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ANTIBIOTIC RESISTANCE SURVEILLANCE IN A PEDIATRIC CARDIAC SURGERY

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Background. The aim of this study was to identify etiological organisms and antibiotic resistance rates of bacterial infection in Department of pediatric cardiac surgery.

Methods. Our database consisted of 2816 consecutive samples from pediatric patients who underwent cardiac surgery between January 2011 and December 2019 at a single center. Identification of isolates and antibiotic susceptibility testing were performed by Vitek-2 automated system.

Results: The most frequently isolated microorganisms in our Department of pediatric cardiac surgery were as follows: *Psedomonas aeruginosa* 19.7%, *Klebsiella pneumoniae* 16%, Staphylococcus aureus 13.2%, and *Acinetobacter baumannii* 8.8%. During study period there is tendency increasing the percentage of detection *Ps.aeruginosa* from 16.1% to 30.2% (p=0.048) and *K.pneumoniae* from 7.5% to 19.3% (p=0.014). There are tendency of increasing resistance to 3rd generation cephalosporins, carbapenems and quinolones.

Conclusion. Based on our results, we report that respiratory tract infection was found to be the most common site for bacterial infection and *P.aeruginosa* and *K. pneumoniae* were the most frequent pathogens with high level of resistance. Our findings are posing necessitates for improvement preventive measures, including microbiological monitoring, good hygiene, and well-designed hospital infection control strategy.

Key words: *bacterial infection, antibiotic resistance, microbiologic monitoring.*

Резюме

ИССЛЕДОВАНИЕ РЕЗИСТЕНТНОСТИ К АНТИБИОТИКАМ В ОТДЕЛЕНИИ ДЕТСКОЙ КАРДИОХИРУРГИИ

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Целью настоящего исследования явилось определение бактериальной структуры и уровня антибиотикорезистентности основных возбудителей инфекционных осложнений после проведенных операций на сердце и крупных сосудах в отделении детской кардиохирургии.

Методы: Проведено проспективное микробиологическое исследование 2816 клинических образцов (культуры крови, раневое отделяемое, респираторный тракт, центральный венозный катетер, катетер из трахеобронхиального дерева и др.), полученные от пациентов отделения детской кардиохирургии в период с 2010 по 2019 годы. Идентификацию выделенных изолятов и их антибиотикочувствительность проводили на микробиологическом автоматическом анализаторе Vitek 2 - Compact.

Результаты: За исследуемый период часто встречающимися патогенами были: *Pseudomonas aeruginosa* – 19,7%, *Klebsiella pneumoniae* - 16%, *Staphylococcus aureus* – 13,2%, *Acinetobacter baumannii*– 8,8% от общего количества выделенных микроорганизмов. В динамике отмечается увеличение частоты обнаружения *Ps.aeruginosa* с 16,1% до 30,2% (p=0,048), *K.pneumoniae* с 7,5% до 19,3% (p=0,014). Данные штаммы показывают тенденцию достоверного увеличения резистентности к цефалоспоринам III-IV поколения, к хинолонам и карбапенемам.

Заключение: Результаты исследования показывают что *P.aeruginosa* и *K. pneumoniae* были наиболее частыми возбудителями бактериальных инфекций в отделении детской кардиохирургии, высокий уровень резистентности которых побуждают необходимость улучшения профилактических мер, включая микробиологический мониторинг, хорошо разработанную стратегию борьбы с нозомиальными инфекциями.

Ключевые слова: *бактериальные инфекции, резистентность к антибиотикам, микробиологический мониторинг.*

Түйіндеме

БАЛАЛАР КАРДИОХИРУРГИЯЛЫҚ БӨЛІМІНДЕГІ БАКТЕРИЯЛАРДЫҢ ТҰРАҚТЫЛЫҒЫ

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Осы зерттеудің **мақсаты** балалар кардиохирургиясы бөлімшесінде жүрекке және ірі тамырларға ота жүргізілгеннен кейінгі инфекциялық асқынулардың негізгі қоздырғыштарының бактериалдық құрылымын және антибиотикке төзімділігінің деңгейін анықтау болып табылады.

