



ORIGINAL

Lung diffusion capacity and quality of life 6 months after discharge from the ICU among survivors of acute respiratory distress syndrome due to influenza A H1N1[☆]

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Abstract

Objective: An evaluation is made of lung function and quality of life 6 months after discharge from the Intensive Care Unit (ICU) among survivors of acute respiratory distress syndrome (ARDS) due to pandemic 2009 influenza A H1N1, based on studies of lung function and the EQ-5D health questionnaire.

Design: Case series.

Setting: The ICU of Dr. Leónidas Lucero Acute Cases Municipal Hospital, Bahía Blanca, Argentina.

Patients: Patients discharged from the ICU who had been admitted with ARDS in 2009 due to influenza A H1N1.

Results: Eleven patients were studied. Seven were positive for influenza H1N1 and four were negative. The mean age was 37 ± 9.5 years, and 73% were males. Quality of life, as measured by the EQ-5D, showed changes in the 5 components in all patients, particularly in the pain/discomfort dimension 1.55 ± 0.52 ; health status (EQ%health) was $70\% \pm 24$. The indices adjusted for Argentina were Time Trade Off (TTO) 0.903 ± 0.085 and visual analog scale (VAS) 0.827 ± 0.153 . In all patients, spirometry and the study of pulmonary diffusion (DLCO) showed values of $>80\%$. There was no correlation between lung diffusion and quality of life (%DLCO and EQ%health). A correlation was observed between quality of life and TTO (EQ%health and TTO), and between quality of life and the VAS score (EQ%health and VAS).

Conclusion: Although the sample is small, our results suggest that patients with ARDS due to influenza A H1N1 evaluated 6 months after discharge from the ICU show no deterioration of lung function, and the impact on quality of life is moderate-in contrast to the situation found in patients with ARDS of other etiologies.

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PALABRAS CLAVE

Gripe humana;
 Síndrome de distrés
 respiratorio agudo;
 Calidad de vida;
 Pruebas de función
 pulmonar

Capacidad de difusión pulmonar y calidad de vida a los 6 meses del alta de la unidad de cuidados intensivos en sobrevivientes a síndrome de distrés respiratorio agudo por influenza A H1N1

Resumen

Objetivo: Evaluar la función pulmonar y la calidad de vida a los 6 meses del alta de la unidad de cuidados intensivos (UCI), a pacientes que tuvieron síndrome de distrés respiratorio agudo (SDRA) por influenza A H1N1 pandémica 2009, mediante estudios de función pulmonar y cuestionario de salud EQ-5D.

Diseño: Serie de casos.

Ámbito: La UCI del Hospital Municipal de Agudos Dr. Leónidas Lucero, Bahía Blanca, Argentina.

Pacientes: Pacientes de alta de UCI, ingresados en 2009 con SDRA por influenza A H1N1.

Resultados: Se estudiaron 11 pacientes, 7 de ellos fueron positivos para influenza A H1N1 y 4 fueron negativos. La edad media fue de $37 \pm 9,5$ años, (73%) varones. La calidad de vida de todos los pacientes evaluado por EQ-5D mostró cambios en los 5 componentes, siendo mayor en la dimensión dolor/malestar $1,55 \pm 0,52$, y el estado de salud (EQ%health) fue de $70\% \pm 24$. Los índices ajustados para Argentina fueron *Time Trade Off* (TTO) $0,903 \pm 0,085$ y *Visual Analog Scale* (VAS) $0,827 \pm 0,153$. En todos los pacientes, la espirometría y el estudio de difusión pulmonar (DLCO) mostraron valores $>80\%$. No hubo correlación entre difusión pulmonar-calidad de vida (%DLCO-EQ%health), y si hubo correlación entre calidad de vida-índice TTO (EQ%health-TTO) y entre calidad de vida-índice VAS (EQ%health-VAS).

Conclusión: Aunque la muestra es pequeña, nuestros resultados sugieren que los pacientes con SDRA por influenza A H1N1 evaluados a los 6 meses del alta de UCI no presentaron deterioro en la función pulmonar y la repercusión en la calidad de vida fue moderada, a diferencia de lo que ocurre en los pacientes con SDRA de otras etiologías.

