ORIGINAL ARTICLE

Effect of sodium bicarbonate 8.4% on respiratory tract pathogens

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ABSTRACT

Background and aim: Microbes grow within a particular range of external pH, change of this pH may affect the respiratory pathogens. Our aim was to evaluate the effect of sodium bicarbonate (SB) 8.4% on the retrieved lower respiratory tract pathogens.

Patients and methods: One hundred and twenty two patients with suspected lower respiratory tract infections were assigned randomly into 2 groups; 66 patients in group 1, who were subjected to broncho alveolar lavage (BAL) with 50 mL of 0.9% saline, then the retrieved BAL was divided into two equal volumes; one diluted with equal volume of saline and the other diluted with equal volume of SB (*in vitro*) and 56 patients in group 2, BAL with 10 mL of saline (a relatively small volume to avoid dilution and for detection of the organisms before the effect of SB) followed by BAL with 50 mL SB (*in vivo*). All samples were subjected to pH measurement and microbial detection.

Results: There was a statistically significant decrease in median number of colony forming unit for bacteria and fungi in SB samples when compared to saline samples in group1 (*in vitro*) and in group 2 (*in vivo*). As regard to Mycobacterium TB, the number of positive cases for acid fast bacilli and culture for TB was less in SB samples when compared to saline samples in both groups. No significant complications related to the procedure were reported.

Conclusions: SB 8.4% is a safe material and inhibitory for bacterial, fungal, and mycobacterial growth in the specific cultures and affects acid fast bacilli staining with Ziehl Neelsen.

Key Words: *BAL; Respiratory pathogen; Sodium bicarbonate*

INTRODUCTION

Pulmonary infections are caused by bacteria, viruses, fungi, and parasites [1]. All microbes grow within a particular range of external pH which affects many biological actions as enzyme activity, reaction rates, protein stability and structure of nucleic acids [2].

The airway surface liquid (ASL) contains a complex mixture of antimicrobial factors that kill inhaled or aspirated organisms and act as a first line of defense. The composition of ASL is critical for antimicrobial effectiveness [1]. Changes in the local media occur with inflammation or infection as local acidosis that is attributed to the local increase of lactic-acid production by the anaerobic, glycolytic activity of infiltrating neutrophils and to the presence of short chain fatty acid by-products of bacterial metabolism [3]. The abnormally acidic pH partially inhibits bacterial killing by ASL. In addition, Gram-negative bacteria have increased resistance to antimicrobial peptides when grown at low pH [4].

The pH of the macrophage compartment, in which *Mycobacterium tuberculosis* bacilli resides, ranges from pH 6.2 to 4.5, depending on the activation state of the macrophage. *M. tuberculosis* bacilli can resist killing by low pH in macrophages [5]. In empyema, bacterial metabolism and neutrophil phagocytic activity induced by bacterial cell wall-derived fragments and proteases lead to increased lactic acid production and a fall in pleural fluid pH and glucose [6]. Sodium bicarbonate (SB) is frequently used in cardiopulmonary resuscitation after establishment of ventilatory and circulatory support and in hyperkalemia [7-10]. However, administration of SB may lead to metabolic alkalosis, pulmonary edema, congestive heart failure, hyperosmolar syndrome, hypervolemia, hypernatremia, and hypertension [11,12].

THEORY

In respiratory tract infections caused by bacteria, viruses, fungi and mycobacteria, there will be an expected local acidic medium in the lung secretions. Changing the local pH of lower respiratory tract secretions to alkaline side by adding SB 8.4% can affect growth and/or may be lethal for the respiratory tract pathogens. The aim of this study was to evaluate the effect of SB 8.4% on the retrieved lower respiratory tract bacteria, mycobacteria and fungi.

PATIENTS AND METHODS

Patients

This is a prospective randomized case control study carried out at Chest Medicine and Medical Microbiology and Immunology departments; Mansoura University, Egypt; in the period from March, 2014 to July, 2016. It included 122 patients with clinical and radiological signs suggestive of lower respiratory tract infections (LRTI) as consolidation, lung abscess or infiltration with or without cavitation either community or hospital acquired. Patients with no radiological signs of LRTI and those unfit for FOB according to Waxman [13] were excluded from the study.

