A Prospective Study on the Pathogenesis of Catheter-associated Bacteriuria in Critically Ill Patients

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Abstract

Background

Updating the pathogenesis of catheter-associated bacteriuria (CA-bacteriuria) in intensive care unit (ICU) is needed to adapt prevention strategies. Our aim was to determine the main pathway, endoluminal or exoluminal, of CA-Bacteriuria in ICU patients.

In a prospective study, quantitative urine cultures were sampled from days 1 to 15 after catheterization, from catheter sampling sites, collection bags and catheter outer surface near the meatus. Endoluminal pathway was CA-bacteriuria (defined as $10^2$ CFU/mL) first in collection bag then in catheter. Exoluminal pathway was CA-bacteriuria first in catheter, on day 1 in early cases and after day 1 in late cases.

Results

Of 64 included patients, 20 had CA-bacteriuria. Mean of catheterization days and incidence density were 6.81 days and 55.2/1000 catheter-days. Of 26 microorganisms identified, 12 (46.2%) were Gram positive cocci, 8 (30.8%) Gram negative bacilli and 6 yeasts. Three (11.5%) CA-bacteriuria were endoluminal and 23 (88.5%) exoluminal, of which 10 (38.5%) were early and 13 (50%) late. Molecular comparison confirmed culture findings. Quality audit showed good compliance with guidelines.

Conclusion

Exoluminal pathway of CA-bacteriuria in ICU patients predominated and surprisingly occurred early despite good implementation of guidelines. This finding should be considered in guidelines for prevention of CA-bacteriuria.

Background

With a prevalence of up to 40%, urinary tract infections (UTI) are the first cause of nosocomial infections [1–5]. The presence of a urinary catheter is the main risk factor for nosocomial UTI [2, 3]. A diagnosis of catheter-associated bacteriuria (CA-Bacteriuria) is established when no distinction is made between catheter-associated asymptomatic bacteriuria and catheter-associated urinary tract infection (CA-UTI) [1]. CA-Bacteriuria is correlated with the duration, mainly six days, of catheterization [1, 6]. The risk of CA-UTI increases in the intensive care unit (ICU), where incidence rates range between 3.6 and 14.71 per 1,000 urine catheter days [1, 3, 5, 7, 8]. The first step in the pathogenesis of CA-UTI is the endoluminal or exoluminal colonization of the urinary catheter, which is more frequently involved than the blood-borne pathway [1, 6, 9]. Some studies have reported that endoluminal CA-Bacteriuria involves exogenous flora originating from the colonization of the collector bag, or a breach of the closed system during manipulations of the urinary catheter [10–13]. Exoluminal CA-Bacteriuria involves endogenous flora from the urinary meatus. This kind of colonization occurs early during the insertion of the catheter or later as a result of the colonization of the urinary meatus by the digestive flora [11–18]. After adhesion, the
microorganisms migrate within a biofilm along the endoluminal and exoluminal sides of the urinary catheter. In 1999 a study reported the predominance of the exoluminal pathway in a non-selected population [9]. No study has explored the pathway mechanisms of CA-Bacteriuria solely in critically ill patients. The impact of guidelines on the pathogenesis of pathways for CA-Bacteriuria is unknown [1, 2, 4, 19, 20]. Up-to-date knowledge of these pathways is needed to improve the prevention of CA-Bacteriuria and thereby CA-UTI [1, 2, 4, 19], which is one of the most frequent nosocomial infections in the ICU and is associated with a heavy health burden [1, 2, 19, 21, 22].

The main aim of this prospective study was to explore the pathways (exoluminal vs endoluminal) of CA-Bacteriuria in critically ill patients. Secondarily, we investigated the characteristics of patients and microorganisms involved in the infection and performed a quality audit on urinary catheterization.

