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Human cytomegalovirus is the cause of IgA Nephropathy

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Abstract

Objective: The present publication investigates the relationship between the presence of Human cytomegalovirus (HCMV) in renal tissue and IgA Nephropathy (IgAN).

Methods: A systematic review and re-analysis of studies which investigated the relationship between HCMV and IgAN was conducted aimed to answer the following question. Is there a cause-effect relationship between HCMV and IgAN? The method of the conditio sine qua non relationship was used to proof the hypothesis whether the presence of HCMV guarantees the presence of IgAN. In other words, without HCMV no IgAN. The mathematical formula of the *causal relationship* k was used to proof the hypotheses is, whether there is a cause-effect relationship between HCMV and IgAN. Significance was indicated by a p-value of less than 0.05.

Results: The studies analyzed were able to provide strict evidence that HCMV is a necessary condition (a conditio sine qua non), a sufficient condition and a necessary and sufficient condition of IgAN. Furthermore, the cause-effect relationship between HCMV and IgAN was highly significant.

Conclusions: On the basis of published data and ongoing research, sufficient evidence is given to conclude that HCMV is the cause of IgA Nephropathy.

Keywords: *Human cytomegalovirus, IgA Nephropathy, causal relationship.*

Introduction

IgA Nephropathy (IgAN) or Berger's disease which presents itself with a wide variety of histologic patterns (Haas, 1997) on renal biopsy is characterized by the presence of IgA-dominant or co-dominant immune deposits within glomeruli (Roberts, 2014) and was first described by the renal pathologist *Jean Berger* (1930–2011) in the year 1968 (Berger &

Hinglais, 1968; Feehally & Cameron, 2011). Berger's disease is a chronically progressive disease and the most common (McGrogan, Franssen, & de Vries, 2011) form of primary glomerulonephritis in the world. The incidence of IgA nephropathy as the leading cause (Donadio & Grande, 2002) of end-stage renal disease in patients with primary glomerulopathy is at least 2.5/100000/year in adults (McGrogan et al., 2011). At present, treatment options for Berger's disease are still very limited. Disease management mainly consists of reducing proteinuria by angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), controlling blood pressure, lipid levels and other supportive treatment. Persistent proteinuria ($\geq$1 g/d and eGFR > 50 ml/min per 1.73 m^2) in IgA Nephropathy patients (Palevsky et al., 2013) is treated with a 6-month course of corticosteroids therapy. Regarding treatment options for immunoglobulin A nephropathy there are encouraging results and increasing evidence of the efficacy and safety of CMV drugs (Avery et al., 2010; John, Manivannan, Chandy, Peter, & Jacob, 2004; Sudarsanam, Sahni, & John, 2006) like *ganciclovir* (Ortmanns et al., 1998) and *leflunomide* (Lou et al., 2006; Min et al., 2017; Rong & Liu, 2007; Wu et al., 2016). Human cytomegalovirus (HCMV) infects more or less asymptomatically (Priel, Wohl, Teperberg, Nass, & Cohen, 2015) about 50% to 90% of the adult (Najafi, Ghane, Poortahmasebi, Jazayeri, & Yousefzadeh-Chabok, 2016; Yi et al., 2013) human population. To date, even if an increasing amount of literature suggests that HCMV is involved in the etiology of IgAN the pathogenesis of IgAN is still an unresolved issue. Gregory et al. (Gregory, Hammond, & Brewer, 1988) documented in 1988 the first description of mesangial staining of polyclonal antihuman cytomegalovirus (anti-HCMV) antibodies in IgAN patients. However, the presence of HCMV in the renal tissue of IgAN has been investigated with a variety of different techniques and conflicting results (Béné, Tang, & Faure, 1990; Dueymes, Mignon-Conté, Dueymes, Vernier, & Conte, 1989; Lai, Tam, Lo, & Lai, 1990; Okamura, Kanayama, Negoro, Takeda, & Inoue, 1989; Tomino et al., 1989) have been reported. Hung et al. (Hung et al., 1996) in 1996 were not able to provide evidence of a higher frequency of positive antibody titers for several common viruses in IgAN patients while Nagy et al. (Nagy et al., 1995) found that the concentration of HCMV-IgA antibodies in IgAN patients is significantly higher than in controls. Whether other viruses (Kunimoto et al., 1993) or human cytomegalovirus is causally involved in the pathogenesis of IgA nephropathy is still not cleared beyond any reasonable doubt and remains controversial.