After approval of the local ethical committee of Faculty of Medicine, Mansoura University and registration of the study on PACTR with unique identification number (PACTR201508001233590), all patients signed their written consents after detailed explanation of the study protocol.

All patients were subjected to

a) Thorough clinical history taking and physical examination.

b) Chest X-ray and computed tomography.

c) Complete blood count, liver enzymes, serum creatinine and bleeding profile.

d) Fiberoptic bronchoscopy (FOB) and collection of bronchoalveolar lavage (BAL) samples:

Before bronchoscopy, the orophayngeal cavity was cleaned according to oral hygiene instructions. The FOB (Pentax FB 19 TV; Tokyo, Japan) was used after local instillation of 2% lidocaine and IV 5-10 mg midazolam 5 min before the procedure. Through the oral route, FOB was wedged into the targeted segment or lobe with suspected infection as localized with CT chest.

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The enrolled patients were randomly assigned into two groups according to the mode of application of SB to the expected respiratory pathogens; Group (1) 66 patients in group 1, who were subjected to BAL with 50 mL saline, then the retrieved BAL samples were divided into two equal volumes; one sample diluted with equal volume of saline (group 1a) and the other sample diluted with equal volume of SB (group 1b *in vitro*) and 56 patients in group 2, BAL was done with 10 mL of saline (group 2a for detection of the organism(s) before application of SB and small volume to avoid dilution) followed by BAL with 50 mL SB (group 2b).

The retrieved BAL was collected in sterile containers with tight seal and transported immediately in ice tank to Microbiology and Immunology laboratory, Faculty of Medicine, Mansoura University.

Methods

All BAL samples were subjected to pH measurement (Jenway 3305 pH meter; UK), Gram staining, aerobic bacterial culture and antibiotic susceptibility testing, Ziehl–Neelsen (ZN) staining for acid fast bacilli (AFB) and *M. tuberculosis* culture on Lowenstein Jensen medium, fungal wet mount stain and fungal culture on Sabouraud dextrose agar (SDA) slants.

Gram staining

After the BAL container was vortexed, 5 µL loopful sample was spread on 2 cm^2 diameter area on microscopy slides. The smears were allowed to dry then fixed and stained with Gram stain.

Aerobic bacterial culture

BAL specimens were neither diluted nor concentrated prior to culture. Semi-quantitative loop method was used for culture using a 0.01 mL calibrated loop to streak sample on Mac Conkey's agar, chocolate agar (plate kept in candle jar) and blood agar plates and incubated aerobically at 37°C. Culture plates were examined 24 and 48 hours later. Colony counts were determined from the blood agar plate with one visible colony representing 100 cfu/mL of the original specimen (1 col. x multiplication factor of 100 [0.01 cal. loop] = 100 cfu/mL). Gram positive and gram-negative bacteria were identified by standard procedures Antimicrobial susceptibility was tested for the isolated bacteria according to CLSI recommendations using disc diffusion method on Muller-Hinton agar plates [14].

M. tuberculosis **study**

ZN staining for AFB: Five to ten mL of BAL samples were centrifuged at 4000 RPM for 20 min and the deposit was stained with ZN staining for AFB while the remaining amount of the deposit was stained for fungi. Grading of positive BAL for AFB was performed according to Lohmann et al. [15].

Culture on Lowenstein Jensen (LJ) slants: After decontamination and concentration, LJ slants were inoculated for mycobacterial culture. LJ tubes were incubated at 37°C in 5% CO_2 for one week, at 37°C in air for another 7 weeks and thereafter were checked once a week for mycobacterial growth. Growth of mycobacteria was confirmed by typical colony morphology and microscopy for AFB.

Fungus study

Staining with wet mount stain: The deposit after centrifugation used for Dimethyl Sulfoxide-Potassium Hydroxide (DMSO-KOH) wet mount by adding KOH 10% to the deposit with cover slips and examine with X10 and X40 lenses.

