

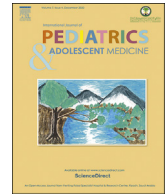
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Full length article

The first report of Methicillin-resistant *Staphylococcus aureus* (MRSA) in cystic fibrosis (CF) patients in Saudi ArabiaHanaa Banjar^{a,*}, Hend Al-Qahtani^a, Waseem Yasin^{a,b,c}, Waad Al-wgait^a, Hanan Al-Amer^a, Rawia raja^b, Ali Al-Nakhli^b, Kawthar Karkour^b^a Department of Pediatrics, King Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia^b College of Medicine, Al-Faisal University, Riyadh, Saudi Arabia^c Alfaisal University, Saudi Arabia

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ABSTRACT

Introduction: Methicillin-resistant *Staphylococcus aureus* infections have been increasingly reported in patients with cystic fibrosis (CF) who have progressive deterioration in their pulmonary function.**Objectives:** To determine the prevalence of MRSA infections in CF in a tertiary care center in Saudi Arabia.**Methodology:** This is a retrospective chart review conducted as part of the CF registry data from 1 January 2002 to 1 June 2016. All patients with confirmed CF of all age groups who had a respiratory culture positive for MRSA were included in the study.**Results:** Among 385 patients with CF who had respiratory samples, 43 (11%) were positive for MRSA at a mean age of 10.4 ± 7.2 years. Twenty-two patients out of the 43 (51%) were treated with different regimens: nasal Bactroban in 13/22 (59%); a combination of nasal Bactroban, oral vancomycin, and rifampicin for 2 weeks in 5 patients (23%); Bactroban and linezolid in one patient (5%); and oral vancomycin and rifampicin in 3 patients (14%). Eight out of the 22 treated patients (36%) achieved MRSA eradication. Six out of the 22 treated (27%) had experienced MRSA recurrence within 3–6 months, and another 5/22 (23%) continued to have MRSA colonization up to 2–4 years of follow-up despite using a proper eradication protocol. Twelve out of the 43 (28%) patients with MRSA infection died.**Conclusion:** MRSA infection in our population with CF is common. Therefore, an eradication protocol should be instituted at an early stage to prevent chronic colonization. Children with persistent MRSA colonization have high morbidity and mortality rate.© 2020 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Cystic fibrosis (CF) is an inherited recessive disorder of chloride transport characterized by recurrent and persistent pulmonary infections due to resistant organisms, resulting in lung function deterioration and early mortality [1]. CF is due to mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [2]. It is the most common life-threatening autosomal recessive

disease among Caucasian populations, with a frequency of 1 in 2000–3000 live births [3]. Deletion of phenylalanine in amino acid position 508 (deltaF508) on chromosome 7 is considered the most common mutation in North America and western Europe [4]. By contrast, in Saudi Arabia, the most common mutations described were *c.1418delG (p.G473EfsX54)*, Exon 11 (Legacy name: 1548delG), Exon 10 and *c.3700A > G (p.I1234V)*, Exon 22 (Legacy name: I1234V), Exon 19. [5,6].

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are the major causative agents of numerous hospital- and community-acquired infections [7].

MRSA infections have been increasingly reported among populations with CF worldwide [8]. There has been a hypothesis that MRSA infection of the airways in CF could be associated with more severe disease than that seen with methicillin-sensitive *Staphylococcus aureus* (MSSA) [9]. Patients with MRSA infection were

* Corresponding author. Al-Faisal University, Department of Pediatrics, (KFSHRC), P.O. Box. 3354, MBC-58, Riyadh, 11211, Saudi Arabia.

E-mail addresses: hanaa@kfshrc.edu.sa (H. Banjar), ahend@kfshrc.edu.sa (H. Al-Qahtani), wysin@alfaisal.edu (W. Yasin), waalwgait@kfshrc.edu.sa (W. Al-wgait), haalamer@kfshrc.edu.sa (H. Al-Amer).

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Abbreviation list

MRSA	Methicillin-Resistant <i>Staphylococcus aureus</i>
CF	Cystic Fibrosis
BAL	Bronchoalveolar lavage
NPA	Nasopharyngeal aspirates
CFTR	Cystic fibrosis transmembrane conductance regulator
MSSA	Methicillin-Sensitive <i>Staphylococcus aureus</i>

described to have frequent exacerbations and poorer lung function; thus, infection control is important, and patients should be adequately monitored [10]. A chromogenic selective medium for *MRSA* detection may improve its surveillance in patients with CF [11].

