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Recurrent Pneumonia in Children Admitted to Assiut University Children Hospital. Magnitude of the Problem and Possible Risk Factors

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ABSTRACT

Background: Incidence data indicate that recurrent pneumonia occurs in 7.7–9% of all children with community acquired pneumonia. We aim by this study to assess the prevalence of recurrent pneumonia among the admissions with diagnosis of pneumonia in Assiut university children hospital for one year and to try to define the possible related risk factors. **Patients and methods:** This is a prospective hospital based study in Assiut University Children's Hospital. Children younger than 16 years admitted with a hospital diagnosis of pneumonia to Assiut University Children's Hospital for one year from 1 February 2017 to 31 January 2018 were included.

Results: Approximately 1 in 12 children with pneumonia in our locality have recurrent pneumonia with percentage of 12.61%. Cardiac diseases especially congenital heart diseases was the cause among 25.45% of the cases, immunodeficiency diseases represented 20.9% of the cases, while bronchial asthma was the cause of recurrent pneumonia among 16.36% of the cases. As regard to risk factors in studied group, prematurity was detected among 7.27% of the cases while more than 50% were formula fed and more than 60% exposed to pollution. Father smoking was detected among 36.36% of cases. Patients aged > 6 years showed significantly higher frequency in risk factors as obesity, indoor and outdoor pollution and use of steroids in comparison to other age groups. However, patients aged 0-3 years exhibited significantly higher % frequency of having heart disease, oro-motor in coordination /swallowing dysfunction, gastro esophageal reflux and under nutrition as risk factors for recurrent pneumonia in comparison to other age groups.

Conclusions: The most frequent underlying cause for recurrent pneumonia in Assiut University Children's Hospital which presents the largest referral pediatric hospital in Upper Egypt for one year according to our study was cardiac diseases; the second most frequent cause was immunodeficiency diseases, followed by bronchial asthma. Risk factors for recurrent pneumonia include socio-economic status of studied cases, prematurity, exposure to passive smoking and in or outdoor pollution, obesity, under nutrition, lack of breast feeding, gastro esophageal reflux and steroids usage.

Key words: Recurrent pneumonia, community acquired pneumonia congenital heart disease, gastro esophageal reflux disease, immunodeficiency diseases, bronchial asthma, socio-economic status, chronic lung diseases, pulmonary tuberculosis, aspiration syndrome, anatomical congenital respiratory anomalies, cystic fibrosis.

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Introduction

Pneumonia is the top infectious killer of children under 5 years worldwide, resulting in 935,000 deaths each year. According to the "Global Action Plan for Prevention and Control of Pneumonia", around 20% of the child deaths that occurred globally in 2007 were

caused by pneumonia, and more than 90% of these deaths were in developing countries [3]. In Egypt, it was estimated that 10% of children deaths below the age of 5 years is likely caused by pneumonia and other acute respiratory infections [4]. Egypt has around 2 million cases of children with pneumonia every year [5], and 42,000 Egyptian children under 5 die annually [6]. Ap-

proximately 6% of infants experience at least one episode of pneumonia during the first two years of life [7]. Recurrent pneumonia (RP) is defined as at least two episodes of pneumonia in one year or three episodes ever, with intercritical radiographic clearing of densities [8]. Incidence data indicate that RP occurs in 7.7–9% of all children with community acquired pneumonia (CAP) [1, 2]. As a result, RP represents a frequent presenting manifestation in the general pediatric practice and is a very common reason for referral to pediatric chest physicians [1].

The challenge for the physician approaching RP is to discriminate between children with self-limiting or minor problems, that do not require a diagnostic work-up, and those with an underlying disease, for whom further investigation is mandatory. Therefore, determining which child should be investigated relies on clinical judgment, that should take into account the patient's history, the clinical course of the episode, and any symptoms and/or signs indicating the presence of an underlying disease [9]. Most of the children hospitalized during the first episode of pneumonia had a known predisposing condition for pneumonia recurrence including neuromotor disorders with feeding problems, gastro-esophageal reflux, congenital heart disease, asthma, airway malacia and vascular malformations [10].

The aim of the study is to assess the prevalence of recurrent pneumonia among the admissions with diagnosis of pneumonia in Assiut university children hospital for one year and to try to define the possible related risk factors.

Patient and methods

This is a prospective hospital based study in Assiut University Children's Hospital. Children younger than 16 years admitted with a hospital diagnosis of pneumonia to Assiut University Children's Hospital for one year from 1 February 2017 to 31 January 2018 were included.

All admissions to Assiut University Children Hospital were recorded over one year. Cases of pneumonia were identified and examined for criteria of recurrent pneumonia either on prospective bases.

Studied cases were subjected to the following:

History

Including age, sex, residence, neonatal history, socio-economic status for health research in Egypt (2012), duration of symptoms and treatment given, history suggestive of immunodeficiency (e.g. persistent diarrhea, cutaneous infections as boils, abscesses etc.). History of recurrent upper respiratory tract infections (defined as more than six serious URI with fever, cough, sore throat and running nose per year and history of previous hospitalization, history of contact with tuberculosis patient,

immunization status, developmental milestones and history of risk factors as prematurity, co morbid conditions as (heart diseases, GERD, oromotor or swallowing dysfunction) parental smoking and environmental pollution.

Clinical Examination

Complete physical examination including vital signs, anthropometric measurement and calculating body mass index (BMI) which equal weight divided by square of the body height in units of kg/m² for children more than 2 years old, calculating weight for height, weight for age and height for age percentiles for children less than 2 years old for assessment of nutritional status. Also presence and degree (if present) of respiratory distress, clubbing and full chest and cardiac examination were assessed.