**Results**

Of the 225 patients admitted to the ICU (Fig. 1), 64 were included. CA-Bacteriuria was identified in 20 patients (31.2%), of which 15 were monomicrobial and 5 polymicrobial, corresponding to an incidence density of 55.2 per 1000 urinary catheter-days. There was no difference in patient characteristics between those with CA-Bacteriuria and those without, except for the sex/ratio (Table 1). Most of the urinary catheters were manufactured with 100% silicone (n = 54, 84.4%). The mean duration of catheterization was 6.81 ± 0.58 days, with no difference between patients with or without CA-Bacteriuria (Table 1). For 39 (60%) patients, the duration of catheterization was less than 6 days. Three patients had CA-UTI, which gave an incidence density of 6.9 per 1000 urinary catheter-days.
Table 1
Comparison of included patients with and without catheter-associated bacteriuria (CA-bacteriuria)

| Variables                              | CA-bacteriuria (n = 20; 31.2%) | No CA-bacteriuria (n = 44; 68.8%) | p. value |
|----------------------------------------|-------------------------------|----------------------------------|----------|
| Age (years)                            | 71 ± 12,9                     | 63,7 ± 15,5                     | 0,06*    |
| Male/Female (number)                   | 8/12                          | 37/7                            | 0,001*   |
| Length of stay (days)                  | 11,3 ± 10,1                   | 11,3 ± 8,8                      | 0,99     |
| Admission weight (Kg)                  | 82,9 ± 25,7                   | 76,4 ± 24,7                     | 0,34     |
| BMI (kg/m²)                            | 30,5 ± 9,5                    | 30,6 ± 30,2                     | 0,98     |
| SAPS II score                          | 50,3 ± 29,2                   | 50,3 ± 21,8                     | 0,69     |
| Death (%)                              | 1 (5%)                        | 5 (11,4%)                       | 0,65     |
| Mechanical ventilation (%)             | 8 (40%)                       | 22 (50%)                        | 0,59     |
| Non-invasive ventilation (%)           | 10 (50%)                      | 27 (61,4%)                      | 0,42     |
| Vasoactive amine (%)                   | 9 (45%)                       | 16 (36,4%)                      | 0,58     |
| Acute renal failure (%)                | 5 (25%)                       | 9 (20,5%)                       | 0,74     |
| Chronic kidney disease (%)             | 4 (20%)                       | 5 (11,4%)                       | 0,44     |
| Dialysis (%)                           | 3 (15%)                       | 6 (13,6%)                       | 1,00     |
| Diabetis mellitus (%)                  | 3 (15%)                       | 4 (9,1%)                        | 0,66     |
| 100% silicon catheter                  | 16 (80%)                      | 38 (86,3%)                      | 0,71     |
| Silicon-coated-latex catheter          | 4 (20%)                       | 6 (13,7%)                       | 0,71     |
| Mean duration of catheterization (days) | 6,45 ± 0,94                   | 6,98 ± 0,73                     | 0,89     |
| Mean duration of anti-infective therapy (days) | 33.4 ± 18,9                  | 32.1 ± 18,7                     | 0,79     |

* Statistical significance: P values of < 0.05

Of the 26 microorganisms identified, 12 (46.2%) were Gram positive cocci with a predominance of *E. faecalis* (n = 5, 19.2%) and *S. epidermidis* (n = 4, 15.4%), 8 (30.8%) were Gram negative bacilli with a predominance of *E. coli* (n = 4, 15.4%), and 6 (23.1%) were *Candida sp* (Fig. 1 and Table 2).
Table 2
Dynamics of Catheter-Associated bacteriuria (CA-bacteriuria) and microorganisms identified