Eradication of *MRSA* is advised to be applied in most CF treatment centers [12]. Effective microbiological eradication of *MRSA* in patients with CF can be achieved, but its effect is not always clear-cut in terms of spirometric indices [13]. Intravenous vancomycin, a time-dependent antibiotic that is extensively eliminated by the kidneys, is frequently used to treat *MRSA* infections. Its therapeutic levels are difficult to achieve in patients with CF because of increased renal clearance [14].

Yurdakul et al. reported the prevalence of *MRSA* infection among 604 patients with CF in Turkey between October 2003 and January 2010, and the percentage of *MRSA*-positive patients was 3.9% [7].

Several proposed eradication protocols have been reported thus far (Table 1) [12–16]. Lo, D. et al. found that patients who clear *MRSA* within one year have the same risk of death as those who never had a positive culture for *MRSA*, which leads us to the importance of having clear guidelines on how to eradicate *MRSA*

infection in patients with CF [1].

Chmiel J. et al. reviewed lung infections in patients with CF in a two-part series study. They reported that the prevalence of *MRSA* infection is increasing in the USA, 25% as compared to that of 3–11% in Canada and Europe, and chronic *MRSA* infection is associated with a high decline rate of lung function, failure to recover lung function after a pulmonary exacerbation, and decreased survival. They found that the most successful treatment regimens included two oral antibiotics (one of which was rifampicin) and nebulized vancomycin, and these drugs were found to be safe and well tolerated [17]. On the other hand, monotherapy developed resistance. They also suggested the use of the fosfomycin tobramycin inhalation (FTI) solution, as it has activity against anaerobic, gram-negative, and gram-positive organisms including *MRSA*. They also found that the most difficult-to-treat patients with *MRSA* infection are those with chronic infection and who do not present enough symptoms to start the administration of IV antibiotics but have persistent respiratory symptoms. They suggested the administration of 250 mg of IV formulation of vancomycin in 5 ml of sterile water through nebulization mist treatment, twice daily for 28 days. Albuterol is often inhaled before the administration of the antibiotic [17].

1.1. Objective

This retrospective study is the first of its kind conducted in Saudi Arabia, with an aim to identify, recognize, and determine the prevalence of *MRSA* infection in patients with CF and to further study the methods and protocols of treatment and prevention.

1.2. Methodology

After obtaining ethical approval, we retrospectively reviewed the charts of 385 patients with confirmed CF of all age groups who

Table 1
Literature Review on Cystic Fibrosis and *MRSA* management.

Author	No. Pts.	Age (Yrs)	Treatment protocol	Eradication success (%)
Vanderhelst et al. 2013 [12]	11	Range 1-43	Six-month course: 1. o. Rifa 15 mg/kg/day 2. o. Fusidic acid 30 mg/kg/day 3. t. decolonization including muoircin-containing n. oitment applied to all pts. 3× daily for 5 days Two pts. had to switch to a combination of Rifa.and Clin (one after two weeks, and one after four weeks)	90% Within 6-month period The 10% failure was due to lack of adherence of the treatment
Vanderhelst et al. 2013 [13]	6	Median 21.4	Six-month course: 1. o. Rifa 15 mg/kg/day 2. o. FA 30 mg/kg/day 3. t. decolonization including muoircin-containing n. oitment applied to all pts 3× daily for 5 days	83%
Fung, L 2012 [14]	3	3,17, and 15	continuous infusion of Vanco (50/40/31) mg/kg/day respectively every 8 h	Eradication is unknown No Nephrotoxicity
Burdge 1995 [15]	2	28 and 31	Two-month course: 1. o. rifa 600 mg daily 2. clin 600 mg bid	100% At 8-month follow up
Kiefer A. 2018 [16]	7	Range 4-30	7-day course: 1. o. Rifa (7.5–10 mg/kg, max. 300 mg twice daily) 2. o. FA (15 mg/kg max. 500 mg three times daily) 3. inhalation therapy with Vanco (4 mg/kg, max. 250 mg, dissolved in 4 ml NaCl 0.9% twice daily)	86%
Banjar 2019	22	Mean 10 ± 7.2	2-weeks course divided: 1. n. Bac in 13 pts. 2. n. Bac + Linezolid in 1 pt. 3. n. Bac + Vanco + Rifa in 3 pts. 4. Vanco + Rifa in 5 pts.	36%

MRSA: Methicillin Resistant *Staphylococcus Aureus*. Pts. = Patients, Yrs = Years, NaCl = Sodium Chloride. Vanco = Vancomycin, Rifa = Rfampin, Bac = Bactroban, Clin = Clindamycin. n. = Nasal, o. = Oral, t. = Topical, IV = Intravenous. bid = twice-daily, max. = maximum, FA = Fusidic Acid, No. = number of.