Fungal culture

For fungus culture; Sabouraud dextrose agar (SDA) plates were used for fungus culture. Plates were incubated aerobically at 25°C and 37°C for at least 48 hours and was identified according to the standard method.

Safety assessment of the procedure

Patients in group 2 were followed up for 24 hours for the following: a) Chest symptoms as new or exacerbation of the present symptoms as fever, cough, heamoptysis and chest pain. b) Chest X ray was done 2 hour after the procedure. c) ECG was monitored for one hour after the procedure. d) Systemic side effects as nausea, vomiting, muscle twitches and camps for one hour. e) Arterial blood gases immediately after the procedure.

Statistical analysis

The statistical analysis of data was done using SPSS program version 21.0. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Categorical data were presented as numbers (percentage). Chi-square (or Fisher's Exact Test if needed) were used to compare the results between the two groups. For data with normal distribution; descriptive statistics were used to calculate mean ± standard deviation (SD); independent samples t test was used to compare the results between 2 groups. For data without normal distribution; descriptive statistics were used to calculate median; non-parametric two-related-samples test (Wilcoxon type) was used to compare the results in the same group. Mc Nemar Test was used to compare paired proportions. Statistical significance was defined as p value less than 0.05.

RESULTS

Sixty six pateints in group 1 and 56 patients in group 2 were enrolled in the study. Table 1 illustrates demographic, clinical and radiological data for both groups. Apart from fever, patients in both groups were well matched with no statistically significant difference.

Consolidation was the most common radiologic abnormality in both groups (62.1% and 41.1 % in group 1 and 2 respectively), followed by cavitary lesions (27.3% in group 1 and 35.7% in group 2) Table 1.

The mean of pH of saline samples was 6.39 ± 0.32 and for bicarbonate samples was 8.22 ± 0.33, with a significant difference between both groups P<0.001

Klebsiella pneumoniae was the most common organism detected in group 1 (21.2%) and *Pseudomonas aeuroginosa* was the most common in group 2 (17.9%) Table 2. *Candida albicans* was the most common fungus detected in both groups (37.9%, 42.9% in groups 1 and 2 respectively) Table 2. Mixed bacteria and fungi were reported in 42.4 % in group 1 and 42.86 % in group 2.

There was a statistically significant decrease in median colony forming unit (CFU)/ mL in SB (b) samples when compared to saline (a) samples in both groups for bacteria and fungi (Figures 1, 2 and Tables 3, 4).

In group 1, the number of positive cases for AFB by ZN staining in SB samples (b1) was less than that of saline samples (a1) (3 *versus* 7), but this difference was statistically insignificant (p=0.125) Table 5 and Figure 3. But, there was a statistically significant difference between saline (a1) and SB (b1) in M.TB culture (7 versus 1, p=0.031) Table 5. Also in group 2, the number of positive cases for AFB by ZN staining was less in SB samples (b2) than in saline samples (a2) (3 *versus* 6); with no statistically significant difference between the two samples (p=0.250 (Table 6). There was a reduction in

TABLE 1
Demographic clinical and radiological data of the studied groups

		Group 1 (n =66)	Group 2 (n =56)	P value
Age (mean ± SD)		48.62 ±15.16	45.41± 17.17	0.364
Gender (n (%))	Male	43 (65.2%)	40 (71.4%)	0.459
	Female	23 (34.8%)	16 (28.6%)	
Fever (n (%))		49 (74.2%)	32 (57.1%)	0.046
Cough (n (%))		53 (80.3%)	44 (78.6%)	0.813
Expectoration (n (%)		53 (80.3%)	41 (73.2%)	0.353
Hemoptysis (n (%)		24 (36.4%)	20 (35.7%)	0.941
Dyspnea (n (%)		42 (63.6%)	35 (62.5%)	0.897
Chest pain n (%)		19 (28.8%)	16 (28.6%)	o.999
Consolidation (n (%)		41 (62.1)	23 (41.1)	
Cavitary lesions (n (%)		18 (27.3)	20 (35.7)	
Bronchiectasis (n (%)		5 (7.6)	2 (3.6)	
Lobar collapse (n (%)		2 (3)	2 (3.6)	0.564*

*: Fischer Exact Test

The mean of pH of saline samples was 6.39 ± 0.32 and for bicarbonate samples was 8.22 ± 0.33, with a significant difference between both groups P<0.001.