| Patient no. | Sex | Origin of CA-Bacteriuria | Microorganism               | Time occurrence (days) |
|-------------|-----|--------------------------|------------------------------|------------------------|
| 30          | F   | Endoluminal              | *Escherichia coli*           | 6                      |
| 33          | M   | Endoluminal              | *Staphylococcus. epidermidis*| 1                      |
| 76          | F   | Endoluminal              | *Morganella morganii*        | 2                      |
| 23          | F   | Early exoluminal         | *Candida albicans*           | 1                      |
| 34          | M   | Early exoluminal         | *Candida albicans*           | 1                      |
| 46          | M   | Early exoluminal         | *Candida albicans*           | 1                      |
| 60          | F   | Early exoluminal         | *Candida glabrata*           | 1                      |
| 76          | F   | Early exoluminal         | *Corynebacterium aurimucosum*| 1                      |
| 19          | F   | Early exoluminal         | *Enterococcus faecalis*      | 1                      |
| 59          | F   | Early exoluminal         | *Enterococcus faecalis*      | 1                      |
| 22          | M   | Early exoluminal         | *Klebsiella pneumoniae*      | 1                      |
| 30          | F   | Early exoluminal         | *Streptococcus agalactiae*   | 1                      |
| 33          | M   | Early exoluminal         | *Streptococcus agalactiae*   | 1                      |
| 26          | M   | Late exoluminal          | *Candida albicans*           | 5                      |
| 51          | F   | Late exoluminal          | *Candida albicans*           | 2                      |
| 44          | F   | Late exoluminal          | *Escherichia coli*           | 12                     |
| 60          | F   | Late exoluminal          | *Escherichia coli*           | 4                      |
| 75          | F   | Late exoluminal          | *Escherichia coli*           | 2                      |
| 24          | F   | Late exoluminal          | *Enterococcus faecalis*      | 6                      |
| 54          | F   | Late exoluminal          | *Enterococcus faecalis*      | 4                      |
| 73          | F   | Late exoluminal          | *Enterococcus faecalis*      | 9                      |
| 56          | M   | Late exoluminal          | *Morganella morganii*        | 3                      |
| 26          | M   | Late exoluminal          | *Proteus mirabilis*          | 12                     |
| 11          | M   | Late exoluminal          | *Staphylococcus epidermidis* | 3                      |
| 30          | F   | Late exoluminal          | *Staphylococcus epidermidis* | 3                      |
| 66          | M   | Late exoluminal          | *Staphylococcus epidermidis* | 3                      |
The median time of occurrence was 2 days (1 to 6 days) for endoluminal CA-bacteriuria and 4 days (2 to 12 days) for late exoluminal CA-bacteriuria.

There were 3 (11.5%) endoluminal and 23 (88.5%) exoluminal cases of CA-Bacteriuria (n = 23, 88.5%), of which 10 (38.5%) were early and 13 (50%) late (Figs. 2A, 2B and 2C). Molecular comparison confirmed culture findings in all but one patient, in whom early exoluminal developed into endoluminal CA-Bacteriuria (S. epidermidis, patient 33). In 16 cases (69.5%), comparison with microorganisms identified on swabs confirmed early exoluminal (n = 7/10) and late exoluminal CA-Bacteriuria (n = 9/13).

The quality audit on urinary catheterization showed that there were no problems in following catheterization international guidelines [2, 4, 19]. All hand hygiene procedures were complied with but 50% were performed with alcohol-based products (Table 3).
## Table 3
Quality audit of the insertion of a urinary catheter

| Questions                                                                 | % of answers in accordance with recommendations |
|---------------------------------------------------------------------------|--------------------------------------------------|
| Knowledge of protocol                                                     | 100% (10/10)                                     |
| Two people performing urinary catheterization                            | 80% (8/10)                                       |
| Genital cleaning                                                         | 100% (10/10)                                     |
| Hand hygiene before genital cleaning                                      | 100% (10/10)                                     |
| **Alcohol-based hand rubbing**                                            | 50% (5/10)                                       |
| Plain soap handwashing                                                   | 20% (2/10)                                       |
| Antiseptic soap handwashing                                              | 30% (3/10)                                       |
| Use of vinyl gloves                                                      | 100% (10/10)                                     |
| Hand hygiene after genital cleaning                                       | 80% (8/10)                                       |
| **Alcohol-based hand rubbing**                                            | 50% (4/8)                                        |
| Plain soap handwashing                                                   | 25% (2/8)                                        |
| Antiseptic soap handwashing                                              | 25% (2/8)                                        |
| Installer : mask, hygiene cap, disposable apron                          | 100% (10/10)                                     |
| Antisepsis of urinary meatus with sterile gloves                         | 100% (10/10)                                     |
| Hand hygiene after sterile glove removal                                  | 100% (10/10)                                     |
| **Alcohol-based hand rubbing**                                            | 50% (5/10)                                       |
| Plain soap handwashing                                                   | 20% (2/10)                                       |
| Antiseptic soap handwashing                                              | 20% (2/10)                                       |
| Sterile urinary catheterization                                          | 100% (10/10)                                     |
| Hand hygiene after catheterization                                       | 90% (9/10)                                       |
| **Alcohol-based hand rubbing**                                            | 56% (5/9)                                        |
| Plain soap handwashing                                                   | 22% (2/9)                                        |
| Antiseptic soap handwashing                                              | 22% (2/9)                                        |
| Securing the collection bag in a sloping position                         | 100% (10/10)                                     |
Questions | % of answers in accordance with recommendations
--- | ---
Traceability = Date of catheterization | 100% (10/10)
On collector bag | 100% (10/10)
In patient file | 90% (9/10)

10 observations were performed by one investigator of 10 consecutive catheterizations. The audit grid was established in accordance with national recommendations [4]

**Discussion**

This study focused on the pathways of CA-Bacteriuria. The exoluminal pathway was predominant and accounted for more than one third of cases of early exoluminal CA-Bacteriuria. This result was not related to the quality of urinary catheterization.