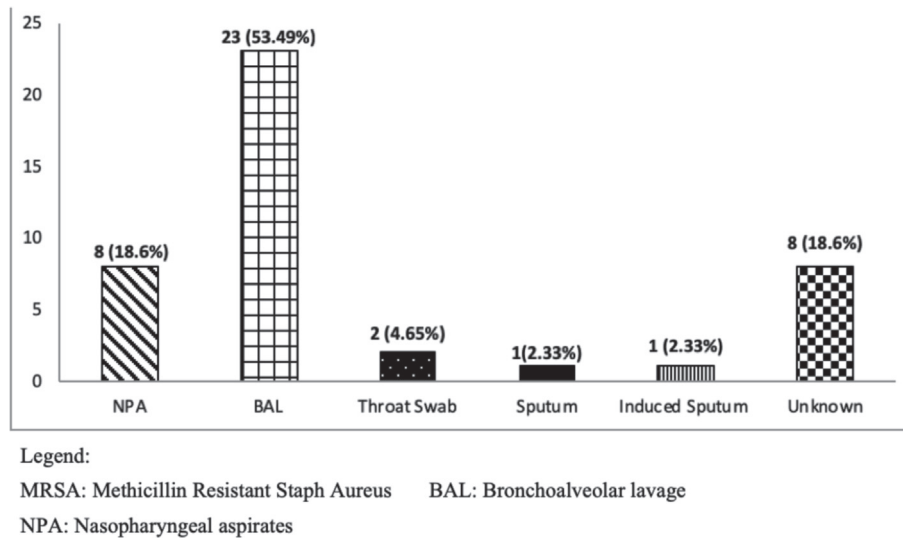


Fig. 1. Source of respiratory culture of MRSA (total of 43).

had respiratory samples with positive culture for MRSA on regular follow-up or during respiratory exacerbation from January 2002 to June 2016.

1.3. Definitions

Patients with CF are defined as those who have typical pulmonary manifestations and/or typical gastrointestinal manifestations (GI) and/or a history of CF in the immediate family in addition to a sweat chloride concentration of 60 mmol/L or if they have the pathologic CFTR mutations on both chromosomes [18].

1.4. Inclusion criteria

We included all patients with confirmed CF of all age groups who had MRSA infection during their follow-up period in CF clinic from 1 January 2002 to 31 June 2016.

1.5. Types of samples

Nasopharyngeal aspirates (NPA) were collected from patients who were unable to expectorate below the age of 4 years. Induced sputum samples were obtained from patients above 4 years of age. Bronchoalveolar lavage (BAL) samples were collected from patients with severe CF pulmonary disease. MRSA cultures were repeated every 3–6 months until complete clearance of MRSA infection or death.

2. Method of sample collection

Bronchoalveolar lavage and NPA samples were collected for bacterial cultures and processed according to standard methodology [19]. Samples were collected following standard hospital precautions.

2.1. Statistical method

For continuous variables, mean, standard deviation, and median were calculated using the Student t-test. Chi-square was calculated for all nominal variables. Results were presented at a level of significance of $P < .05$. All values were expressed as mean, standard deviation (SD).

2.2. Method used to assess lung capacity

Pulmonary function test (PFT) was performed according to standard procedure. FEV1 less than 35% predicted for age is considered very severe, 35–49% is severe, 50–59% is moderately severe, 60–69% is moderate, and more than 70% is considered mild [20].

2.3. Eradication protocol

Nasal Bactroban is routinely prescribed to all patients with a positive MRSA culture 4 times for 7 days [15,16]. Recently, oral vancomycin and rifampicin were used for 2 weeks [12–16].