Әдістер: 2010 мен 2019 жылдар аралығында балалар кардиохирургиясы бөлімшесінің пациенттерінен алынған 2816 клиникалық үлгілердің (қан культурасы, жара бөліндісі, тыныс жолдары, орталық веноздық катетер, трахеобронхиалды ағаштан алынған катетер және т.б.) проспективті микробиологиялық зерттеуі жүргізілді. Оқшауланған изоляттардың анықтау және олардың антибиотиктерге сезімталдығын анықтау Vitek 2 - Compact автоматты микробиологиялық анализаторында жүргізілді.

Нәтижелер: Зерттеу бойынша кезеңіндегі жиі қоздырғыштар анықталды: оқшауланған микроорганизмдердің жалпы санынан *Pseudomonas aeruginosa* - 19,7%, *Klebsiella pneumoniae* - 16%, *Staphylococcus aureus* - 13,2%, *Acinetobacter baumannii* - 8,8% құрады. Динамикада *Ps.aeruginosa* үшін 16,1% -дан 30,2% -ға дейін (p = 0.048), *K.pneumoniae* үшін 7,5% -дан 19,3% -ке дейін (p = 0.014) анықтау жиілігінің жоғарылауы белгіленеді. Бұл штаммдар III-IV буынды цефалоспориндерге, хинолондар мен карбапенемдерге қарсы төзімділігінің едәуір артуы тенденциясын көрсетеді.

Қорытынды: балалар кардиохирургиясы бөлімшесінде *Ps.aeruginosa* және *K.pneumoniae* штамдарының анықталу жиілігі мен олардың төзімділігінің артуы медициналық персоналдың тиісті гигиенасын, микробиологиялық мониторинг пен ауруханаішілік бақылауды қосатын жақсы құрастырылған инфекциялық бақылау стратегиясын жасау қажет етеді де, бұл нозокомиялдық инфекцияларға шалдығу қаупін азайтуға мүмкіндік береді.

Түйінді сөздер: *бактериалдық инфекциялар, бактериялардың тұрақтылығы, микробиологиялық мониторинг.*

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Introduction

Patients with pediatric cardiac surgery operations (congenital heart defects and heart diseases a child gets after birth) are at high risk of bacterial infections [1-2]. There are a number of factors contribute to this risk, including younger age of patients (especially neonates and infants), higher complexity of surgery and limited choice of treatment. Therefore, bacterial infection are the cause of frequent complication in these patients and responsible for ICU admissions [3]. Nevertheless, of the improvements and recent advances in treatments in critical care, mortality remains high, particularly caused by health care associated infections [4-5].

As is known, the rate of bacterial infections related to multidrug resistance bacteria in pediatric cardiac surgery patients is widespread globally and are the basic cause of morbidity and mortality. Moreover, treatment options are limited for choice of antibiotic for virulent nosocomial strains in these departments [6-7]. Reserve antibiotics, such as carbapenems are antibiotics of choice for infections caused ESBL-producing *Klebsiella pneumonia* and *E.coli*, but not appropriate for infections caused *Stenotrophomonas maltophilia, Burkholderia cepacia*, or *Acinetobacter baumannii, Pseudomonas aeruginosa*, for which resistance rates to carbapenems increasing constantly [8-10].

With this background in mind, we decided to study etiological organisms and antibiotic resistance rates of bacterial infection in our Department of pediatric cardiac surgery.

Materials and Methods

Study design

This was a prospective study of microbial landscape and antibiotic resistance rates of strains conducted in the Department of pediatric cardiac surgery of tertiary hospital in Central Kazakhstan during the study period 2010-2019.

Data collection

Data were collected from newborns and children of the first three years hospitalized in Department of pediatric cardiac surgery undergoing cardiac surgery (surgery on the heart and major blood vessels). All patients were monitored

for bacterial infection at body sites for a period at least one month. Strains analyzed by infection site and pathogen type.

Bloodstream strains were collected from patient with either two or more positive blood cultures. Respiratory tract specimens included nasopharyngeal swabs and sputum. Other types of specimens obtained from the patients were: swabs from cardiac surgical wounds, bronchoalveolar lavage, central venous catheter (CVC), aspiration catheter, tracheostomy, pleural cavity, peritoneal fluid. All specimens were collected at the bed site, transported to the Laboratory of Microbiology and were inoculated on proper culture media within two hours according to the guidelines.