CA-Bacteriuria occurred in one third of patients of the Medical ICU, a proportion consistent with that in other ICU studies in [23, 24]. We observed a greater number of cases of exoluminal CA-Bacteriuria (88.5%) and a low rate of endoluminal CA-Bacteriuria (11.5%). In our study, the main pathway was exoluminal and occurred at a higher rate than in the study of Tambyah et al., in which 46%, 23.2% and 30.8% of CA-Bacteriuria cases were exoluminal, endoluminal and indeterminate CA-Bacteriuria, respectively [9]. The authors reported a 10% rate of disconnections between urinary catheters and collector bags, which is a risk factor for endoluminal CA-Bacteriuria. During the four months of our study, only two disconnections (3%) were observed, which could explain the very low proportion of endoluminal CA-Bacteriuria cases. These findings suggest that the guidelines concentrate attention on preventing disconnection thereby leading to a large reduction in the endoluminal pathway [1, 2]. Another explanation could be the increasing use of 100% silicon urinary catheters, which delays the obstruction caused by biofilm encrustation [27].

Tambyah et al. observed 12.4% (n = 31) of early exoluminal catheter-associated bacteriuria among 250 identified microorganisms [9] as against 38.5% in our study. Early exoluminal colonization could be related to a defect in the aseptic procedure during insertion of the catheter. To assess this assumption, we performed a quality audit on catheter insertion in accordance with the most recent guidelines [2, 4, 19]. The only flaw observed was a low observance of hydro-alcoholic hand rubbing (approximately 50%) during the different stages of insertion where alcohol-based products are recommended [26]. This failure was not a major infringement of the guidelines but could have been involved in early exoluminal CA-Bacteriuria. However, the microorganisms of early exoluminal colonization in our study did not come only from the skin flora. Another cause of early exoluminal CA-Bacteriuria could be the presence of microorganisms in the final centimeters of the urethra carried away during catheterization. In our study, 69.5% of the micro-organisms of exoluminal CA-Bacteriuria were also identified on samples of urinary
meatus. This is consistent with other reports which showed that in 75% of cases the microorganisms of exoluminal bacteriuria preexisted in the urethral flora [15, 16] and that a positive culture of urinary meatus increased the incidence of CA-Bacteriuria [17, 18, 27]. However, meatal care does not result in a reduction in CA-UTI or urethral colonization [1, 20]. Before insertion, there is a physical inability to access the inside of the urethra during the antisepsis [9].

After insertion, the persistence of CA-Bacteriuria could be related to the formation of biofilm at the interface of the catheter and the urethra, to repeated catheter manipulations or to inadequate residual activity of the antiseptic [1]. Consequently, the strict implementation of guidelines by health workers does not avoid early exoluminal CA-Bacteriuria.

The first limitation of our study is the low number of patients included. However, this was compensated by the large number of samples (n = 1008 with a maximum of 27 samples for 15 days), which is indicative of a good follow-up of each patient. A second limitation was the viable non-cultivable bacteria that we were unable to isolate. To reduce this bias, it would have been necessary to remove the urinary catheter and culture its end or to carry out a molecular analysis by 16S PCR. However, as we were performing a real-life observational study we used the usual microbial analysis techniques. However, this is the first report to confirm microbial results by molecular comparison of the same microorganisms isolated. A final limitation was the choice of a threshold of $10^2$ CFU/mL in bladder urine to define CA-Bacteriuria: in French and American guidelines, it is set at $10^3$ CFU/ml [1, 4]. This could have artificially increased the detection of CA-Bacteriuria. However, our aim was earlier detection of bacteriuria. The change in threshold was possible because standardization of the microbiological technique allowed a detection threshold of 10 CFU/mL. We do not rule out an impact of anti-infective therapy on the detection threshold. However, there was no difference of anti-infective therapy between the two groups. In addition, it is established that in patients with a urinary catheter not receiving antimicrobial therapy bacteriuria or candiduria $\geq 10^2$ CFU/ml will increase to $>10^5$ CFU/mL in one to three days if the urinary catheter remains in place [1, 4].