Material and Methods

Especially, the lack of a uniform operational definition of positivity in IgA Nephropathy and the use of different methodological approaches and other factors may have been a source of

bias. Finally, an impressive HCMV PCR DNA presence in a high percentage of IgA Nephropathy cases has been reported by view studies.

Material

Search Strategy

For the questions addressed in this paper, the database PubMed was search for serologically based studies conducted in any country which investigated the relationship between HCMV and IgAN by polymerase chain reaction (PCR) technology. Furthermore, only those articles which provided access to data without a significant data access barrier were formally considered for a review.

The Data of the Studies Analyzed

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed		
Google Scholar	12	
Web of Science	0	
Additional records identified from other sources	1	13
2. Clean-up of search (Screening)		
Records removed after verifying duplication	0	
Records excluded by title		
Records excluded due to other reasons (Articles outside the inclusion criteria)	7	
3. Eligibility		
Articles evaluated for eligibility	6	
Articles excluded for various reasons		
- Data were self-contradictory (Table 2)	2	
- Data access barriers	0	
4. Included		
Articles included in the meta-analysis (Table 1)		4

Table 1: Diagram of the article selection process. Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

Studies considered for re-analysis

The study of Müller et. al., (1991)

Müller et. al. (Müller et al., 1991) investigated the presence of HCMV in human kidneys and its contribution to the pathogenesis of IgA nephropathy by PCR amplification of a HCMV DNA fragment of *the immediate early gene* as described by Einsele (Einsele et al., 1991). Müller et. al. (Müller et al., 1991) detected HCMV DNA in all renal biopsies from patients with IgA Nephropathy but only in 3 biopsies of 9 normal kidneys.

Table 2. The study of Müller et. al., (1991).

		IgA Nephropathy		
		Yes	No	
HCMV (PCR DNA)	Yes	10	3	13
	No	0	6	6
		10	9	19

Statistical analysis (Table 2).

Causal relationship k =	**+0,716**	95 % CI (k): (0,203 -	1,000)	IOU =	0,211
P value (k | HGD) =	**0,003**	**Chi Sq.(k) =**	**9,744**	IOI =	0,158
Odds ratio (OR) =	#DIV/0!	#DIV/0!	#DIV/0!	**p(IOU) + p(IOI)=**	**0,368**
p (SINE) =	1,000	**Chi Sq. 1(SINE) =**	**0,000**	**Chi Sq. 2(SINE) =**	**0,000**
p (IMP) =	0,842	**Chi Sq. 1(IMP) =**	**1,000**	**Chi Sq. 2(IMP) =**	**0,692**
p (SINE ^ IMP) =	0,842	**Chi Sq. 1(SINE ^IMP) =**	**1,000**	**Chi Sq. 2(SINE ^IMP) =**	**0,692**
p (EXCL) =	0,474	Chi Sq. 1(EXCL) =	10,000	Chi Sq. 2(EXCL) =	7,692

The study of Müller et al. (1992)

The presence of human cytomegalovirus in the renal tissue of IgAN has been investigated while using a variety of different techniques. As one of the consequences, conflicting results have been reported in literature. However, Müller et al. (Müller et al., 1992) detected in a second study HCMV-DNA in 14 of 19 analyzed frozen renal biopsies from patients with IgAN but only in 4 of 18 frozen normal kidneys.

Table 3. The study of Müller et al. (1992).

		IgA Nephropathy		
		Yes	No	
HCMV (PCR DNA)	Yes	14	**4**	18
	No	**5**	14	19
		19	18	37

Statistical analysis (Table 3).

