics could become incurable. In that case, it is reasonable to propose that the high mortality rate of 45.2% observed in our study could have been caused by antibiotic resistance. Hence, it becomes even more important for hospitals to prioritize the rational prescription of antibiotics in their infection control plans.

Our study had a few limitations. The Iranian Nosocomial Infections Surveillance System does not cover different scoring systems that can predict mortality among patients with critical

conditions based on clinical and laboratory findings, such as acute physiology and chronic health evaluation (APACHE), sequential organ failure assessment (SOFA), and mortality in emergency department sepsis (MEDS) scores. Thus, we were unable to evaluate the impact of such variables on mortality at ICU admission. The system does not record the hospitalization data of patients who did not contract healthcare-associated infections in ICUs. Therefore, we could not perform further analysis to identify the risk factors for healthcare-associated infections. Taking these factors into account, we strongly recommend conducting a prospective study, possibly with a larger sample size, to capture as much information as possible at ICU admission. Regardless of its limitations, our study offers valuable insight into the epidemiology and aetiology of healthcare-associated infections in ICUs in northeast Islamic Republic of Iran.

Conclusion

We documented a high incidence of healthcare-associated infection in ICUs in northeast Islamic Republic of Iran. Because of the emergence of resistant microorganisms in ICUs, healthcare-associated infections in nearly half of ICU patients eventually lead to death, especially when caused by Acinetobacter spp., Klebsiella spp., or Pseudomonas spp. The use of endotracheal tubes and urinary catheters may further expose patients to the risk of healthcare-associated infection. Therefore, to reduce these infections, effective strategies to combat antibiotic-resistant bacteria must be implemented, along with stricter adherence to infection prevention and control programmes and enhancement of infection control using feasible and affordable tools and resources. Our findings could be used by policymakers to develop more practical protocols for hand hygiene, reducing contact with patients, and using invasive devices. Staff training programmes, along with continuous supervision and monitoring, are also essential to prevent the spread of infection.

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Competing interests: None declared.

Caractéristiques épidémiologiques, profil de résistance aux antimicrobiens et résultats cliniques relatifs aux infections associées aux soins de santé en République islamique d'Iran

Résumé

Contexte : Les infections associées aux soins de santé représentent une cause majeure de mortalité dans le monde, en particulier dans les unités de soins intensifs où les patients gravement atteints disposent d'un espace physique limité.

Objectif : Étudier l'incidence, l'étiologie microbienne, le profil de résistance aux antimicrobiens et le taux de mortalité relatifs aux infections associées aux soins de santé dans les unités de soins intensifs en République islamique d'Iran.

Méthodes : La présente étude d'observation a rétrospectivement passé en revue les dossiers médicaux de 1722 patients hospitalisés en unités de soins intensifs présentant des infections associées aux soins de santé confirmées dans des hôpitaux affiliés à l'Université des sciences médicales de Mashhad entre 2017 et 2019. Les données ont été analysées à l'aide du logiciel SPSS pour Windows, version 11. Les variables catégorielles ont été décrites en recourant à la fréquence et au pourcentage, tandis que les variables continues ont été définies à l'aide de la moyenne (écart type) avec un intervalle de confiance (IC) à 95 % pour la précision. L'analyse de régression logistique a été utilisée pour estimer l'odds ratio brut (OR) et l'odds ratio ajusté (ORa) avec un IC à 95 %, et pour identifier les facteurs prédictifs univariés et multivariés de la mortalité liée aux infections associées aux soins de santé.

Résultats : Au total, 4077 agents pathogènes ont été isolés, ce qui correspond à un taux d'incidence des infections associées aux soins de santé de 22,1 %. Les organismes les plus fréquemment retrouvés étaient Acinetobacter spp. (25,0 %), Klebsiella spp. (15,1 %), Staphylococcus spp. (14,0 %) et Candida spp. (12,3 %). Les principaux types d'infections étaient des événements liés à la ventilation mécanique (39,5 %), des infections des voies urinaires (22,7 %) et des infections sanguines (14,8 %). Les comorbidités, les infections de la peau et des tissus mous et les infections dues à Acinetobacter spp., Klebsiella spp., Pseudomonas spp. et Candida spp. étaient significativement associées à une mortalité plus élevée chez les patients en unité de soins intensifs. Les bactéries à Gram positif étaient les plus résistantes à la ciprofloxacine (49,2 %), à la clindamycine (38,0 %) et à l'érythromycine (37,1 %). Les bactéries à Gram négatif étaient les plus résistantes à la ceftazidime (71,0 %), à la ciprofloxacine (65,2 %) et au céfotaxime (60,5 %). Le taux de mortalité global était de 45,2 %.

Conclusion : Les infections associées aux soins de santé chez près de la moitié des patients en unité de soins intensifs ont été mortelles, en particulier lorsqu'elles étaient causées par Acinetobacter spp., Klebsiella spp., Pseudomonas spp. ou Candida spp. Par conséquent, des

stratégies efficaces pour lutter contre les bactéries résistantes aux antibiotiques doivent être mises en œuvre, ainsi qu'une observance plus stricte des programmes de lutte contre les infections.

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WHO EMRO | Epidemiological features, antimicrobial resistance profile and clinical outcomes of healthca

بأنواعها ارتباطًا كبيرًا بارتفاع معدل الوفيات بين مرضى وحدات العناية المركزة .
وكانت الجراثيم الإيجابية الغرام أكثر مقاومة للسيبروفلوكساسين (49.2%)
والكليندامايسين (38.0%) والإريثرومايسين (37.1%). وأما الجراثيم السلبية الغرام
فكانت أكثر مقاومة للسيفتازيديم (71.0%) ، وسيبروفلوكساسين (65.2%) ، وسيفوتاكسيم
(60.5%). وبلغ المعدل الإجمالي للوفيات 45.2%.

: لقد وُجد أن العدوى المرتبطة بالرعاية الصحية في ما يقرب من نصف المرضاالاستنتاجات
في وحدة الرعاية المركزة قاتلة، لا سيما عندما تسببها الجرثومة الراكدة بأنواعها، أو
الكلبسيلة بأنواعها، أو الزائفة بأنواعها، أو المبيضات بأنواعها . لذلك يجب تنفيذ
استراتيجيات فعالة لمكافحة البكتيريا المقاومة للمضادات الحيوية، إلى جانب الالتزام
الصارم ببرامج مكافحة العدوى .

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