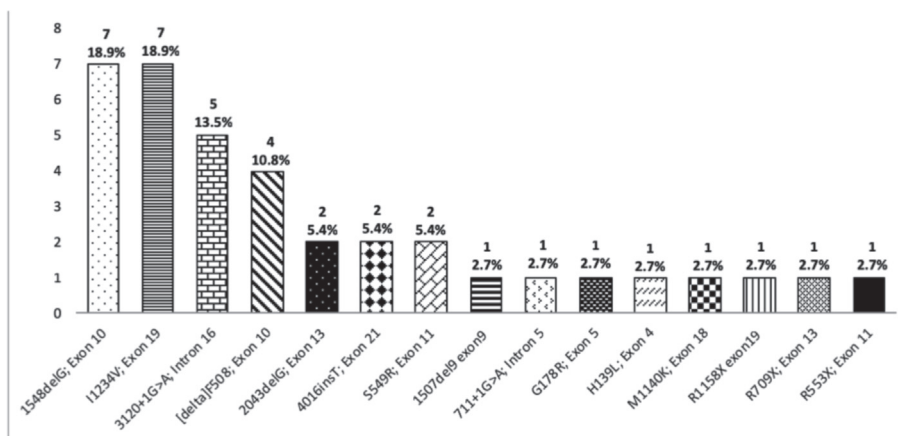
3. Results

We examined (NPA/sputum and BAL) samples from 385 patients with CF at respiratory exacerbation or during the follow-up period. Out of 385 patients, 43 (11%) tested MRSA-positive from respiratory samples (Fig. 1), at a mean age of 10.4 ± 7.2 years. The source of the cultures was BAL in 23/43 patients (53%) and 8 samples (19%) from NPA. Twenty-two patients out of 43 (51%) were males as compared to 21 (49%) females.

The number of MRSA-positive infections was studied during the periods 2002–2009 and 2010–2016. Eleven out of 43 (26%) patients were reported to be MRSA positive during 2002–2009 when compared with 32 (74%) patients during 2010–2016.

Of the total 43 patients with MRSA infection, 22 (51%) received medical treatment, whereas 21 (49%) did not receive medical treatment.

These 22 (51%) patients with MRSA infection were treated with the following different regimens: 13 (59%) were treated with nasal Bactroban, 5 (23%) were treated with a combination of nasal Bactroban and oral vancomycin + rifampicin, 1 (0.5%) received a combination of nasal Bactroban and linezolid, and 3 (14%) were treated with oral vancomycin and rifampicin. Microbiological eradication was achieved in 8 of the 22 (36%) patients within 3–6 months of applying the eradication protocol. One out of these 8 (13%) patients received the vancomycin–rifampicin combination, 3 (38%) received a combination of nasal Bactroban and oral vancomycin + rifampicin, 1 (13%) received a combination of nasal Bactroban and linezolid, and 3 (38%) received nasal Bactroban



Legend:

CFTR: Cystic fibrosis transmembrane conductance regulator

Fig. 2. CFTR mutations in MRSA population (total of 37).

alone. In 6 of the 22 patients (27%), MRSA infection recurred within the 6-month follow-up period: 1 (17%) who received vancomycin and rifampicin, 2 (33%) who received the combination of nasal Bactroban and vancomycin + rifampicin, one (17%) who received linezolid and Bactroban, and 2 (33%) who received nasal Bactroban only. Five out of these patients (83%) remained colonized with the MRSA up to 2–4 years. Two out of the 22 (9%) died (1 from the group treated with vancomycin, rifampicin, and Bactroban and 1 from the group treated with Bactroban).

Twenty-one (49%) out of 43 patients did not receive medication, and five of the nontreated (24%) achieved spontaneous MRSA eradication. MRSA recurred in 3 out of 21 (14%). Ten (48%) of those 21 died.

3.1. Pulmonary function test results

Twenty (47%) out of 43 patients underwent PFT analysis for the detection and determination of disease severity. Twelve (60%) out of the 20 had normal PFT, 3 (15%) mild, 2 (10%) moderate, 2 (10%) moderately severe, and 1 (5%) severe.