Investigations

All cases of recurrent pneumonia were subjected to the following investigations:

1. Pulse oximeter assessment.
2. Chest X- ray.
3. Complete blood count with differential count.
4. C- reactive protein assay.
5. Mantoux test (Tuberculin sensitivity test).
6. Echocardiography.

Moreover, some cases with recurrent pneumonia will be subjected

(According to every case individually based on history and clinical examination) to:

1. Computerized tomography of the chest in cases suspected of chronic lung diseases, anatomical congenital respiratory anomalies and suspected F.B inhalation.
2. Abdominal ultrasound and barium or gastro-graffin swallow with x-ray study in cases suspected gastro-esophageal reflux and recurrent aspiration.
3. Laryngoscopy or flexible fiber-optic bronchoscopy in cases of recurrence of pneumonia on the same side, suspected laryngo or bronchomalacia and suspected F.B inhalation
4. Immunoglobulin quantitative assay, number of T and B lymphocytes and flow cytometric quantitative determination of leukocyte oxidative burst for children suspected to have immunodeficiency.
5. Cystic fibrosis DNA analysis for cases clinically suspicious having Cystic fibrosis.
6. Enzyme linked immunosorbant assay (ELISA) for human immunodeficiency virus (HIV) infection for suspected cases.

Inclusion criteria

Infants and children below 16 years old diagnosed on clinical and radiological grounds as recurrent

Table 1. Socio-economic status according to EL Sherbini Modified Score (2012)

Name of head of family:		Address:																																																	
<p>Definition of the family: It includes nuclear cc joint family Married couple with unmanied children or without children. Head of the family will be either husband/wife. Dependent father/mother/brother/sister does not become member of the family unless he/she is earning and one kitchen with pooled income is managed by him/her.</p> <p>This scale includes 7 domains with a total score of 84.</p> <p>Sodoeconomic level: to be classified into very low, low, middle and high levels depending on the quartiles of the score calculated.</p> <p>NB In case of death or retirement of husband or wife, record the education and occupation before death or retirement</p>																																																			
<p>Education and cultural domain (for both husband & wife) (score — 30)</p> <table border="1"> <thead> <tr> <th>Highest level of education</th> <th>Husband</th> <th>Wife</th> </tr> </thead> <tbody> <tr> <td>Illiterate</td> <td>0</td> <td>0</td> </tr> <tr> <td>Read & write</td> <td>2</td> <td>2</td> </tr> <tr> <td>Primary</td> <td>4</td> <td>4</td> </tr> <tr> <td>Preparatory</td> <td>6</td> <td>6</td> </tr> <tr> <td>Secondary (general & technical of 3 or 5 years)</td> <td>8</td> <td>8</td> </tr> <tr> <td>Intermediate (2 years) institutes</td> <td>10</td> <td>10</td> </tr> <tr> <td>University graduate</td> <td>12</td> <td>12</td> </tr> <tr> <td>Postgraduate degree</td> <td>14</td> <td>14</td> </tr> </tbody> </table> <p>Access to health information (1 each for the following items): Printed materials, e.g. books, posters, booklets, etc.; Audiovisual message on television &/or radio</p>		Highest level of education	Husband	Wife	Illiterate	0	0	Read & write	2	2	Primary	4	4	Preparatory	6	6	Secondary (general & technical of 3 or 5 years)	8	8	Intermediate (2 years) institutes	10	10	University graduate	12	12	Postgraduate degree	14	14	<p>Occupation domain (for both husband & wife) (score — 10)</p> <table border="1"> <thead> <tr> <th>Occupation</th> <th>Husband</th> <th>Wife</th> </tr> </thead> <tbody> <tr> <td>Non-working/housewife</td> <td>0</td> <td>0</td> </tr> <tr> <td>Unskilled manual worker</td> <td>1</td> <td>1</td> </tr> <tr> <td>Skilled manual worker/farmer</td> <td>2</td> <td>2</td> </tr> <tr> <td>Trades/business</td> <td>3</td> <td>3</td> </tr> <tr> <td>Semi-professional/clerk</td> <td>4</td> <td>4</td> </tr> <tr> <td>Professional</td> <td>5</td> <td>5</td> </tr> </tbody> </table> <p>Family possessions domain (score — 12: 1 each for the presence of items given below) Refrigerator — Radio — Television — Washing machine — Telephone/ mobile phone — Car — Agricultural land — Non-agricultural land for housing — Shop or animal shed — Other house (beside the house in which the family is living) — Animals/poultry — Computer/ Internet</p> <p>Home sanitation domain (score — 12) Services (1 each for the presence of the following items): Pure water supply — Electricity — Natural gas — Sewerage system — Municipal collection of solid wastes — Flush latrine — Air conditioning Type of house: Owned, ≥ 4 rooms — 4; Owned, < 4 rooms — 3; Rented, ≥ 4 rooms — 2; Rented, < 4 rooms — 1; No place to reside — 0 Crowding index: (number of family members divided by number of rooms): ≤ 1 person per room — 1; > 1 person per room — 0</p>		Occupation	Husband	Wife	Non-working/housewife	0	0	Unskilled manual worker	1	1	Skilled manual worker/farmer	2	2	Trades/business	3	3	Semi-professional/clerk	4	4	Professional	5	5
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<p>Family domain (score —10) Residence: Urban slum — 0; Rural -1; Urban — 2 Number of family members (parents, children & all dependents): < 5 members — 2; ≥ 5 members — 1 Number of earning family members: 1 member — 1; 2 members — 2; ≥ 3 members — 3 Education of children (aged ≥ 5 years, whether free or private education): All children going or ever gone to school/university — 3; ≥ 50% going or ever gone to school/university — 2; <50% going or ever gone to school/university — 1; None go/gone to school/university/not applicable — 0</p>		<p>Health care domain (score — 5) Usual source of health care: Private health facilities — 5; Health insurance — 4; Free governmental health service — 3; More than one of the above sources — 2 Traditional healer/self care — 1</p>																																																	
<p>Economic domain (score — 5) Income from all sources: In debt — 0; 1 Just meet routine expenses — 1; Meet routine expenses and emergencies — 2; Able to save/invest money — 3 Family receives governmental support: Yes — 1; No — 0 Family pays tax: Yes — 1; No — 0</p>																																																			