Samples cultivation

Clinical specimens were inoculated onto 5% sheep blood agar, Mannitol salt agar, Endo agar, Sabouraund dextrose agar (Himedia, India). Plates were incubated at 37°C for 18-24 hours.

Identification of isolates

Methods used for confirmation of identification included test of colonial morphology, haemolytic activity on appropriate agar media, Gram strain, rapid tests (coagulase, oxidase, catalase, indole) and use of automated identification system Vitek 2 – Compact (bioMerieux, Marcy l'Etoile, France).

Antibiotic susceptibility testing

For antimicrobial susceptibility testing, we used the following antibiotics: amoxicillin/clavulanic acid, ceftazidime, ceftriaxone, cefepime, meropenem, imipenem, amikacin, gentamicin, ciprofloxacin, levofloxacin. Susceptibility tests were performed with broth microdilution method (Vitek 2 – Compact (bioMerieux, Marcy l'Etoile, France) according to the manufacturer's guideline recommendations. Colonies from 18-24 hours culture were used to inoculate the microdilution cards.

All data analyzed by using Microsoft Access and Excel. Trends over time of antibiotic resistance rates determined by linear regression with the yearly data. A p value of < 0.05 considered statistically significant.

Results

During study period (from January 2010 to December 2019) 2816 isolates from 7712 clinical samples (bloodstream, wound samples, respiratory tract, tracheobronchial tree, and central venous catheter) were included to the study. Respiratory tract were most frequent isolates 54.3% (1530), followed by tracheobronchial tree 25.6% (721), wound samples 8.5% (240), bloodstream infections (BSI) 5.7% (161) and CVC 3.9% (112). The causative organisms for bacterial infection in our patients, is as shown in (Table 1). The percentage of Gram-negative bacilli 53.1% (1498), Gram-positive cocci was 33.5% (944), and fungi 9% (253).

Table 1.

Isolates reported from pediatric cardiac intensive care unit according to the site of infection.

Microorganism	Bloodstream	Tracheo bronchial aspirte	Respiratory tract	Surgical site	Central venous catheter	Urinary tract	Others[1]	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Staphylococcus aureus	6 (3.7)	32 (4.4)	300(19.6)	25 (10.4)	6 (5.3)	0	3(13.6)	372 (13.2)
CN[2]-staphylococci	25 (15.5)	100 (14.4)	0	88 (36.6)	40(35.7)	2(2.6)	0	259 (9.2)
Enterococcus faecalis	2 (1.2)	30 (4.1)	61 (3.9)	24 (10)	8 (7.1)	7 (23.3)	6 (27.2)	138 (4.9)
Escherichia coli	1 (0.6)	28 (3.8)	129 (8.4)	11 (4.5)	0	4 (13.3)	2 (9)	175 (6.2)
Enterobacter cloacae	5 (3.1)	18 (2.4)	64 (3.5)	8 (3.3)	7 (6.25)	0	0	92 (3.3)
Klebsiella pneumoniae	31(19.2)	107 (14.8)	275(17.9)	12 (5)	16 (14.2)	5 (16.6)	5 (22.7)	451 (16)
Pseudomonas aeruginosa	16 (9.9)	176 (24.4)	321(20.9)	27 (11.2)	11 (9.8)	1 (3.3)	2 (9)	554 (19.7)
Acinetobacter baumannii	12 (7.4)	91 (12.6)	123 (8)	17 (7)	4 (3.5)	1 (3.3)	0	248 (8.8)
Stenotrophomonas maltophilia	8 (4.9)	55 (7.6)	31 (2)	4 (1.6)	3 (2.6)	0	2 (9)	103 (3.7)
Burkholderia cepacia	27 (16.7)	13 (1.8)	3 (0.9)	3 (1.2)	4 (3.5)	0	0	50 (1.8)
Candida albicans	25 (15.5)	49 (6.7)	153 (10)	8 (3.3)	8 (7.1)	8 (26.6)	2 (9)	253 (9)
Other	3 (1.8)	18 (2.4)	80 (5.2)	13 (5.4)	5 (4.4)	2 (6.6)	0	121 (4.3)
Total	161	721	1530	240	112	30	22	2816