Conclusions

This prospective observational study assessed the occurrence of CA-Bacteriuria in a medical ICU. The exoluminal pathway was shown to be predominant, and even when guidelines were fully complied, 38.5% of cases of CA-Bacteriuria were early exoluminal. Two factors could explain these findings: the inability to remove the microorganisms from the final centimeters of the urethra during meatal care, and the design of catheter materials. To explore the first hypothesis, a better knowledge of urethral and perineum microbiota is needed. Measures could then be taken to act on the balance of these microbiota to prevent their adhesion to urinary catheters. To explore the second hypothesis, the mechanisms of CA-Bacteriuria and biofilm formation on urinary catheters need to be elucidated to guide research into new and safe devices. It would be interesting to study bacterial adhesion to different kinds of urinary catheters according to variations in the environment such as the composition or pH of urine. This could lead to the development of new devices or to medical modification of the composition of urine. The prevention of
CA-Bacteriuria and, even more importantly, of CA-UTI is a challenge for the medical community, which should now develop interdisciplinary innovation projects.

**Methods**

**Population study**

We conducted a four-month (from May to September, 2015) observational and prospective clinical study in a 16-bed medical intensive care unit of the University Hospital of Clermont-Ferrand, France. The study was approved by the regional ethics committee of South-East France 6: Comité de Protection des Personnes Sud-Est 6 (reference # N°2015/CE 59 - IRB00008526). Patients were informed of the study as requested in the French guidelines. Informed consent is obtained from all participants and in case of participants who are dead now informed consent is obtained from their legal guardian. Inclusion criteria were adult patients with urinary catheter inserted for a duration of more than 48 hours. Exclusion criteria were no urinary catheter or catheter inserted for a duration of less than 48 hours, identification of a microorganism by cytobacteriological examination of the urine (CBEU) on the day the catheter was inserted (day-0), pregnant or breastfeeding women and subjects protected by law. Patient care, choice and management of the urinary catheter were left to the discretion of the healthcare team. Infections were defined according to American and French guidelines [1, 2, 4].

**Sampling**

Two investigators from the infection control team performed the sampling. For each patient, the length of follow-up was 15 days maximum depending on the duration of catheterization and hospital stay. Samples were taken daily from the first to the sixth day of catheterization and then on the ninth, twelfth and fifteenth days. Each time, three samples were taken: (i) bladder urine at the urinary catheter sampling site according to national recommendations using a needle or suitable adapter [4]; (ii) urine from the collection bag after disinfection of the drain end-piece with chlorhexidine-alcohol 0.5%; (iii) swabs with transport media (Transystem®, COPAN®, Brescia, Italy) of the outer surface of the urinary catheter near the urinary meatus. All samples were collected in CBEU tubes (BD Vacutainer®, BD Diagnostics©, Le Pont de Claix, France).