pneumonia. Recurrence is evidenced by the presence of documented previous episodes of pneumonia, 2 or more per year or 3 or more episodes in life time based on radiological evidence of two chest x rays with diagnosis of pneumonia with completely resolved chest x ray from pneumonia in-between.

Exclusion criteria

Age more than 16 years old , lack of radiographic evidence of pneumonia , lack of radiographic evidence of definite recurrence (for recurrent pneumonia cases) and cases of non resolving or persistent pneumonia.

Patients with obvious neurological diseases that lead to recurrent pneumonia also were excluded.

Patient clinically diagnosed as recurrent pneumonia, and those with non recurrent pneumonia will be subjected to x-ray examination for radiographic evidence of pneumonia .Only patient with radiographic evidence of pneumonia will be continued to be investigated.

Results

This study was done in Assiut University Children Hospital for one year from 1 February 2017 to 31 Janu-

ary 2018 .All cases with pneumonia admitted to all units in the hospital have pneumonia were (872) case and (110) cases fulfilled the inclusion criteria of recurrent pneumonia with percentage of 12.61%.

Investigations were done:

- Mantoux test was done for tuberculin sensitivity using 1T purified protein derivative (PPD) which was administered intradermally and reading was taken after 48-72 hours for all cases which included as recurrent pneumonia in the study. It was found that five cases had positive tuberculin testing. Gastric lavage and sputum study for acid fast bacilli were positive in two cases.
- Echocardiography was done to all cases included in the study and have recurrent pneumonia and twenty eight cases were found to have congenital heart disease.
- Gastro — esophageal reflux disease (GERD) was diagnosed in four children by clinical suspicion and confirmed by barium swallow.
- Abdominal ultrasound was done for all cases with clinically palpable organomegaly, cases with gastro esophageal reflux disease and for all cases with suspected to have immunodeficiency.
- Flexible fiberoptic bronchoscopy was performed for three cases with radiological evidence of recurrent atelectasis in same side showing chronic inflammatory process and for two cases diagnosed as bronchiectasis and two cases diagnosed as vascular ring.
- C.T scanning for chest examination was done for nine cases with atelectasis and lobar pneumonia and for all cases with chronic lung disease (Bronchiectasis, Interstitial lung fibrosis (IPF).
- Cystic fibrosis DNA analysis also shows only one case with Cystic fibrosis from clinically suspicious included patients.

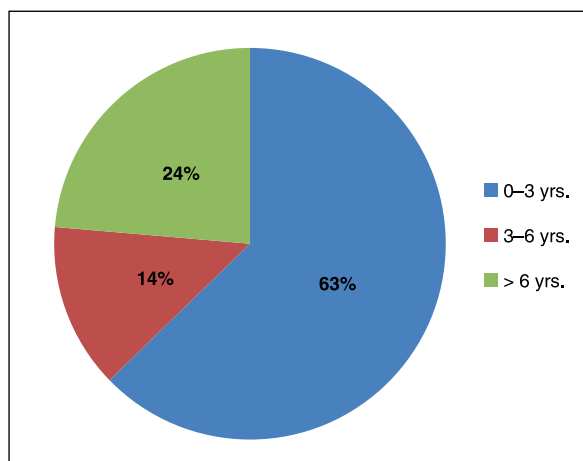


Figure 1. Distribution of age (years) among the studied patients.

- Enzyme linked immunosorbant assay (ELISA) for human immunodeficiency virus (HIV) infection to suspected five cases but all results were negative.
- Seven cases with recurrent pneumonia, the etiology of recurrence was unknown inspite of most of previous investigations were done to them.

Table 2 and figure 1 show demographic data of the studied cases. It was found that (65.5%) of cases were males. The age ranged from 0.2-16 years with mean age 3.91 ± 0.40 years. The majority of the included patients were belonged to age group 0-3 years (62.72%). About (77.27%) of studied cases was from urban areas.

Table 3 shows socio-economic status of studied cases according to El Sherbini modified classification Score, (2012). According to maternal domain about half of mothers read & write (54.54%). About (77.2%) of studied cases were from urban areas. Regarding occupation parents domain, there were (54.54%) of the parents were skilled manual worker. About family possessions domains there were (59.09%) had score 7. In economic domain the majority of cases (84.54%) had met routine expenses & emergencies. Also all cases had number of family members more than 5 members. Regarding crowding index there were about (94.5%) of cases had more than one person/room. According to El Sherbini modified score (48.18%) of the families belonged to middle class, while (43.64%) were classified as low class.

Table 4 shows history in the included patients. The mean value of disease duration was 11.84 ± 3.29 days. There was history of cough among (94.54 %) of the patients, while (56.36%) had history of fever and (50.0%) had recurrent upper respiratory tract infection. About (22.72%) cases had history of atopy/allergy and about (11.81%) of cases had history of immuno-deficiency from first months of age.