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Introduction

During the influenza virus H1N1 pandemic of 2009, a small proportion of patients developed severe pneumonia leading to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction syndrome (MODS), associated to a prolonged stay in the Intensive Care Unit (ICU) and important mortality (15–54%).^{1–3} In Argentina, according to the epidemiological report of the Ministry of Health, up until 6 February 2010, a total of 1,479,998 cases of influenza-type disease had been reported, and of the 28,627 samples analyzed in the laboratory, 12,010 were confirmed as corresponding to influenza (H1N1) 2009. The hospital admission rate due to severe respiratory disease was 34.89 cases per 100,000 inhabitants, and the number of confirmed deaths reached 626.⁴

In influenza, including H1N1, experimental and clinical studies have identified deregulated systemic inflammation as an important pathogenic mechanism correlated to the severity and progression of the disease.⁵

In response to the influenza epidemic, and based on the clinical trials of the treatment of ARDS with corticosteroids,⁶ in Bahía Blanca (Argentina) we developed an integral protocol for treating patients with suspected pneumonia due to influenza virus H1N1 and ARDS admitted to the ICU. This protocol was applied to 13 patients, comprising a series that was published in 2010.⁷

Among survivors of ARDS due to causes other than H1N1 infection, a series of functional alterations are observed that mostly disappear over time. The initial phases of patient recovery are characterized by restrictive-type ventilatory disorders.⁸ Approximately one third of the patients show diminished total lung capacity, and almost one half suffer

a decrease in pulmonary carbon monoxide diffusing capacity (DLCO).⁹ The most important late functional alterations are gas exchange anomalies. All these functional alterations may be attributable to the presence of lung fibrosis, as has been shown in the few cases where histopathological studies are available.¹⁰ Long-term quality of life is largely dependent upon the diagnostic category involved; in this context, patients with ARDS, prolonged mechanical ventilation, severe trauma and severe sepsis are those who suffer important worsening in quality of life—fundamentally as refers to mental and emotional aspects.¹¹

Taking into account the impact of ARDS, we decided to follow-up on 11 survivors of the above mentioned series published in 2010, evaluating their lung function and quality of life after 6 months.

Materials and methods

The study was approved by the Institutional Review Board, and informed consent was obtained from all patients.

The 11 patients were evaluated 6 months after discharge from the ICU. At the time of the control visit they received an explanation of the study and were given the self-administered EuroQoL-5D (EQ-5D) health questionnaire.

We used the validated Spanish version of the EQ-5D, a simple generic instrument is divided into three parts. The first part comprises a descriptive system defining health condition in terms of 5 dimensions: mobility, personal care, daily life activities, pain/discomfort and anxiety/depression. Each dimension in turn is divided into three levels: level 1 = no problems, level 2 = some/moderate problems, and level 3 = many problems. A given health condition

is a combination of one level for each dimension. The second part of the EQ-5D consists of a visual analog scale (VAS) measuring 20 cm in length and scored from 0 to 100, where 0 and 100, respectively represent the worst and best health condition imaginable, expressed as EQ%health. The third part of the questionnaire involves the obtainment of preference indices based on 243 possible health conditions generated by the EQ-5D using a scoring technique such as the Time Trade Off (TTO) method,¹² where the index ranges from 1 (best health condition) to 0 (death)—though there are also negative index values, corresponding to those health conditions that are rated as worse than death. The use of these techniques helps take into account that improvement in one dimension may not have the same value for those interviewed as an improvement of the same magnitude in some other dimension. As reference values for these indices, we used those described by Augustovski et al.,¹³ who developed reference values based on the EQ-5D, using the VAS and TTO with logistic regression models, to assess the health conditions in the Argentinean population. The proposed values were VAS: 0.858 and TTO: 0.908.

The respiratory function studies were made after completing the EQ-5D questionnaire, and consisted of force spirometry before and after bronchodilator administration, and the pulmonary carbon monoxide diffusing capacity (DLCO) test. The latter was carried out using the single respiration method with the determination of pulmonary capillary blood volume (V_c) and the membrane diffusion factor (D_m). DLCO was interpreted from its components: alveolar volume (AV) and the permeability coefficient (K_{co}). The Ultima™ Series Med Graphics® computerized system was used.