TABLE 2
Organisms detected in the retrieved BAL samples of the studied groups

Type	Group1 (n = 66) n (%)	Group 2 (n = 56) n (%)
Bacteria		
No growth	14 (21.2)	19 (33.9)
K.pneumoniae	14 (21.2)	5 (8.9)
P.aeuroginosa	8 (12.1)	10 (17.9)
E. coli	6 (9.1)	4 (7.1)
Alpha-hemolytic Streptococci	5 (7.6)	0
Staph. aureus (MSSA)	2 (3)	3 (5.4)
Proteus mirabilis	4 (6.1)	5 (8.9)
Serratia marcescens	2 (3.0)	1 (1.8)
Strept. Pneumonia	2 (3.0)	5 (8.9)
Enterococci	1 (1.5)	0
H.influenzae	0 (0)	4 (7.1)
Mixed bacteria:	8 (12.1)	0
Fungi		
No growth	36 (54.5)	23 (41.1)
Candida albicans	25 (37.9)	24 (42.9)
Aspergillus	5 (7.6)	5 (16.1)

MSSA: methicillin-sensitive Staph aureus.

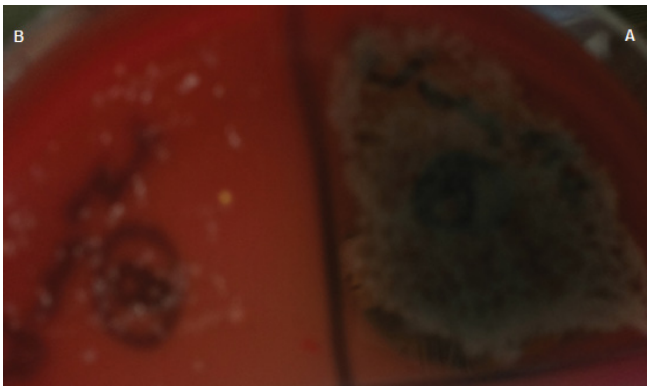

Figure 1) *Bacterial culture; A: saline sample, B: Sodium bicarbonate sample. There was confluent bacterial growth in saline sample with minimal growth in sodium bicarbonate sample*

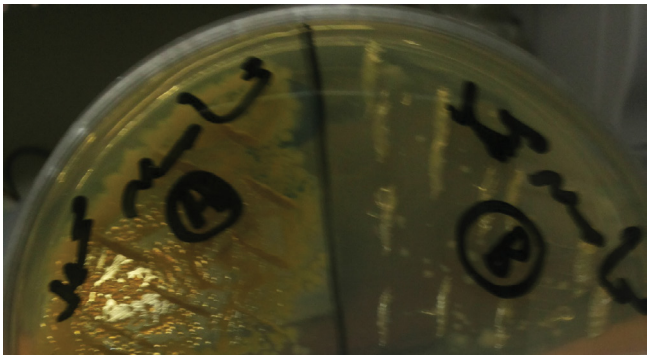

Figure 2) *Fungal culture for Candia; A: saline sample, B: Sodium bicarbonate sample. There was confluent fungal growth in saline sample with no growth in sodium bicarbonate sample*

median grading for AFB by ZN staining with no statistically significant difference between saline and SB samples in both groups (p=0.066) Table 7.

Regarding safety of the procedure, immediately after instillation of SB through FOB for BAL, all patients developed mild cough for one to 5 minutes and no other side effects.