[1] *Aspiration catheter, tracheostomy, pleural cavity, peritoneal fluid*

[2] *Coagulase-negative*

The percentages of most frequently isolated microorganisms in our Department of pediatric cardiac surgery were as follows: *Ps.aeruginosa* 19.7% (554), *K.pneumoniae* 16% (451), *Staphylococcus aureus* 13,2% (372) and *A.baumannii* 8.8% (248). During study period, the rate of positive hemocultures was increased from 1.5% to 22.3% in the mean of 18.8%. The most frequent pathogens from blood samples were *K.pneumoniae* (19.2%) and *Burkholderia cepacia* (16.7%).

In tracheobronchial tree site *Ps.aeruginosa* (24.4%), was the most commonly pathogen, which was followed by *K.pneumoniae* (14.8%). Wound and CVC infections mostly caused by coagulase-negative staphylococci (36.6% and 35.7% respectively); more than 19% *S.aureus* isolates reported from respiratory tract.

During study period there is tendency increasing the percentage of detection *Ps.aeruginosa* from 16.1% to 30.2% (p=0.048), *K.pneumoniae* from 7.5% to 19.3%

(p=0.014), *A.baumannii* from 3.2% to 13.6% (p=0.059). At the same time, there is decreasing percentage of *Enterococcus faecalis* from 8.6% to 1.9% (p=0.007) and *Candida albicans* from 10.7% to 6.6% (p=0.002).

Gram-negative bacilli are frequently associated with bacterial infections in pediatric cardiac surgery patients. *Ps.aeruginosa* showed high proportion and increasing of resistance against to cephalosporins (ceftazidime from 26.6% to 76.7% p=0.001, cefepime from 13.3% to 81.1% p=0.001), to aminoglycosides (gentamicin from 6.6% to 63.5% p<0.001, amikacin from 0% to 64.1% p=0.002) and to carbapenems (meropenem from 0% to 67.9% p<0.0001) (Table 2). Not found resistance to colistin.

Table 2.

Antibiotic resistance of Pseudomonas aeruginosa isolated from infections in Department of pediatric cardiac surgery.

Antibiotic	2010 n=15	2011 n=21	2012 n=8	2013 n=12	2014 n=78	2015 n=89	2016 n=69	2017 n=38	2018 n=65	2019 n=159	p-value*
Ceftazidime	4 (26.6)	6 (28.5)	1 (12.5)	1 (8.3)	31 (39.7)	63 (70.7)	46 (66.6)	23 (60.5)	55 (84.6)	122 (76.7)	0.001
Cefepime	2 (13.3)	10 (47.6)	2 (25)	3 (25)	22 (28.2)	49 (55)	50 (72.4)	21 (55.2)	57 (87.6)	129 (81.1)	0.001
Meropenem	0	0	1 (12.5)	3 (25)	29 (31.1)	50 (56.1)	52 (75.3)	26 (68.4)	58 (89.2)	108 (67.9)	0.000
Imipenem	1 (6.6)	1 (4.7)	2 (25)	4 (33.3)	32 (41)	53 (59.5)	53 (76.8)	27 (71)	58 (89.2)	106 (66.6)	0.000
Amikacin	0	6 (28.5)	1 (12.5)	1 (8.3)	14 (17.9)	56 (62.9)	57 (82.6)	23 (60.5)	56 (86.1)	102 (64.1)	0.002
Gentamicin	1 (6.6)	6 (28.5)	1 (12.5)	1 (8.3)	19 (24.3)	47 (52.8)	47 (68.1)	25 (65.7)	57 (87.6)	101 (63.5)	0.000
Ciprofloxacin	3 (20)	1 (4.7)	1 (12.5)	1 (8.3)	8 (10.2)	15 (16.8)	43 (62.3)	22 (57.8)	56 (86.1)	104 (65.4)	0.002
Levofloxacin	3 (20)	2 (9.5)	0	1 (8.3)	22 (28.2)	14 (15.7)	43 (62.3)	24 (63.1)	53 (81.5)	103 (64.7)	0.001

** Linear regression*

K.pneumoniae isolates showed tendency of increasing resistance to 3rd generation cephalosporins (ceftriaxone from 35.7% to 79.4% (p=0.011) to cefepime from 28.5% to 78.4% (p=0.0001) and aminoglycosides (amikacin from 7.1% to 14.7% (p=0.0001) and gentamicin from 7.1% to 65.6% (p=0.002) (Table 3).