The 11 patients were diagnosed in 2009 from the analysis of nasopharyngeal swab samples using a real-time polymerase chain reaction (RT-PCR) technique, in compliance with the guidelines published by the United States Centers for Disease Control (CDC).¹⁴

Statistical analysis

The statistical analysis was carried out with the SPSS version 15.0 package. Discrete variables were recorded as percentages, while continuous variables were reported as means \pm one standard deviation (SD), the median and range (minimum–maximum). Nonparametric univariate tests and a general linear model were used. In relation to the clinical and functional characteristics of the patients, the differences between the groups were evaluated using the chi-squared test and the Kolmogorov–Smirnov Z-test for one sample. Correlations were established between variables using the rho coefficient of Spearman and Pearson—statistical significance being accepted for $p \leq 0.05$.

Results

The study included 11 patients who suffered ARDS during the 2009 pandemic. The mean age was 37 ± 9 years, and most were males (8/11). The mean stay in the ICU was 14 ± 7 days, with a hospital stay of 20 ± 10 days, and 11 ± 6 days of mechanical ventilation. Seven patients proved positive

and four negative for influenza A H1N1 infection, as diagnosed by RT-PCR. Eighty-five percent of the patients had stopped smoking (6/7), and only one remained an active smoker. Obesity was frequent: 73% of the patients had a body mass index (BMI) of $>25 \text{ kg/m}^2$ (8/11), and two showed BMI $> 40 \text{ kg/m}^2$ (Table 1).

Perceived quality of life in the 11 patients evaluated with the EQ-5D six months after discharge from the ICU showed changes in the 5 components—particularly in the dimension pain/discomfort (P/D), with a mean score of 1.55 ± 0.52 , and to a lesser extent in the dimension personal care (PC), with a mean of 1.09 ± 0.30 . Regarding health condition reported by the VAS expressed as EQ%health, the mean score was $70\% \pm 24$, with a range of 30–100%. The mean preference indices adjusted to the values validated for Argentina were 0.903 ± 0.085 for TTO and 0.827 ± 0.153 for the VAS (Table 2).

Basal and post-bronchodilator spirometry revealed normal lung function in all patients, with mean values of over 80% (Table 3).

The lung volumes and DLCO also reflected normal lung function in all cases, with mean values above 87% (Table 4).

There were no statistically significant differences among the variables subjected to analysis of variance (ANOVA): DLCO $p=0.95$; EQ5health $p=0.52$; TTO $p=0.52$ and VAS $p=0.82$. Likewise, no significant differences were recorded on applying the chi-squared test: DLCO $p=1.0$; EQ%health $p=0.99$; TTO $p=0.48$ and VAS $p=0.55$.

No correlations were found among the variables, lung diffusion capacity as expressed by %DLCO, and perceived quality of life as evaluated by EQ%health ($p=0.265$) (Fig. 1). Paired correlation of the variables EQ%health–TTO and EQ%health–VAS showed good correlation between these variables, with $p=0.009$ and $p=0.001$, respectively (Fig. 2).

Discussion

Although our study sample is small, the results obtained suggest that patients with ARDS secondary to influenza A H1N1 evaluated 6 months after discharge from the ICU show no worsening of lung function, as reflected by both the spirometric findings and the carbon monoxide diffusion test. We consider that the observed functional behavior is attributable to the triggering cause, and since this is a viral infection in which the underlying pathogenic mechanism involves an important deregulated inflammatory response, the severity and course of the disease during the active viral replication phase would largely explain the situation and would also explain why the process is more self-limiting and involves fewer sequelae after the acute phase in those patients who survive. Regarding quality of life, and although moderate worsening was observed in all the EQ-5D dimensions (particularly pain/discomfort, motor function, and daily life activities), none proved statistically significant. A recent multicenter prospective study found ARDS survivors evaluated after 6 months to have poor quality of life¹⁵; however, in contrast to the descriptions in the literature, the impact in our series of patients was moderate. The above observations suggest that the behavior of ARDS secondary to viral infection is different from that of ARDS due to other causes.

Table 1 General characteristics 6 months after discharge from the Intensive Care Unit.