Causal relationship k =	**+0,515**	95 % CI (k): (0,147-	0,882)	IOU =	0,000
P value (k | HGD) =	**0,002**	**Chi Sq.(k) =**	**9,799**	IOI =	0,027
Odds ratio (OR) =	9,800	95 % CI (OR): (2,167 -	44,324)	**p(IOU) + p(IOI)=**	**0,027**
p (SINE) =	0,865	**Chi Sq. 1(SINE) =**	**1,316**	**Chi Sq. 2(SINE) =**	**1,316**
p (IMP) =	0,892	**Chi Sq. 1(IMP) =**	**0,889**	**Chi Sq. 2(IMP) =**	**0,889**
p (SINE ^ IMP) =	0,757	**Chi Sq. 1(SINE ^IMP) =**	**2,205**	**Chi Sq. 2(SINE ^IMP) =**	**2,205**
p (EXCL) =	0,622	Chi Sq. 1(EXCL) =	10,316	Chi Sq. 2(EXCL) =	10,889

The study of Gregory et al., (1988)

In contrast to the study of Müller et al., the in situ hybridization technique used by Okamura et al. (Okamura et al., 1989) was not able to solve the problem of the cause of IgA Nephropathy. Gregory et al. investigated renal deposition of cytomegalovirus antigen in renal biopsy

specimens from patients with immunoglobulin-A nephropathy and in renal biopsy specimens from patients with various other glomerular disorders "by indirect immunofluorescence microscopy with three different heterologous antibodies directed against cytomegalovirus" (Gregory et al., 1988). Gregory et al. detected mesangial staining with cytomegalovirus antiserum *in all 31 IgA Nephropathy samples* whereas no sample from 37 control group patients with other forms of glomerulonephritis was positive.

Table 4. The study of Gregory et. al., (1988).

		IgA Nephropathy		
		Yes	No	
HCMV (Antibodies)	Yes	31	**0**	31
	No	**0**	37	37
		31	37	68

Statistical analysis (Table 4).

Causal relationship k =	**+1,000**	95 % CI (k): (0,729-	1,000)	IOU =	**-0,088**
P value (k | HGD) =	**0,000**	**Chi Sq.(k) =**	**68,000**	IOI =	**0,000**
Odds ratio (OR) =	#DIV/0!	#DIV/0!	#DIV/0!	**p(IOU) + p(IOI)=**	**0,088**
p (SINE) =	1,000	**Chi Sq. 1(SINE) =**	0,000	**Chi Sq. 2(SINE) =**	0,000
p (IMP) =	1,000	**Chi Sq. 1(IMP) =**	0,000	**Chi Sq. 2(IMP) =**	0,000
p (SINE ^ IMP) =	1,000	**Chi Sq. 1(SINE ^IMP) =**	0,000	**Chi Sq. 2(SINE ^IMP) =**	0,000
p (EXCL) =	0,544	Chi Sq. 1(EXCL) =	31,000	Chi Sq. 2(EXCL) =	31,000

The study of Liu et al., (1992)

Liu (Liu, 1992) analyzed the sera of patients with IgAN for the presence of CMV-DNA with polymerase chain reaction and detected serum CMV-DNA in 9/20 in IgAN patients and only in 2/20 controls.

Table 5. The study of Liu et al., (1992).

		IgA Nephropathy		
		Yes	No	
HCMV (SERUM PCR DNA)	Yes	9	**2**	11
	No	**11**	18	29
		20	20	40

Statistical analysis (Table 5).

Causal relationship k =	**+0,392**	95 % CI (k): (0,038 -	0,745)	IOU =	-0,225
P value (k | HGD) =	**0,014**	**Chi Sq.(k) =**	**6,144**	IOI =	0,225
Odds ratio (OR) =	7,364	95 % CI (OR): (1,337-	40,549)	**p(IOU) + p(IOI)=**	**0,450**
p (SINE) =	0,725	Chi Sq. 1(SINE) =	6,050	Chi Sq. 2(SINE) =	4,172
p (IMP) =	0,950	**Chi Sq. 1(IMP) =**	**0,200**	**Chi Sq. 2(IMP) =**	**0,364**
p (SINE ^ IMP) =	0,675	Chi Sq. 1(SINE ^IMP) =	6,250	Chi Sq. 2(SINE ^IMP) =	4,536
p (EXCL) =	0,775	Chi Sq. 1(EXCL) =	4,050	Chi Sq. 2(EXCL) =	7,364

Studies not considered for re-analysis

The study of Park et al. (1994)

Park et al. (Park et al., 1994) investigated the presence of HCMV DNA in 10 IgAN and 14 non-IgAN renal tissues by amplifying a fragment of the immediate early gene of HCMV and indirect immunofluorescence staining with anti-CMV antibody. Park et al. detected HCMV DNA in 6 of 10 IgAN tissues and 10 of 14 other GN by polymerase chain reaction.