TABLE 3
CFU for bacteria and fungi in the retrieved BAL samples of group (1)

Items	Group 1 (n=66) Median	Min-Max	Test of sig. p-value
Bacteria (n=46)			
Saline (a1)CFU/ml	$1X10^5$	$3X10^2$-$1X10^8$	Z =6.03
SB (b1) CFU/ml	$1X10^2$	0-$1X10^7$	P <0.001
Fungi (n=27)			
Saline (a1) CFU/ml	$1X10^4$	0-$1X10^7$	Z = 3.99
SB (b1) CFU/ml	0	0-$1X10^7$	P <0.001

CFU; colony forming unit

TABLE 4
CFU for bacteria and fungi in the retrieved BAL samples of group (2)

Items	Group (2) n=56 Median	Min-Max	Test of sig. p-value
Bacteria (AS TABLE 3)			
Saline (a2) CFU/ml	$1X10^4$	$1X10^2$-$1X10^7$	Z=5.256
SB (b2) CFU/ml	$1X10^3$	0-$1X 10^7$	P<0.001
Fungi (AS TABLE 3)			
Saline (a2) CFU/ml	$1X10^5$	10- 10^7	Z=4.867
SB (b2) CFU/ml	50	0-$1X 10^5$	P<0.001

TABLE 5
Ziehl–Neelsen staining and TB culture results for patients in group (1)

	Saline (a1)		**Group(1) n=66** **SB** (b1)		**Test of sig.** **p-value**
	N	%	n	%	
Ziehl–Neelsen staining					
Positive	7	10.6	3	4.5	McNemar Test P=0.125
Negative	59	89.4	63	95.5	
Culture for TB					
Positive	7	10.6	1	1.5	McNemar Test P=0.031*
Negative	59	89.4	65	98.5	

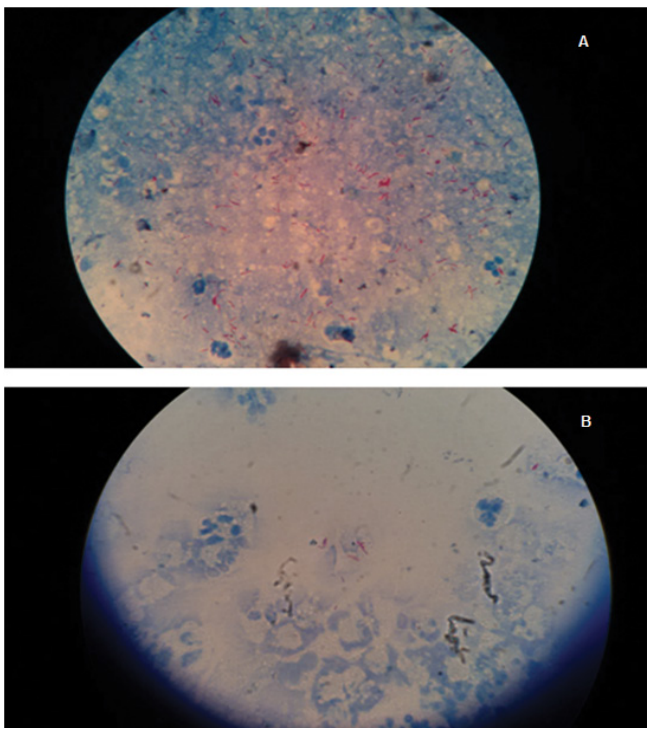

Figure 3) *ZN stain acid fast bacilli; A: saline sample, B: Sodium bicarbonate sample. There is a significant decrease in number of AFB in sodium bicarbonate sample compared to saline sample*

TABLE 6
Ziehl–Neelsen staining and TB culture results for patients in group (2)

	Group(2) n=56				Test of sig.
	Saline sample (a2)		SB sample (b2)		p-value
	N	%	N	%	
Ziehl–Neelsen staining					
Positive	6	10.7	3	5.4	P = 0.250
Negative	50	89.3	53	94.6	
Culture for TB					
Positive	7	12.5	4	7.1	P = 0.250
Negative	49	87.5	52	92.9	

TABLE 7
Median grading of positive BAL for AFB in both groups

	Saline AFB (a samples)	SB AFB (b samples)	P value
Median	4	0	Z= 1.841
(Min-Max)	(1-5)	(0-4)	P=0.066

DISCUSSION

Inflammation leads to local acidosis, which is attributed to the local increase of lactic-acid production by the anaerobic, glycolytic activity of infiltrating neutrophils and to the presence of short chain, fatty acid by-products of bacterial metabolism [3]. The interstitial fluid of tumors and abscesses also has shown pH values of less than 6.0, averaging 0.2–0.6 units lower the mean extracellular pH of normal tissues [16]. Adaptation of pH is essential to enable organisms to invade the blood stream and tissues that cause infection dissemination [17]. The acidic microenvironments may play a role in inhibiting immune function in certain respiratory conditions such as cystic fibrosis [16,18,19].