	Gender	Age	Days ICU	Days MV	Days hospital	Height (cm)	Weight (kg)	BMI	History
H1N1									
<i>Negative</i>									
1	Male	32	8	7	12	164	84	31.34	Ex-smoker
2	Male	27	8	7	14	171	91	31.16	Obese
3	Male	45	6	5	11	166	62	22.54	Arterial hypertension
4	Male	44	17	14	23	170	75	25.95	Ex-smoker
	Mean	37.00	9.75	8.25	15.00	167.75	78.00		
	Median	38.00	8.00	7.00	13.00	168.00	79.50		
	SD	8.907	4.924	3.948	5.477	3.304	12.517		
<i>Positive</i>									
1	Female	16	30	26	47	144	90	43.47	Tracheal stenosis, severe obesity, diabetes.
2	Male	39	14	12	20	156	56	23.04	Ex-smoker
3	Female	44	16	14	22	165	96	35.29	Obese
4	Female	34	10	9	13	150	47	23.5	Ex-smoker
5	Male	40	20	13	26	168	98	34.75	Ex-smoker, obese
6	Male	49	8	6	12	165	110	40.44	Smoker, severe obesity
7	Male	40	14	12	17	169	82	28.77	Ex-smoker, overweight
	Mean	37.43	16.00	13.14	22.43	159.57	84.14		
	Median	40.00	14.00	12.00	20.00	165.00	95.00		
	SD	10.518	7.303	6.283	11.900	9.710	24.423		
<i>Total 11</i>									
	Mean	37.27	13.73	11.36	19.73	162.55	81.91		
	Median	40.00	14.00	12.00	17.00	165.00	84.00		
	SD	9.498	7.016	5.870	10.393	8.768	20.359		

The data are reported as the mean, median and standard deviation (SD).

MV: mechanical ventilation; BMI: body mass index; ICU: Intensive Care Unit.

Table 2 Quality of life perception scored with the EQ-5D questionnaire 6 months after discharge from the Intensive Care Unit.

	EQ MO	EQ PC	EQ DLA	EQ P/D	EQ A/D	EQ %health*	TTO ^a	VAS ^b
H1N1								
<i>Negative</i>								
1	1	1	1	1	1	100	1.000	1.000
2	1	1	1	2	1	50	0.887	0.792
3	1	1	1	1	1	90	1.000	1.000
4	1	1	1	2	2	85	0.887	0.737
Mean	1.00	1.00	1.00	1.50	1.25	81.25	0.94350	0.88225
Median	1.00	1.00	1.00	1.50	1.00	87.50	0.94350	0.89600
SD	0.000	0.000	0.000	0.577	0.500	21.747	0.065241	0.137808
Minimum	1	1	1	1	1	50	0.887	0.737
Maximum	1	1	1	2	2	100	1.000	1.000
<i>Positive</i>								
1	2	2	2	1	2	30	0.813	0.508
2	2	1	2	2	1	40	0.788	0.770
3	1	1	1	1	1	90	1.000	1.000
4	2	1	1	2	1	80	0.788	0.852
5	1	1	2	2	2	50	0.887	0.649
6	1	1	1	2	1	60	0.887	0.792
7	1	1	1	1	1	95	1.000	1.000
Mean	1.43	1.14	1.43	1.57	1.29	63.57	0.88043	0.79586
Median	1.00	1.00	1.00	2.00	1.00	60.00	0.88700	0.79200
SD	0.535	0.378	0.535	0.535	0.488	25.284	0.091573	0.178705
Minimum	1	1	1	1	1	30	0.788	0.508
Maximum	2	2	2	2	2	95	1.000	1.000
<i>Total 11</i>								
Mean	1.27	1.09	1.27	1.55	1.27	70.00	0.90336	0.82727
Median	1.00	1.00	1.00	2.00	1.00	80.00	0.88700	0.79200
SD	0.467	0.302	0.467	0.522	0.467	24.597	0.085562	0.163580
Minimum	1	1	1	1	1	30	0.788	0.508
Maximum	2	2	2	2	2	100	1.000	1.000

The data are reported as the mean, median, standard deviation (SD) and minimum and maximum values.

EQ-5D dimensions: EQ A/D: anxiety/depression; EQ DLA: daily life activities; EQ PC: personal care; EQ P/D: pain/discomfort; EQ MO: mobility;

^a EQ%health: health condition on a visual analog scale (VAS) from 0 to 100%.