Table 2. Demographic data of studied cases with recurrent pneumonia.

Item	Descriptive "n=110"
1. Gender:	
• Male	72(65.45%)
• Female	38(34.54%)
2. Age "years"	
Mean \pm SE	3.91 ± 0.40
(min-max)	(0.2-16)
• 0-3 yrs.	69(62.72%)
• > 3-6 yrs.	15(13.63%)
• > 6 yrs.	26(23.63%)
3. Residence:	
• Rural	25(22.73%)
• Urban	85(77.27%)

Table 5 shows descriptive data of investigations were done to the studied group including pulse oxime-

Table 3. Socio-economic status of studied cases according to ElSherbini modified Score (2012) in Egypt.

Item	Descriptive "n=110"
1. According to maternal education domain:	60 (54.54%)
• Read & write	32 (29.29%)
• Preparatory	18 (16.36%)
• Secondary	85 (77.27%)
2. Family Domain:	25 (22.72%)
• Urban	
• Rural	30 (27.27%)
3. Occupation parents domain:	60 (54.54%)
• Unskilled manual worker	10 (9.09%)
• Skilled manual worker	0.0
• Semi-Professional	
• Professional	62 (59.09%)
4. Family possessions domains:	33 (30.0%)
• Score 7	15 (13.63%)
• Score 5-6	
• Score <4	
5. Economic domain:	
• In debt	0.0
• Just meet routine expenses	3 (2.70%)
• Meet routine expenses & emergencies	93 (84.54%)
• Able to save money	14 (12.72%)
6. Number of family members:	0.0
• < 5 members	110 (100%)
• ≥ 5members	
7. Crowding index" "number of family member/divided by number of rooms":	
• ≤ person/room=1	6 (5.45%)
• > 1person/room	104 (94.5%)
8. Home sanitation domain:	
• Score 4	61 (55.45%)
• Score 2	49 (4.54%)
9. Elsherbini modified score:	
• Very low	3 (2.73%)
• Low	48 (43.64%)
• Middle	53 (48.18%)
• High	6 (5.45%)

Table 5. Investigations done for the studied group.

Item	0-3yrs. "n = 69"	> 3-6yrs. "n = 15"	> 6yrs. "n = 26"
1-Pulse oximetry"%"	94.05 ± 0.99	92.60 ± 0.91	96.11 ± 2.26
CBC:			
2-WBCs "Cell/mm ³ "	11.64 ± 6.42	13.04 ± 3.47	13.79 ± 4.97
3-Eosinophil "Cell/mm ³ "	2.45 ± 0.39	4.83 ± 0.91	3.38 ± 0.67
4-Hb "g/dL"	10.05 ± 1.55	11.42 ± 1.60	11.31 ± 1.52
5-MCV "FL"	70.53 ± 13.35	76.44 ± 3.89	70.41 ± 16.34
6-MCH "pg"	25.04 ± 8.84	27.09 ± 4.38	25.52 ± 3.85
7-Platelets "10 ³ /uL"	393.26 ± 185.56	364.40 ± 78.43	308.30 ± 88.20
8-CRP "mg/dL"	36.30 ± 22.42	38.61 ± 22.41	42.32 ± 36.73

ter, C - reactive protein and complete blood count with differential count.

Table 6 and figure 2 show causes of recurrent pneumonia. The patients with cardiac disorders showed the highest % frequency of cases of recurrent pneumonia (25.45%), followed by (20.9%) those with immuno-deficiency, while (16.36%) of cases were due to bronchial asthma. However, (6.36%) of the cases, the etiology was unknown.

Table 7 shows classification of cardiac causes of recurrent pneumonia. Patients with cyanotic heart diseases diagnosed as TGA (17.8%) of the cases, while (28.7%) of cardiac patients with a cyanotic heart diseases had ventricular septal defect.

Table 8 among 23 cases diagnosed with immunodeficiency, (52.17%) were due to B-cell deficiency, while (26.08%) were diagnosed as phagocytic cell defect.

Table 9 shows risk factors in study group. Prematurity was detected among (7.27%) of the cases while more than 50% were formula fed and more than 60%

Table 4. History analysis in the studied group.

Item	Descriptive "n = 110"
1. Duration of disease "days"	11.84 ± 3.29
2. Cough	104 (94.54%)
3. Fever	62 (56.36%)
4. Wheezing	20 (18.18%)
5. Chronic rhino-sinusitis with post-nasal drip	00
6. Recurrent upper respiratory tract infections	55 (50.0%)
7. Atopy/allergy	25 (22.72%)
8. Asthma	19 (17.27%)
9. Unexplained death, severe infections or multisystem diseases in family.	8 (7.27%)
10. Unusual organism or feature of systemic immunodeficiency	00
11. History suggesting Immuno-deficiency from first months of age	13 (11.81%)
12. Continuous, unremitting or worsening symptoms	10 (9.09%)

Table 6. Causes of recurrent pneumonia in the studied cases.