Table 3.

Antibiotic resistance of Klebsiella pneumoniae isolated from infections in Department of pediatric cardiac surgery.

Antibiotic	2011 n=14	2012 n=12	2013 n=21	2014 n=61	2015 n=88	2016 n=63	2017 n=39	2018 n=44	2019 n=102	p-value*
Amoxicillin/ clavulanic acid	7 (50)	5 (41.6)	9 (42.8)	39 (63.9)	52 (59)	53 (84.1)	35 (89.7)	37 (84)	88 (86.2)	0.001
Ceftazidime	5 (35.7)	4 (33.3)	10 (47.6)	37 (60.6)	63 (71.5)	39 (61.9)	32 (82)	30 (68.1)	78 (76.4)	0.000
Ceftriaxone	5 (35.7)	5 (41.6)	12 (57.1)	44 (72.1)	66 (75)	54 (85.7)	32 (82)	29 (65.9)	81 (79.4)	0.011
Cefepime	4 (28.5)	4 (33.3)	11 (52.3)	36 (59)	65 (73.8)	44 (69.8)	31 (79.4)	29 (65.9)	80 (78.4)	0.000
Meropenem	0	0	0	1 (1.6)	2 (2.2)	0	1 (2.5)	1 (2.2)	0	0.172
Amikacin	1 (7.1)	1 (8.3)	2 (9.5)	4 (6.5)	8 (9)	7 (11.1)	5 (12.8)	6 (13.6)	15 (14.7)	0.000
Gentamicin	1 (7.1)	1 (8.3)	11 (52.3)	18 (29.5)	38 (43.1)	29 (46)	23 (58.9)	27 (61.3)	67 (65.6)	0.002
Ciprofloxacin	2 (14.2)	2 (16.6)	7 (33.3)	18 (29.5)	18 (20.4)	16 (25.3)	11 (28.2)	11 (25)	30 (29.4)	0.364
Levofloxacin	2 (14.2)	2 (16.6)	6 (28.5)	19 (31.1)	16 (18.1)	14 (22.2)	9 (23)	9 (20.4)	20 (19.6)	0.734

** Linear regression*

Antibiotic resistance patterns of *A.baumannii* isolates are shown in Table 4; statistically significant increasing resistance was to all tested antibiotics with the higher resistance to carbapenems, more than 63% and quinolones, 66%. Not found resistance to colistin.

Table 4.

Antibiotic resistance of Acinetobacter bumannii isolated from infections in Department of pediatric cardiac surgery.

Antibiotic	2011 n=13	2014 n=39	2015 n=89	2016 n=69	2017 n=38	2018 n=65	2019 n=159	p-value*
Meropenem	0	11 (28.2)	7 (33.3)	9 (34.6)	15 (39.4)	11 (42.3)	45 (62.5)	0.003
Imipenem	0	10 (25.6)	9 (42.8)	10 (38.4)	16 (42.1)	11 (42.3)	46 (63.8)	0.008
Amikacin	0	11 (28.2)	7 (33.3)	9 (34.6)	14 (36.8)	10 (38.4)	34 (47.2)	0.014
Gentamicin	0	4 (10.2)	3 (14.2)	8 (30.7)	14 (36.8)	9 (34.6)	30 (41.6)	0.000
Tobramycin	0	0	0	2 (7.6)	4 (10.5)	5 (19.2)	22 (30.5)	0.009
Ciprofloxacin	0	12 (30.7)	7 (33.3)	11 (42.3)	15 (39.4)	12 (46.1)	47 (65.2)	0.004
Levofloxacin	0	11 (28.2)	8 (38)	9 (34.6)	13 (34.2)	11 (42.3)	48 (66.6)	0.009