^b Perception or indices according to validation for Argentina; TTO: Time-Trade Off; VAS: visual analog scale.

Over 60 causes of ARDS have been identified, though epidemiological studies show most ARDS episodes to be associated to predisposing factors. Among the possible causes, mention must be made of sepsis as the most common factor, followed by others including bronchial aspiration, infectious pneumonia, severe trauma or burns, massive blood transfusion, plasma transfusion, airway obstruction, organ transplantation, etc.¹⁶

The patients who survive ARDS present sequelae affecting respiratory function, health-related quality of life, physical activity, and cognitive and emotional function.¹⁷

The appearance of the influenza A virus (H1N1) 91 years ago gave rise to a global pandemic with catastrophic consequences. In 2009, the influenza A virus (H1N1) was an emergent respiratory agent in Mexico, followed by further cases in other countries, and reaching level 6 (pandemic status) according to the World Health Organization (WHO).¹⁶ At present, the literature offers many reports of ARDS secondary to the influenza A H1N1 pandemic of 2009,^{17,18} though little is known about the long-term pulmonary function and quality of life of these patients. As a result, the

data obtained in our study would indicate important and relatively rapid recovery on the part of patients with this particular type of viral infection, in contrast to situations involving other causes of ARDS.

In order to determine whether the loss of health-related quality of life in ARDS patients is secondary to the actual syndrome or to other aspects related to the disease process causing ARDS, Davidson et al. conducted a paired case study of 73 patients with ARDS and 73 patients with risk factors for ARDS. The health condition of the patients was assessed using generic health (Medical Outcomes Study 36-Item Short Form Health Survey, Standard Form [SF-36]) and specific lung function scales (St George's Respiratory Questionnaire [SGRQ]). The patients with ARDS showed significant reductions on both scales, and the greatest limitations corresponded to the dimensions referred to physical and pulmonary capacity.^{14,19}

Other authors using these scales or other instruments such as the Quality of Well-Being Scale (QWB) have also reported worsened quality of life among survivors 6 and 12 months after hospital discharge. In our series the EQ-5D

Table 3 Spirometry 6 months after discharge from the Intensive Care Unit.

	PB % Pron FVC	PtB % Pron FVC	PB % Pron FEV1	PtB % Pron FEV1	PB % Pron FEV1/FVC	PtB % Pron FEV1/FVC	PB % Pron FEF 25–75	PtB % Pron FEF 25–75
H1N1								
<i>Negative</i>								
1	78	81	81	87	106	109	97	121
2	77	72	85	84	111	117	117	134
3	92	90	102	102	111	114	158	173
4	103	100	108	109	105	109	127	134
Mean	87.50	85.75	94.00	95.50	108.25	112.25	124.75	140.50
Median	85.00	85.50	93.50	94.50	108.50	111.50	122.00	134.00
SD	12.396	12.010	13.038	11.958	3.202	3.948	25.435	22.517
Minimum	77	72	81	84	105	109	97	121
Maximum	103	100	108	109	111	117	158	173
<i>Positive</i>								
1	52	55	57	57	113	109	63	58
2	74	83	78	92	107	112	96	172
3	80	80	94	95	117	118	183	185
4	101	108	92	98	92	92	63	103
5	72	71	84	82	116	115	157	110
6	87	91	59	57	69	63	29	27
7	94	93	98	98	105	106	113	105
Mean	80.00	83.00	80.29	82.71	102.71	102.14	100.57	108.57
Median	80.00	83.00	84.00	92.00	107.00	109.00	96.00	105.00
SD	16.176	16.961	16.600	18.382	17.134	19.196	54.924	56.453
Minimum	52	55	57	57	69	63	29	27
Maximum	101	108	98	98	117	118	183	185
<i>Total 11</i>								
Mean	82.73	84.00	85.27	87.36	104.73	105.82	109.36	120.18
Median	80.00	83.00	85.00	92.00	107.00	109.00	113.00	121.00
SD	14.745	14.758	16.255	16.949	13.675	15.867	46.399	48.205
Minimum	52	55	57	57	69	63	29	27
Maximum	103	108	108	109	117	118	183	185

The data are reported as the mean, median, standard deviation (SD) and minimum and maximum values.