Item	Descriptive “n = 110”
1. Cardiac diseases	28 (25.45%)
2. Immuno-deficiency	23 (20.90%)
3. Bronchial asthma	18 (16.36%)
4. Chronic lung diseases	15 (13.63%)
• Bronchiectasis	7 (6.36%)
• Interstitial lung disease	8 (7.27%)
5. Aspiration syndrome:	7 (6.36%)
• GERD	4 (3.63%)
• Aspiration pneumonia	3 (2.72%)
6. Unknown	7 (6.36%)
7. Tuberculosis	7 (6.36%)
8. Anatomical congenital respiratory anomalies:	4 (3.63%)
• Tricho-esophgeal fistula	1 (0.90%)
• Vascular ring	2 (1.81%)
• Cleft palate	1 (0.90%)
9. Cystic fibrosis	1 (0.90%)

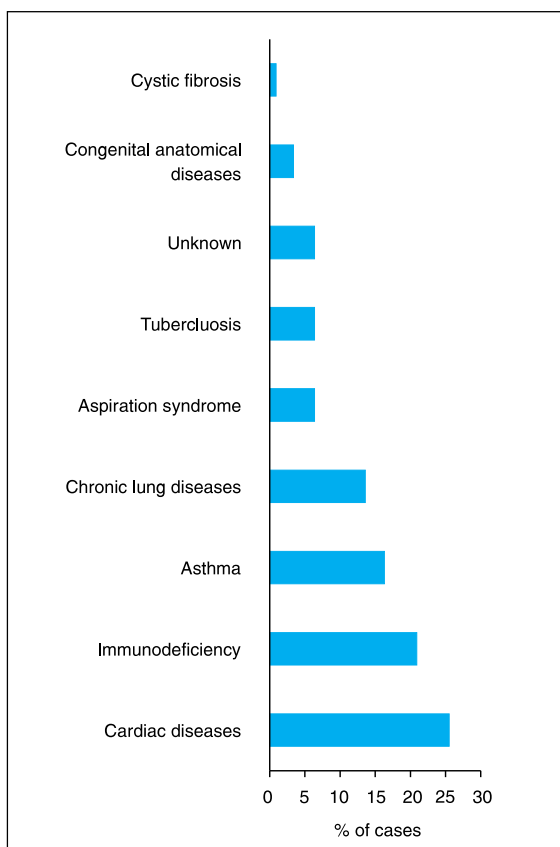


Figure 2. Causes of recurrent pneumonia among the studied patients.

exposed to pollution. Regarding vaccination for T.B and measles it was found that more than 95% of cases received these vaccines. Father smoking was detected among (36.36%) of cases.

Table 7. Classification of cardiac causes among patients with recurrent pneumonia.

Item	“N=28”
A. Cyanotic heart disease:	
1. <i>With decreased pulmonary flow:</i>	
— Double outlet Rt. Ventricle (with pulmonary stenosis).	1 (3.57%)
2. <i>With increased pulmonary flow:</i>	
— Transposition of great arteries.	5 (17.85%)
— Total anomalous pulmonary venous drainage (without pulmonary stenosis).	3 (10.71%)
B-A cyanotic heart diseases:	
1. ventricular septal defect.	8 (28.71%)
2. Atrial septal defect	4 (14.28%)
3. Atrio-ventricular septal defect	2 (7.14%)
4. Patent ductus arteriosus.	5 (17.85%)
5. Pink Fallot’s tetralogy.	2 (7.14%)

Table 8. Classification of causes of immunodeficiency among patients presented with recurrent pneumonia.

Item	“N = 23”
• Phagocytic cell defect”chronic granulomatous defect disease”.	6 (26.08%)
• T-cell deficiency	2 (8.69%)
• B-cell deficiency	12 (52.17%)
• Combined T,B cell deficiency	3 (13.04%)

Table 9. Risk factors Of recurrent pneumonia in the studied group.

Item	Descriptive “n = 110”
1. Prematurity	8 (7.27%)
2. Feeding history(4. 6months):	
Breast feeding	53 (48.18%)
Formula fed	57 (51.81%)
3. Co.morbid conditions:	
Heart disease	30 (27.27%)
Oro-motor incoordination/ swallowing dysfunction	7 (6.36%)
Primary or acquired immunodeficiency	
GERD	10 (9.09%)
Overweight/obesity	8 (7.27%)
4. Smoking (father)	7 (6.36%)
5. Respiratory disease/previous allergy	40 (36.36%)
6. Vaccinations:	
T.B	108 (98.2%)
Influenza	10 (9.09%)
Measles	106 (96.36%)
7. Use steroid	9 (8.18%)
8. Indoor pollution	42 (38.18%)
9. Outdoor pollution	38 (34.54%)
10. undernutrition	21 (19.09%)

Table 10 shows risk factors in relation to age groups among the studied cases. Patients aged > 6 years showed significantly higher frequency in risk factors as obesity, indoor and outdoor pollution and use of

Table 10. Risk factors of recurrent pneumonia in relation to age groups among the studied cases.

Item	0-3yrs. "n = 69"	> 3-6yrs. "n = 15"	> 6yrs. "n = 26"	P-value
1. Prematurity	12 (17.39%)	3 (20.0%)	2 (7.69%)	P = 0.442n.s
2. Feeding history(4.6months):				
Breast feeding	35 (50.72%)	6 (40.0%)	12 (46.15%)	P = 0.732n.s
Formula fed	34 (49.27%)	9 (60.0%)	14 (53.84%)	
3. Co-morbid:				P < 0.006
Heart disease	26 (37.68 %)	1 (6.66%)	3 (11.53%)	P = 0.108n.s
Oro-motor incoordination/swallowing dysfunction	7 (10.14%)	0	0	
Primary or acquired immunodeficiency	9 (13.04%)	8 (53.33%)	6 (23.07%)	P = 0.135n.s
GERD				
Overweight/obesity	4 (3.63%)	0	0	P = 0.077n.s
4. Smoking in parents:	0	1 (6.66%)	6 (23.07%)	P < 0.000
5. Respirator disease/previous allergy	16 (23.9%)	7 (46.7%)	17 (65.4%)	P < 0.001
6. Vaccinations:	22 (31.88%)	5 (33.3%)	4 (15.38%)	P < 0.001
T.B	68 (98.6%)	(100%)	5 (96.2%)	P = 0.628n.s
Influenza	0	3 (20%)	7 (26.9%)	P < 0.03
Measles	67 (97.9%)	15 (100%)	26 (95.7%)	P = 0.493n.s
8. Use steroid	2 (2.9%)	0	7 (26.9%)	P < 0.01
9. Indoor pollution	23 (33.33%)	5 (33.33%)	14 (53.84%)	P < 0.01
10. Outdoor pollution	19 (27.53%)	4 (26.67%)	15 (57.69%)	P < 0.04
11. undernutrition	16 (23.18%)	3 (20.0%)	2 (7.69%)	P < 0.001