**Microbiological analysis**

Each sample was streaked on two agar plates, for gram-negative bacilli (Drigalski agar, bioMerieux©) and for gram-positive bacteria and yeasts (Columbia CAP Agar, Oxoid©). Plating was standardized (easySpiral Dilute®, Interscience©) and 100 µL were inoculated on agar to obtain a threshold detection of 10 colony-forming units (CFU)/ml. Each agar plate was incubated at 37 °C for 48 hours and the bacterial count was automatized (Scan® 500, Interscience©). Results were expressed quantitatively for urine samples and semi-quantitatively for swabs because they were drained in 1000 µL of saline solution before being streaked. When the CFU count from the bladder urine sample was higher than or equal to $10^2$ CFU/mL, all strains isolated from the patient were identified by MALDI TOF mass spectrometry.
(Matrix-Assisted Laser Desorption/Ionisation time-of-flight, VITEK® MS, bioMerieux©). For each patient, clonal relatedness was determined either by pulsed-field gel electrophoresis (PFGE) or by ERIC2-PCR on isolates identified during follow-up. PFGE was performed with the GenePath System (Bio-Rad Laboratories, Marnes la Coquette, France) according to the manufacturer's instructions for *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Candida albicans* and *Candida glabrata*. Isolates were grown in 5 mL of Trypticase soy broth at 37 °C for 16 to 20 hours. Following digestion with the restriction enzymes SmaI or BssHII (New England Biolabs is headquartered in Ipswich, MA, USA), DNA fragments were separated using the GenePath instrument. SmaI was used for *Staphylococcus epidermidis* and *Enterococcus faecalis*, and BssHII was used for *Candida albicans* and *Candida glabrata*. The run conditions were 6 V/cm, 22 hours, 120° angle, linear ramp, initial switch 2.2 seconds, final switch 54.2 seconds. DNA banding patterns were interpreted according to Tenover *et al.* [28]. Isolates were considered to be closely related if the PFGE patterns differed by 3 or fewer bands. ERIC2-PCR was performed according to Dumarche *et al.* [29] for *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, and *Proteus mirabilis*. No molecular comparison was performed for *Corynebacterium aurimucousum* and *Streptococcus agalactiae* because these strains are rarely involved in urinary tract infections.

**Establishing the first localization of catheter-associated bacteriuria (CA-Bacteriuria)**

The first localization of CA-Bacteriuria as defined by observing the dynamics of the occurrence of microorganisms in the bladder urine and collection bags. CA-Bacteriuria was defined as a number of microorganisms higher than or equal to $10^2$ CFU/mL in at least one bladder urine sample collected at the urinary catheter collection site. As previously reported [9], the CA-Bacteriuria pathway was identified by comparing the dynamics of the occurrence of microorganisms on the three samples (bladder urine, collection bag urine, urinary catheter swabs). Endoluminal CA-Bacteriuria was defined by the identification of the same microorganism first in collection bag urine and then in bladder urine. Early exoluminal CA-Bacteriuria was defined by the identification of the same microorganism the first day of catheterization in bladder urine with or without identification in urine from the collection bag. Late exoluminal CA-Bacteriuria was defined by the identification of the same microorganism after the first day of catheterization in bladder urine without preliminary identification in urine from the collection bag. A molecular comparison of the strains was then performed that confirmed the culture findings. In some cases, molecular comparison with microorganisms identified on swabs helped to confirm exoluminal CA-Bacteriuria.

**Quality audit of urinary catheter insertion**

We carried out a quality audit on urinary catheter insertion according to our hospital protocol, which is based on the international guidelines [2, 4, 19]. One investigator from the medical ICU observed the insertion of 10 consecutive urinary catheters. The audit grid followed the insertion protocol and included the knowledge of protocol, the number of people performing the insertion, the kind of hand hygiene, the
personal protective equipment used, the respect of asepsis, positioning of the collection bag and traceability of catheter insertion in the medical file.

Statistics

Patients with and without catheter-associated bacteriuria were compared with Student test for quantitative data, and a Fisher or CHI2 test for qualitative data. The occurrence of each microorganism was analyzed as an independent case of catheter-associated bacteriuria. Categorical data were expressed as numbers and percentages, and quantitative parameters as mean ± standard-deviation. \( P \) values of < 0.05 were considered to indicate statistical significance. Analyses were performed with SAS software (SAS Institute, Inc.).

List Of Abbreviations

CA-UTI: Catheter-Associated Urinary Tract Infection; CA-Bacteriuria: Catheter-Associated Bacteriuria; ICU: Intensive Care Unit;

Declarations

Ethical approval and consent to participate

The study was approved by the regional ethics committee of South-East France 6: Comité de Protection des Personnes Sud-Est 6 (reference # N°2015/CE 59 - IRB00008526). All methods were performed in accordance with the relevant guidelines and regulations. Patients were informed of the study as requested in the French guidelines. Informed consent is obtained from all participants and in case of participants who are dead now informed consent is obtained from their legal guardian.

Consent for publication

Not applicable

Availability of data materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interest

The authors have no financial conflicts of interest related to this study

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Authors’ contributions

CA and AL conceived and designed the study; CA, AL, BMA, CH, FR, PAN and BS recruited the participants and collected the data; CA, BMA, AL, CF and OT analyzed and interpreted data; CA, OT, CF and AL draft the report and all authors contributed to reviewed it. All authors approved the final version.

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