3.2. CFTR analysis

Analysis of the most common CFTR mutation in 38 out of 43 (88%) patients who had a culture positive for MRSA showed that the most common CFTR mutations are *c.3700A > G* (*p.I1234V*), Exon 22 (Legacy name: *I1234V*; Exon 19, *c.3700A > G*) that accounted for 7 (18%) patients, followed by *c.1418delG* (*p.G473EfsX54*), Exon 11 (Legacy name: *1548delG*; Exon 10), and *c.2988 + 1G > A* (*IVS18 + 1G > A*), Intron 18 (Legacy name: *3120 + 1G > A*; Intron 16), with 5 (13%) patients for each mutation type (Fig. 2).

4. Discussion

Our study showed that there is an increasing number of MRSA infections from 11 (26%) to 32 (79%) among patients with CF between the 2 periods (2002–2009 and 2010–2016). This is consistent with Cafiso V et al. who reported an increase in the prevalence of MRSA-positive cases from 0.1% in 1995 to 18.9% in 2010 [8].

MRSA eradication is of utmost importance. Lo, D. et al. found that patients who clear MRSA infection within one year have the same

risk of death as those who never had a positive culture for MRSA, which leads us to the importance of having clear guidelines on how to eradicate MRSA in patients with CF [1]. In our study, we found that patients who were able to eradicate MRSA had less mortality rates than those who did not eradicate it.

Different studies used different eradication protocols [12–16], e.g., Vanderhelst, E. et al. [12] used 6-month period of rifampicin and fusidic acid for 6 months with topical decolonization including mupirocin-containing nasal ointment 3 times daily for 5 days and chlorhexidine hair and body wash once a day for 5 days. This method achieved 90% eradication of the disease after finishing the 6-month protocol with 9% recurrence of MRSA infection [12]. They also reported improvement in median forced expiratory volume in 1 s (FEV1) in 6 patients [13], whereas Burdge et al. [15] who used a 2-month course of rifampicin and clindamycin and achieved 100% eradication in an 8-month follow-up. On the other hand, Kiefer et al. [16] used oral rifampicin and fusidic acid for 7 days in addition to the inhalation of vancomycin and achieved 86% eradication.

Our protocol eradicated only 36% of those with MRSA who received treatment, which could be due to the short period of antibiotic use, and we may need to prolong the period up to 6 months to achieve 86–100%, like other studies (Table 1).

These results will help us in concluding that the prevalence of MRSA in the population with CF is increasing. Thus, new recommendations for eradication protocol and prevention should be observed and followed to reduce the morbidity and mortality associated with MRSA in CF.

5. Conclusion

MRSA is common in our CF population. Eradication protocol should be instituted early before it becomes a chronic colonization. Children with persistent MRSA colonization had high morbidity and mortality rate.

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(4)- BIO Pharma, Middle East & Africa, P.O. Box 214989, Dubai, United Arab Emirates. Tel: +971 (4) 3692828, Fax: +971 (4) 3697391, www.biopharma-mea.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpam.2019.10.005>.