Sodium bicarbonate (SB) 8.4% is an alkaline solution of pH of approximately 8.5. It is used in clinical practice as an alkalinizing agent in the treatment of metabolic acidosis which may occur in many conditions including diabetes, starvation, severe dehydration, renal insufficiency and severe diarrhea [20,21].

The aim of this study was to assess the effect of SB 8.4% on the retrieved lower respiratory tract infectious agents as aerobic bacteria, fungi and *M. tuberculosis bacilli.*

In group (1), we performed BAL with 50 mL saline, then the retrieved BAL was divided into two equal volumes; one diluted with equal volume of saline (group 1a) and the other diluted with equal volume of SB (group 1b *in vitro*), and 56 patients in group 2, BAL was done with 10 mL of saline (group 2a for detection of the organism (s) before the effect of SB and a relatively small volume to avoid dilution) followed by BAL with 50 mL SB (group 2b). By measurement of pH of the investigated samples, there was a significant increase of pH in SB samples versus that with saline samples (8.22 ± 0.33 versus 6.39 ± 0.32). This indicates that BAL with SB 8.4% is effective in alkalinization of respiratory tract secretions. *K. pneumoniae* and *P. aeruginosa* were the most common isolated Gram negative organisms, it was isolated from 15.57% and 14.75% of patients respectively.

Streptococcus pneumoniae was the most common single Gram positive bacteria (5.74%) Table 4. These results were near to that reported by *Okesola and Ige* [22] who studied bacterial isolates from the sputum of patients with LRTI. The most prevalent single pathogen was *K. pneumoniae* (38%). Also, *Vishwanath and colleagues* [23] studied sputum and BAL samples from patients with LRTI. *K. pneumoniae* was the most common Gram-negative bacilli (37%) in their study followed by *P. aeruginosa* (28.6%). On the other hand, Khan and colleagues [24] studied 426 patients with suspected LRTIs, the samples used in their study were sputum, endotracheal aspirates and bronchial washings; and Gram-negative bacteria were isolated in 80.9% of the cases with *P. aeruginosa* was the most predominant pathogen (47.2%) followed by *H. influenzae* (27.6%), *K. pneumoniae* (14.6%) and *E. coli* (10.6%). Also, Shrestha et al. [25] studied 240 sputum specimens and found that *Pseudomonas* spp. was the most common isolates obtained followed by *K. pneumoniae*. Graffelman and colleagues [26] studied the aetiology of LRTI in general practice in Netherlands; sputum, blood and throat swabs were collected from patients with LRTI. They found that a bacterial cause was established in 43 (30%), and a viral cause in 57 (39%) of the 145 patients with a LRTI.

In the present study; *Candida albicans* was the most common isolated fungus in the two groups 37.9%, 42.9% respectively Table 2. These results are similar to that reported by Shin et al. [27] who studied 691 BAL samples and found that *Candida albicans* was the most common isolated fungus [106 cases (15.34 %)]. In our study, the median value of CFU/mL in SB samples were lower than saline samples with statistically significant difference for bacteria; as for group 1 the median CFU/mL was 1 X 10^5 for saline samples versus 1 X 10^2 for SB samples with p value < 0.001. For group 2; the median CFU/mL was lower in SB samples than in saline samples (1 X 10^3 versus 1 X 10^4) with statistically significant difference (p value <0.001). To the best of our knowledge, no previous studies addressed the effect of *alkalanization* by SB or other alkaline materials used in medicine on different respiratory organisms. However; AbouAlaiwa et al. [1] studied human β-defensin-3 (hBD-3), and the cathelicidin-related peptide LL-37 which are components of ASL and have broad antimicrobial spectrum, including activity against *Staphylococcus aureus* and *P. aeruginosa*. At neutral pH, they are cationic and kill bacteria by disrupting the phospholipid membrane and dissipating the electrochemical gradient. It was found that a reduced pH inhibits their individual and synergistic actions and could therefore impair airway defense.