steroids in comparison to other age groups. However, patients aged 0-3 years exhibited significantly higher % frequency of having heart disease, oro-motor incoordination/swallowing dysfunction, GERD and undernutrition as risk factors for recurrent pneumonia in comparison to other age groups.

Discussion

In present study, pneumonia was diagnosed in 872 of admitted cases and 110 cases fulfilled the inclusion criteria of recurrent pneumonia 12.61%. This agrees with Saad and his colleges (2013)(11) who found in previous study in Assiut in Upper Egypt that 9.2% of patients with pneumonia met the definition of recurrent/persistent pneumonia, 7% for recurrent and 2.2% for persistent pneumonia. Also Morcos and his colleges (2016)(12) reported that 12% had recurrent pneumonia in El Galaa Teaching Hospital in Egypt. Similarly; 1-9% of patients met the criteria for recurrent pneumonia in previous studies (13, 14). However, other studies, Bolursaz et al (2017) (15) reported prevalence of 34.64 % of RP among patients with pneumonia in Tahrán, Iran.

In present study, 65.5% of cases were males. This agrees with previous study done in Assiut University Hospital by Saad et al (2013)(11) as male patients represent 65% and female represents 35% of included RP cases. Bolursaz et al (2017)(15) also found that 55.0% of cases were males in Iran, that can be explained as

male patients are more vulnerable to infections than female, also the tradition of favoring male to female in the community makes parents seek medical advice for male children earlier and more frequent. The majority of the included patients were belonged to age group 0-3 years (62.7%). This agrees with Bolursaz et al (2017) (15) who reported that 1% had onset of symptoms before 3 months of age, 6% between 3 and 12 months, 65% between 1 and 5 years and 28% after the age of 5 years, that can be explained as the age group 0-3 years had significantly higher % frequency of presence of co morbid conditions as congenital anomalies, congenital heart disease and under nutrition. 77.27% of included cases were from urban areas, while 22.72% of included RP cases were from rural areas. This agrees with Li and his colleges (2017) (16) who reported that incidence of childhood pneumonia generally higher in urban areas with percentage of 73.45% for urban residents versus 26.55% for rural areas.

In the present study, there was history of cough among 94.45% of the patients, and 56.36% had history of fever while 50.0% had history of recurrent upper respiratory tract infection. Less than third of cases 22.72% had history of atopy/allergy and about 11.81% of cases had history of immuno-deficiency from first months of age. This agrees with Çapanoglu et al (2017) (17) who reported the most common presenting symptom was cough 95.5%, followed by fever 59.9% and wheezing 47.9%.

Our results are in line with Çapanoglu et al (2017) (17) who reported congenital heart diseases were the

most important cause for recurrent pneumonia in 33.9% of children with RP. Dilated blood vessels or chambers of the heart may compress the bronchi, causing impaired drainage of pulmonary segments. Also patients with congenital lesions causing left-to-right shunting and an increased pulmonary blood flow have an increased susceptibility to respiratory infections. Previous studies have reported congenital heart disease in 1.2–25.4 % of cases (10, 13, 14). A left-to-right shunt can adversely affect lung function, and superimposed lower respiratory tract infections cause additional compromise and might lead to respiratory failure (18). In agreement with these figures, our results demonstrated that congenital heart diseases was identified among 25.45% of cases and TGA was diagnosed in 17.85% of the cardiac cases, while 28.7% of cardiac patients with a cyanotic heart diseases had ventricular septal defect.

In present study, 6.36 % of studied cases were due to aspiration syndrome, 3.36% with GERD and 2.72% with aspiration pneumonia (in spite of patients with obvious neurological diseases that lead to recurrent pneumonia were excluded from our study). Gastro-esophageal reflux disease was diagnosed in four children by clinical suspicion and confirmed by barium swallow. This agrees with Owayed et al (2000) (10) who reported that in developed countries, aspiration is considered an important cause of RP and could be due to gastro-esophageal reflux disease (GERD) or due to pharyngeal in coordination. Reflux should be confirmed by esophageal P^H study, while video fluoroscopy should be used to confirm in coordination. Technetium scan, esophagoscopy and biopsy may be used if P^H study is not conclusive, although in many cases the history would be sufficient (19).

In present study, 20.9% of studied cases proved to have immune-deficiency diseases. 52.17% of them were due to B-cell defect, 26.08% with chronic granulomatous disease, 13.04% due to combined T and B cell deficiency and 8.69% due to T cell defect. This agrees with Patria & Esposito (2013) and Hoving & Brand (2013) (2, 18) who reported that immune deficiency disorders were present among 7.7–17.75 % of cases of RP. Children with immune defects usually present with highly recurrent and/or severe bacterial infections of the respiratory tract without any seasonality, recurrent gastrointestinal infections and recurrent skin infections. The family history of immunodeficiency is often characterized by recurrent infections and early deaths. There is often a delay of years between the onset of symptoms and the diagnosis being made: this delay increases the risk of bronchiectasis and irreversible lung damage occurring before appropriate treatment is given (20).