Table 6. The study of Park et al., (1994).

		IgA Nephropathy		
		Yes	No	
HCMV (PCR DNA)	Yes	6	10	16
	No	4	4	8
		10	14	24

Statistical analysis (Table 6).

Causal relationship k =	**-0,120**	95 % CI (k): (-0,576 -	0,337)	IOU =	0,083
P value (k | HGD) =	0,286	Chi Sq.(k) =	0,343	IOI =	0,250
Odds ratio (OR) =	0,600	95 % CI (OR): (0,108 -	3,338)	**p(IOU) + p(IOI)=**	**0,333**
p (SINE) =	0,833	**Chi Sq. 1(SINE) =**	**1,600**	**Chi Sq. 2(SINE) =**	**2,000**
p (IMP) =	0,583	Chi Sq. 1(IMP) =	7,143	Chi Sq. 2(IMP) =	6,250
p (SINE ^ IMP) =	0,417	Chi Sq. 1(SINE ^IMP) =	8,743	Chi Sq. 2(SINE ^IMP) =	8,250
p (EXCL) =	0,750	**Chi Sq. 1(EXCL) =**	**3,600**	**Chi Sq. 2(EXCL) =**	**2,250**

The study design of the study of Park et al. was suitable for a re-analysis (IOU =0,083; IOI = +0,250; p(IOU) + p(IOI)=0,333). However, the data published by Park et al. were self-contradictory. The *causal relationship* is *k* = - 0,12 and not significant (P value (k | HGD) = 0,286). The *exclusion relationship* was significant (p (EXCL) = 0,750; Chi Sq. 1(EXCL) =3,600; Chi Sq. 2(EXCL) = 2,250). **A low IOI or p(IOI) is necessary to test the data for an exclusion relationship**. The study of Park et al. has an IOI = 0,25. Thus far, the study of Park et al. could be used to test the data for the existence of an exclusion relationship. Finally, the study of Park et al. demands us to accept that a HCMV infection excludes IgA Nephropathy and vice versa. **However, the same data support the hypothesis, *without* HCMV infection of renal tissues *no* IgAN (p (SINE) =0,833; Chi Sq. 1(SINE) =1,600; Chi Sq. 2(SINE) = 2,000)**, while IOU = 0,08 and is very appropriate to test the data for a conditio sine qua non relationship. At the end, this is a contradiction. Mathematically, it is necessary, that the causal relationship k is positive (k > + 0) if there is a significant conditio sine qua non relationship but this is not the case. Therefore, the data of Park et al. cannot be used for a re-analysis.

The study of Kadereit et al. (1992)

Kadereit et al. (Kadereit et al., 1992) used the polymerase chain reaction to detect cytomegalovirus genome in renal biopsies.

Table 7. The study of Kadereit et al., (1992).

		IgA Nephropathy		
		Yes	No	
HCMV (PCR DNA)	Yes	3	8	11
	No	1	18	19
		4	26	30

Statistical analysis (Table 7).

Causal relationship k =	**+0,312**	95 % CI (k): (-0,096-	0,720	IOU =	-0,500
P value (k | HGD) =	**0,114**	**Chi Sq.(k) =**	**2,921**	IOI =	0,233
Odds ratio (OR) =	6,750	95 % CI (OR): (0,605 -	75,274	**p(IOU) + p(IOI)=**	**0,733**
p (SINE) =	0,967	**Chi Sq. 1(SINE) =**	**0,250**	**Chi Sq. 2(SINE) =**	**0,053**
p (IMP) =	0,733	**Chi Sq. 1(IMP) =**	**2,462**	**Chi Sq. 2(IMP) =**	**5,818**
p (SINE ^ IMP) =	0,700	**Chi Sq. 1(SINE ^IMP) =**	**2,712**	**Chi Sq. 2(SINE ^IMP) =**	**5,871**
p (EXCL) =	0,900	**Chi Sq. 1(EXCL) =**	**2,250**	**Chi Sq. 2(EXCL) =**	**0,818**