**Linear regression*

Discussion

There is a lack of studies with pediatric cardiac surgery patients hospitalized in the ICU with multi-drug resistance infections. Nonetheless, from many different studies around the world, bacterial infections in pediatric cardiac surgery represent a great problem caused of increasing morbidity, mortality and prolonged hospital stays. Prevalence of bacterial infection in pediatric cardiac surgery is necessary to determine prevalent pathogens and resistance rates for better use the effective antibiotics. It is important to known that bacterial agents that affect each different unit were variable among hospitals. For example, in our study the most common systems affected were respiratory tract (54.3%) followed surgical site infections (8.5%) and bloodstream infection (5.7%). The distribution of bacterial infection was more or less similar to that of Sahu et al. [11] (respiratory infection 44.2% followed by SSI 11.6%, BSI 7.5%, and UTI 6.9%. In most of other studies are the commonest infection affected by respiratory tract followed urinary tract infection [12-13]. These results are different of other studies in which bloodstream infection was the common type of bacterial infection [14-17]. In the present study, we found small number of infection related to the central venous catheter (3.9%) it was similar with the study conducted by Sahu et al. [11], (<1%), but contrary to the others studies including Michalopoulos et al. [18] with 22.4%. We found a low incidence of urinary tract catheter infection-associated infection. The rational use of urinary catheters was the major factor accounting for this low incidence.

Our study determined a predominance of Gram-negative bacilli (53.1%) from the culture results, witch comparable with study reported by Sahu et al. [11] and Silva et al. [19], whereas Gram-positive cocci were the most prevalent group of patients studied by Michalopoulos et al. [18] and Lola et al. [16] noted equal level of both group organisms.

In the present study, the most frequently isolated pathogens were *P.aeruginosa* (19.7%), *K.pneumoniae* (16%), and *A.baumannii* (8.8%). In the same study *P.aeruginosa* are the most common pathogen in Italy reported by Valera et al. [20]. Moreover, we found statistically increasing rates of frequency *P.aeruginosa* from 16.1% to 30.2% (p=0.048), *K.pneumoniae* from 7.5% to 19.3% (p=0.014), and *A.baumannii* from 3.2% to 13.6% (p=0.059). In our study, *P.aeruginosa* was responsible for respiratory tract infection 20.9%, tracheobronchial aspirate 24.4% that was comparable with previous study [21]. We also found that *K.pneumoniae* was responsible for most of the BSIs (19.2%) in our study that was comparable with other studies [11, 22]. We found CoNS (36.6%) as prevalent pathogen of SSI that was comparable with similar study [23], whereas Sahu et al. [11] documented that *S.aureus* was the most common pathogen for SSI (58%).

The most common isolated *P.aeruginosa* was found with dramatically increasing resistance to all tested antibioticsб especially to meropenem from 0% to 67.9% (p=0.0001), ceftazidime from 26.6% to 76.7% (p=0.001). In 2018 was found to be highest resistance to meropenem and imipenem 89.2%, to ceftazidime 84.6%, which is much higher, compared to Chinese report [24] with 50% and 33.3% respectively, also to levofloxacin 81.1% and ciprofloxacin 86.1%, which is less in India (86-96% respectively) report [11].

In our study, we found higher levels of ESBL-producing *K.pneumoniae* isolates (72.7%) and statistically significant increasing resistance to aminoglycosides, whereas we not report about carbapanemases producers isolates and higher resistance to quinolones, both these group of antibiotics are the most effective for treatment *K.pneumoniae* associated infections.

A.baumannii was responsible for more than 8.5% of bacterial infection with statistically significant increasing frequency (p=0.059), it is important to note because it contrary to our previous study [21]. Moreover, we report increasing resistance to all tested antibiotics, especially to meropenem 62.5%, ciprofloxacin 65.2% and amikacin 47.2% which more or less similar to other studies [11,25]. As is known, this Gram-negative bacterium becoming is serious hurdle, because there are limited choice of available antibiotics.

Conclusion

In this paper, we report characteristics of microbial landscape and resistance rates of bacterial infections in a postoperative pediatric cardiac surgical facility in tertiary hospital in Kazakhstan. Respiratory tract infection was found to be the most common site for bacterial infection and *P.aeruginosa* and *K. pneumoniae* were the most frequent pathogens with high level of resistance. Our findings are posing necessitates for improvement preventive measures, including microbiological monitoring, good hygiene, and well-designed hospital infection control strategy.

Compliance with ethical standards

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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