In present study, cases with RP have asthma represented 16.36% of studied cases. This agrees with Douglas & Couriel (2001) (21) who reported asthma

was diagnosed among 9.7% of studied patients. Asthma is the most important underlying illness for recurrent pneumonia in children reported by different researchers accounting for 15%–69 % of cases (14, 22, 23). The notion that asthma in children can be complicated by recurrent pneumonia has a long history and contributes to the confusion when assessing these children. This is especially true when the RML is involved. The right middle lobe syndrome is subject to atelectasis because of the anatomy of the bronchus and the lack of collateral ventilation with other lobes. Excess mucus production in hypersecretory asthma can lead to RML atelectasis. It is well recognized that the most common cause of the so-called 'right middle lobe syndrome' is asthma (24). Atopy was considered as an important risk factor for RP due to defective innate immune response of epithelial cells and interleukin 13-dependant reduced mucociliary clearance (25, 26). Allergic inflammation may also suppress the interferon response of innate immunity under certain circumstances (27). In contrast to our study and previous studies, Hoving & Brand (2013) (2) reported that asthma was not diagnosed as an underlying cause of recurrent pneumonia in their study. They believed that asthma is a rare cause of recurrent pneumonia in children, and if occurs this seems to be confined to very unusual and complicated cases of asthma.

Tuberculosis is one of the most common infectious diseases among children in the world. TB is suspected when an ill child has a history of chronic illness of usually more than 3 weeks of duration that includes cough and fever, weight loss or failure to thrive (28). Tuberculosis is a common cause of extra luminal compression of the airways associated with recurrent lung infections (18). In the present study, 6.36% of cases RP was due to tuberculosis. This agrees with Lodha et al (2002) (29) who reported pulmonary TB as a cause of recurrent pneumonia in 7.1% of patients. In addition, Çelebi (2010) and his colleagues (30) reported TB in 4.8% of the cases. The relatively low percentage frequency of TB as a cause for RP in our study may be suggested by the high rate of vaccination 98.6% among our studied cases. In previous studies with recurrent pneumonia, (13, 22) reported pulmonary TB as a cause in 19.2% and 31.5% of patients, respectively. This relatively high prevalence of pulmonary TB should alarm the physicians and health authorities to take more intensive measures for prevention and control of this disease in these areas.

The present study demonstrated that, 13.63% of studied cases have chronic lung diseases, 7.27% with interstitial lung disease while bronchiectasis represented 6.36% of included cases. These results matching with recent hypothesis that RP early in life is a major risk factor for bronchiectasis (31), but only some children actually develop bronchiectasis after the first episodes of pneumonia. The early identification of

the patients at the highest risk of bronchiectasis could allow a diagnosis to be made when the bronchial wall lesions are still mild, thus favoring the implementation of appropriate preventive and therapeutic measures, and a better final prognosis (32). The development of bronchiectasis is a chronic, progressive pulmonary disorder characterized by the permanent dilatation of one or more bronchi due to structural modifications in the bronchial wall (33). In pediatric patients, bronchiectasis causes an accelerated decline in lung function that leads to repeated hospital admissions due to acute infectious exacerbations, a poorer quality of life, and possible premature death in early adult life (34). Recurrent pneumonia was considered as a risk factor for development of bronchiectasis in 6.7%- 8.5% of cases (1, 10).

In the present study, 4 patients 3.63% had congenital anatomical anomalies of the respiratory tract one patient had tracho-esophageal fistula, 2 had congenital vascular ring and one had cleft palate. Previous studies have reported congenital anomalies of the respiratory tract in 3.7-8.5% of cases (2, 10, 29). Recurrent chest infections are often the presenting feature of congenital abnormalities of the airways, lung parenchyma and pulmonary vasculature. For example, repeated episodes pneumonia are often the presenting feature of lobar sequestration, bronchial stenosis and bronchomalacia, and cystic adenomatoid malformations of the lung (35). Such an abnormality should be suspected if one lobe is repeatedly infected or if there is incomplete resolution after treatment. Computerized tomography and magnetic resonance scanning are helpful in defining the anomaly prior to surgical excision (36).

In our study the etiology of recurrent pneumonia was not recognized in 6.36% of studied cases in spite of careful history obtained and full investigation done to these cases. This agrees with Çapanoglu et al (2017) (17) who mentioned that the underlying cause of recurrent pneumonia was no specific in 16.3% of studied cases and Saad and his colleagues (2013) (11) who mentioned also that in 10-20% of studied cases the etiology was unknown.

The current study showed that only one case had cystic fibrosis, diagnosed by cystic fibrosis DNA analysis. Limited data are available regarding CF prevalence among Egyptian children's has been believed to occur infrequently in Egypt; only few papers suggested its presence (37, 38). A history of neonatal jaundice, poor weight gain, steatorrhea and highly recurrent pneumonia may suggest cystic fibrosis, although atypical cases may present with recurrent pneumonia alone, in the absence of malabsorption. Also recovery of *Pseudomonas aeruginosa* from the respiratory tract, especially the mucoid form, is highly suggestive of CF (18, 39).

In present study, according to El Sherbini modified score (2012) 48.18% of the families belonged to middle

class, while 43.63% were classified as low class. This agrees with Wonodi et al (2012); Çapanoglu et al (2017) (17,40) who reported risk factors associating with RP in children especially poor socioeconomic status which represent an important risk factor commonly associated with increase the frequency of illness episodes in children.