PB%Pron (pre-bronchodilation): FEF 25–75: forced expiratory flow 25–75; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

PtB%Pron (post-bronchodilation): FEF 25–75: forced expiratory flow 25–75; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

Table 4 Pulmonary volumes and carbon monoxide diffusion capacity (DLCO) 6 months after discharge from the Intensive Care Unit.

	%SVC ^a	%FRC ^a	%TLC ^a	%RV/TLC ^a	%DLCO cor ^b	%DL/AV ^b	%AV ^b
H1N1							
<i>Negative</i>							
1	87	53	89	97	95	113	85
2	87	56	90	100	88	110	80
3	98	163	130	157	105	114	92
4	105	99	99	75	109	99	109
Mean	94.25	92.75	102.00	107.25	99.25	109.00	91.50
Median	92.50	77.50	94.50	98.50	100.00	111.50	88.50
SD	8.846	51.331	19.201	34.989	9.535	6.880	12.662
Minimum	87	53	89	75	88	99	80
Maximum	105	163	130	157	109	114	109
<i>Positive</i>							
1	59				74	119	62
2	90	102	90	91	93	109	85
3	82	70	88	98	66	92	72
4	103	66	88	50	106	111	95
5	72	47	72	74	82	112	73
6	106	103	119	124	104	88	118
7	100	115	114	128	100	97	104
Mean	87.43	83.83	95.17	94.17	89.29	104.00	87.00
Median	90.00	86.00	89.00	94.50	93.00	109.00	85.00
SD	17.453	26.589	17.826	29.721	15.564	11.633	19.849
Minimum	59	47	72	50	66	88	62
Maximum	106	115	119	128	106	119	118
<i>Total 11</i>							
Mean	89.91	87.40	97.90	99.40	92.91	105.82	88.64
Median	90.00	84.50	90.00	97.50	95.00	110.00	85.00
SD	14.768	35.948	17.660	30.733	14.067	10.088	17.019
Minimum	59	47	72	50	66	88	62
Maximum	106	163	130	157	109	119	118

The data are reported as the mean, median, standard deviation (SD) and minimum and maximum values.

Patient H1N1+ 1 had no registries for %FRC, %TLC and %RV/TLC.

^a *Pulmonary volumes (L)*: FRC: functional residual capacity; RV/TLC: residual volume adjusted to total lung capacity; SVC: vital capacity; TLC: total lung capacity.

^b *Diffusion (ml/min/mmHg)*: DL/AV: lung diffusion adjusted to alveolar volume; DLCO: carbon dioxide diffusion capacity; AV: alveolar volume.

showed increased worsening referred to mobility and anxiety/depression, with a 30% decrease in perceived health, 6 months after discharge from the ICU.

There have been descriptions of alterations in the lung function tests, including a decrease in forced expiratory volume in the first second (FEV1) that can persist during the first year after patient discharge, as well as decreases in forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO).^{20–22} In contrast to these reports, we observed no such alterations in our series, where most of the functional tests proved normal. Although the series is small, the 11 patients with H1N1 infection (confirmed or otherwise) showed disease of similar severity according to the ARDS diagnostic criteria of the European-American consensus,²³ and our observations could indicate a possible behavior or tendency in this type of viral infection.

Physical activity estimated with the SF-36 in 109 survivors has been reported to increase to 25 points after

12 months—the score in the normal population being 84 points. Such physical impairment was confirmed in the mentioned study and in the work published by Schelling et al., based on the 6-min walking test.

Regarding the neuropsychological sequelae, the studies that have examined this aspect have found a significant percentage of survivors to suffer worsened cognitive function at discharge from hospital and at long term.^{24–26} Hopkins et al. found 46% of the survivors to suffer at least one of the following alterations one year after hospital discharge: memory problems, concentration and/or attention difficulties, and slowed mental processing. These same authors evaluated the neuropsychological sequelae after two years and found that these problems persisted in 47% of the patients—fundamentally in the form of anxiety and depression.²⁷ Such mental problems have been related to the development of posttraumatic stress syndrome. These data are similar to those obtained in our own series, where

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