References

- [1] Lo DKH, Hurley MN, Muhlebach MS, Smyth AR. Interventions for the eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) in people with cystic fibrosis. *Cochrane Database Syst Rev* 2015;7. <https://doi.org/10.1002/14651858.CD009650.pub4>. Matched ISSN : 1469-493X.
- [2] Zielenski J, Rozmahel R, Bozon D, Kerem B sheva, Grzelczak Z, Riordan JR, et al. Genomic DNA sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *Genomics* 1991;10(1):214–28. [https://doi.org/10.1016/0888-7543\(91\)90503-7](https://doi.org/10.1016/0888-7543(91)90503-7). Matched ISSN : 0888-7543.
- [3] Anon. Cystic fibrosis foundation patient registry 2013 annual data report to the center directors. *Cyst Fibros Found*; 2014.
- [4] Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME. Cystic fibrosis-related diabetes in children—gaps in the evidence? *Nat Rev Endocrinol* 2010 May 25;6:371. Available from: [https://doi.org/\(View via CrossRef\)](https://doi.org/(View via CrossRef)). Matched ISSN : 1759-5029.
- [5] Banjar H. Geographic distribution of cystic fibrosis transmembrane regulator gene mutations in Saudi arabia. *East Mediterr Health J* 1999;5(6).
- [6] Banjar H. Morbidity and mortality data of cystic fibrosis patients. *Saudi Med J* 2003;7. Matched ISSN : 0379-5284.
- [7] Yurdakul P, Ocal HY, Gulmez D, Yalcin E, Dogru D, Cinel G, et al. Predominance of hospital-associated MRSA among cystic fibrosis patients in a Turkish reference cystic fibrosis centre. *J Chemother* 2012;4:195–200. <https://doi.org/10.1179/1973947812Y.0000000024>. Matched ISSN : 1120-009X.
- [8] Cafiso V, Bertuccio T, Spina D, Campanile F, Bongiorno D, Santagati M, et al. Methicillin resistance and vancomycin heteroresistance in *Staphylococcus aureus* in cystic fibrosis patients. *Eur J Clin Microbiol Infect Dis* 2010;29(10):1277–85. <https://doi.org/10.1007/s10096-010-1000-5>. Matched ISSN : 0934-9723.
- [9] Ren CL, Morgan WJ, Konstan MW, Schechter MS, Wagener JS, Fisher KA, et al. Presence of methicillin resistant *Staphylococcus aureus* in respiratory cultures from cystic fibrosis patients is associated with lower lung function. *Pediatr Pulmonol* 2007. Matched ISSN : 8755-6863.
- [10] Girón RM, Buendía B, Pinedo C, Casanova Á, Hoyos N, Ancochea J. Staphylococcus aureus resistente a meticilina en pacientes adultos con fibrosis quística. *Methicillin-resistant Staphylococcus aureus in patients with cystic fibrosis. J Enfermedades Infecciosas Y Microbiología Clínica* 2009;27(2). <https://doi.org/10.1016/j.eimc.2008.02.008>.
- [11] Perez LRR, Antunes ALS, Bonfanti JW, Pinto JB, Roesch EW, Rodrigues D, et al. Detection of methicillin-resistant *Staphylococcus aureus* in clinical specimens from cystic fibrosis patients by use of chromogenic selective agar. *J Clin Microbiol* 2012;50(7):2506–8. <https://doi.org/10.1128/JCM.00549-12>. Matched ISSN : 0095-1137.
- [12] Vanderhelst E, De Wachter E, Willekens J, Piérard D, Vincken W, Malfroot A. Eradication of chronic methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis patients. An observational prospective cohort study of 11 patients. *J Cyst Fibros* 2013;12(6). <https://doi.org/10.1016/j.jcf.2013.04.009>. Matched ISSN : 1569-1993.
- [13] Vanderhelst E, De Wachter E, Willekens J, Schuermans D, Vincken W, Malfroot A, et al. Increase in ventilated air spaces after eradication of chronic methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis patients. *Acta Clin Belg* 2014;70(1):30–3. <https://doi.org/10.1179/2295333714Y.0000000079>. Matched ISSN : 1784-3286.
- [14] Fung L. Continuous infusion vancomycin for treatment of methicillin-resistant staphylococcus aureus in cystic fibrosis patients. *Ann Pharmacother* 2012;46(10). <https://doi.org/10.1345/aph.1R272>. Matched ISSN : 1060-0280.
- [15] Burdge DR, Nakielna EM, Noble MA. Eradication of methicillin-resistant *Staphylococcus aureus* from the lower respiratory tract of patients with cystic fibrosis. *Can J Infect Dis* 1995;6(2):97–101. <https://doi.org/10.1155/1995/176396>. Matched ISSN : 1180-2332.
- [16] Kiefer A, Bogdan C, Melichar VO. Successful eradication of newly acquired MRSA in six of seven patients with cystic fibrosis applying a short-term local and systemic antibiotic scheme. *BMC Pulm Med* 2018;18(1):1–5. Matched ISSN : 1471-2466.
- [17] Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, et al. Antibiotic management of lung infections in cystic fibrosis: I. The microbiome, methicillin-resistant *Staphylococcus aureus*, gram-negative bacteria, and multiple infections. *Ann Am Thorac Soc* 2014;11(7). <https://doi.org/10.1513/AnnalsATS.201402-050AS>. Matched ISSN : 2329-6933.
- [18] Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. *Gut* 2007;56(8). <https://doi.org/10.1136/gut.2004.062786>. Matched ISSN : 0017-5749.
- [19] Banjar H. Microbiological Data of cystic fibrosis patients in a tertiary care center in Saudi Arabia.pdf. *Kuwait Med J* 2004;6(3):179–81. Matched ISSN : 1607-8047.
- [20] Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948–68. <https://doi.org/10.1183/09031936.05.00035205> [aphylococcus aureus from the lower respiratory tract of patients with cystic fibrosis].