Also high crowding index according to El Sherbini modified score (2012) was detected among 94.5% which represent important risk factor for recurrent pneumonia mostly due to increased exposure to respiratory pathogens (41). The definition of household crowding varies greatly (42). Household crowding was defined as two or more individuals sleeping in the same room as the child (43) or more 7 persons per household (44). Our results match with Çapanoglu et al (2017) (17) who reported overcrowded household as a definitive risk factor of RP.

In our study, we also found that 54.4% of mothers of studied cases only read and write and 29.29% of them had preparatory level of education. This agrees with De Souza et al (2000) (45) who mentioned that mother's education level has an undeniable and important impact on their children's health and understanding of them of the importance of the disease, its severity and use of health services. Also Nirmolia et al (2018) (46) showed lack of maternal education is significantly associated with occurrence of pneumonia.

History of prematurity was detected among 7.27% of studied cases. This agrees with Çapanoglu and his colleagues (2017) (17) who mentioned prematurity as an important risk factor for pneumonia recurrence in children. The two main mechanisms that children with low birth weight put at risk of respiratory infections include low immunity level and defects in lung function. Also, these children also have limited iron, zinc and copper resources (47). Other studies that have been conducted in developing countries, showed the relationship between birth weight and infant mortality due to pneumonia or acute infection of the lower respiratory tract (48). Yoon et al (1997) (49) mentioned that a strong correlation exists between decreased mortality from pneumonia with increasing birth weight.

In the present study, 36.36% of studied cases had history of parental smoking which becomes one of the important risk factors for RP. This agrees with Çapanoglu et al (2017) (17) who reported that exposure to smoking presented in 57.1% of studied cases with RP. Passive smoking is a risk factor for developing respiratory tract infections in children (50). Passive smoking in children leads to suppression of phagocytic function and cilia cell activity, increase the likelihood of adherence of bacteria to the epithelium of respiratory tract (51).

According to our study, 19.09% of studied cases have under malnutrition. This agrees with most of

studies done before in the developing countries which reported strong correlation between under malnutrition and pediatric recurrent infections especially respiratory tract infections (51). Children with malnutrition have deficient immune responses, consequently these childhood infections are more severe in these children. Studies show children who their weight is less than 70% appropriate weight for their age compared to other children, increased an 8 times risk of mortality from pneumonia for them (48).

In present study 51.8% of studied cases were formula fed and only 48.2% were exclusive breast fed. This agrees with Çapanoglu et al (2017) (17) who mentioned that insufficient breastfeeding was one of the definitive risk factors strongly associated with increasing the frequency of RP. Ulshen (2005) (52) reported that breastfeeding can protect children against the risk of lower respiratory infections. In fact, breast milk gives passive protection against pathogens even with change of age infants (53). Complete or partial breast-feeding resulted in a 50% reduction in mortality from acute respiratory tract infections in children fewer than 18 months (54).

In present study 38.18% of cases with recurrent pneumonia exposed to indoor air pollution. There are documentations that the risk of pneumonia is enhanced following exposure to unprocessed solid fuel use by a factor of 1.8 (55) and also there is significant association between ARI and indoor air pollution (56). Nirmolia et al (2018) (46) have documented a significant association between indoor air pollution and pneumonia. It has been recommended that prevention of indoor air pollution from burning of solid fuel to switching over to better quality fuel, improved ventilation or some other measures will substantially reduce morbidity and mortality from pneumonia (55). This agrees with Po, et al (2011) ; Searing and Rabinovitch (2011) (57, 58) who reported that both indoor and outdoor pollution are a definitive risk factors for RP. Dherani et al (2008) (55) also reported that indoor air pollution has been determined to elevate the risk of pneumonia in children by approximately 80%.

Conclusion

1-Approximately 1 in 12 children with pneumonia in our locality have recurrent pneumonia with percentage of 12.61%. The most frequent underlying cause for recurrent pneumonia in Assiut University Children's Hospital which present the largest referral pediatric hospital in Upper Egypt for one year according to our study was cardiac diseases especially congenital heart diseases 25.45% , the second most frequent cause was immunodeficiency diseases 20.9% followed by bronchial asthma 16.36%. Other causes include chronic lung

diseases, pulmonary T.B, aspiration syndrome, anatomical congenital respiratory anomalies and cystic fibrosis arranged respectively, while the etiology of recurrence was unknown in 6.36 % of the cases.

2-Prematurity was detected among 7.27 % of the cases while more than 50% were formula fed and more than 60% exposed to pollution. Father smoking was detected among 36.36% of cases. Patients aged > 6 years showed significantly higher frequency in risk factors as obesity, indoor and outdoor pollution and use of steroids in comparison to other age groups. However, patients aged 0–3 years exhibited significantly higher % frequency of having heart disease, oro-motor in coordination /swallowing dysfunction, GERD and under nutrition as risk factors for recurrent pneumonia in comparison to other age groups.

Finally, we hope that this study will help the pediatricians identify and hence prevent and manage the most common etiologies of recurrent pneumonia in our locality. Determining which case should be investigated relies on clinical judgment, depending on a careful history and physical examination, whether the child is improving clinically and whether there is any feature suggestive of an underlying condition. Early treatment of the child's underlying condition is crucial in order to stabilize lung disease and thus prevent progressive deterioration of most pulmonary diseases.

A wide range of tests is available and there is no evidence base to guide the clinician on the most appropriate timing or sequence of investigations. Ideally, the diagnosis should be confirmed or excluded with the minimum number of the least-invasive tests. The economic burden of an extensive diagnostic work-up should always be kept in mind. Choosing the most appropriate investigations for recurrent pneumonia should be individualized for every case separately according to detailed history and full clinical examination for each case.

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