In this study, the median value of CFU/mL for fungi was lower in SB samples than in saline samples in both groups; as for group 1 the median CFU/ mL value was 1 X 10^4 for saline samples and zero for SB samples with p value < 0.001 Table 3. For group 2; the median CFU/ mL was 10^5 for saline samples to 50 for SB samples with p value <0.001 (Table 4). In a study by Elin and Wolff [28] who evaluated the effect of pH and concentration of iron on the ability of *Candida albicans* to grow on human serum, they found that the growth of *Candida albicans* in human sera is inversely proportional to the pH and directly related to the percentage of iron saturation in the serum. Aboellil and Al-Tuwaijri [29] studied the effect of different pH on growth of Candida albicans and found that the acidic pH (5.6 - 6) leads to the maximum growth and its growth decreases with increasing pH [30]. Vacuolar acidification is clearly linked to the pathogenicity of the yeast [31]. Antifungal drugs target mainly yeast vacuole preventing it from becoming acidic. So, yeast-to-hyphal transition is blocked [32] with inhibition of V-ATPase by emptying yeast membranes of *ergosterol*. This causes alkalization of the vacuole [33].

Aspergillus fumigatus grows optimally at 37°C and a pH 3.7 to 7.6, it can be isolated wherever decaying vegetation and soil reach temperatures range between 12° and 65°C [34] and the pH ranges between 2.1– 8.8 [35]. For growth and survival, M. TB requires an optimal pH range of 6.2 to 7.3 [36]. We found that seven patients in group (1) were positive by ZN stain for AFB on saline samples and 3 only were positive by ZN stain for AFB on SB samples, with no statistically significant difference between saline and SB (p=0.125) Table 5. In addition, there was no statistically significant difference between saline and SB samples in the median grading of positive samples for AFB (grade 4 for saline and grade 0 for SB with p=0.066) Table 7. However, while 7 patients in group (1) demonstrated positive TB culture on saline; only one patient of them demonstrated positive M.TB culture on SB samples, with statistically significant difference between saline and SB samples (p=0.031) Table 5. Also, although there was reduction in number of patients with smear positive TB in group 2 (6 in a2 *vs.* 3 in samples b2); there was no statistically significant difference between the two samples (p=0.250) Table 6. Iivanainen and colleagues [37] studied the occurrence of mycobacteria in aerobic brook sediment. They found that the culturable counts of mycobacteria correlated negatively with water and sediment pH and with alkalinity of water, and that acidity increases the count of *mycobacteria*. Also Parashar et al. [38] studied the effect of neutralization of the gastric aspirate with SB in children with intrathoracic *tuberculosis*. Gastric aspirates were divided into two aliquots, and only one aliquot was neutralized with 1% SB. Both aliquots were processed for smear and culture examinations. There were no differences in smear positivity rates from samples with or without neutralization. The yield of MTB on a Bactec MGIT 960 culture system was significantly lower in the neutralized samples (16.3% [38/232]) than in the non-neutralized samples (21.5% [50/232]) (P=0.023).

CONCLUSION

-Sodium bicarbonate 8.4% is inhibitory for bacterial, fungal and mycobacterial growth in the specific cultures and disturbs staining of Mycobacteria by ZN stain.

-BAL with SB 8.4% is safe to the patients in group 2 with no considerable side effects.

RECOMMENDATIONS

- Application of SB can be used as an adjuvant to the antimicrobial, antifungal or to the antituberculous drugs with its application to the respiratory tract by either inhalation or instillation via bronchoscope or endotracheal tube.

- The methods for application of SB, dose and concentration to the lower respiratory tract are in need for more researches for titration and adjustment.

STUDY LIMITATIONS

-The study included a relatively small number of cases 122.

-Lack of diagnosis of anaerobic bacteria, atypical Mycobacteria, and viruses.

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