The study design of the study of Kadereit et al. (Kadereit et al., 1992) was not really suitable for a re-analysis (IOU = -0,500; IOI = +0,233; p(IOU) + p(IOI)= 0,733) while the data published were self-contradictory too. The *causal relationship* is *k* = +0,312 and not significant (P value (k | HGD) = 0,114). However, the exclusion relationship was significant (p (EXCL) =0,900; Chi Sq. 1 (EXCL)= 2,250; Chi Sq. 2(EXCL) = 0,818). This is a contradiction. Mathematically, it is necessary, that the causal relationship k is negative (k < + 0) if a significant exclusion relationship is given which this is not the case. Therefore, the data of Kadereit et al. cannot be used for a re-analysis even if the conditio sine qua non relationship is significant ((p (SINE) =0,967; Chi Sq. 1(SINE) =0,250; Chi Sq. 2(SINE) =0,053)).

Methods

Definitions

Definition 1. (The 2x2 Table)

Karl Pearson (K. Pearson, 1904) introduced in 1904 the notion of a contingency table (I. Barukčić, 2019a, 2019c) or two by two table. Especially the relationships between Bernoulli (i. e. Binomial) distributed random variables can be examined by contingency tables. Thus far, let a Bernoulli distributed random variable A_t occur/exist et cetera with the probability $p(A_t)$ at the

Bernoulli trial (period of time) t. Furthermore, let another Bernoulli distributed random variable B_t occur/exist et cetera with the probability $p(B_t)$ at the same Bernoulli trial (period of time) t. Let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 8**) may show the relationships in more details.

Table 8. The probabitlities of a contingency table

		Conditioned B		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	$p(a_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A_t})$
	Total	$p(B_t)$	$p(\underline{B_t})$	**1**

In this context, it is *per definitionem*

$$\begin{array}{ccccc} p(A_t) & \equiv & p(a_t)+p(b_t) & = & 1-p(\underline{A_t}) \\ p(B_t) & \equiv & p(a_t)+p(c_t) & = & 1-p(\underline{B_t}) \\ p(a_t) & \equiv & p(A_t \cap B_t) & = & 1-p(b_t)-p(c_t)-p(d_t) \\ +1 & \equiv & p(A_t)+p(\underline{A_t}) & = & p(B_t)+p(\underline{B_t}) \\ +1 & \equiv & p(a_t)+p(b_t) & + & p(c_t)+p(d_t) \\ p(B_t)+p(\Lambda_t) & \equiv & p(A_t) & = & 1-p(\underline{B_t})+p(\Lambda_t) \\ p(\underline{A_t}) & = & 1-\left(1-p(\underline{B_t})+p(\Lambda_t)\right) & = & p(\underline{B_t})-p(\Lambda_t) \\ p(\Lambda_t) & = & p(A_t)-p(B_t) & = & p(b_t)-p(c_t) \\ p(b_t)+p(c_t) & = & \left(2\times p(c_t)\right)+p(\Lambda_t) & = & 1-p(a_t)-p(d_t) \end{array} \quad (1)$$

while +1 denotes *the normalized sample space* of A_t and B_t. Einstein's field equation (A. Einstein, 1916) with the cosmological "constant" Λ (Albert Einstein, 1917) term can be expressed by the tools of probability (I. Barukčić, 2016c, 2016a) theory as $\mathbf{p(B_t) + p(\Lambda_t) = 1 - p(\underline{B_t}) + p(\Lambda_t) = p(A_t)}$ at each point in space-time t while $\mathbf{p(a_t)}$, $\mathbf{p(b_t)}$, $\mathbf{p(c_t)}$ **and** $\mathbf{p(d_t)}$ may denote the four basic fields of nature. There are circumstances were *the probability of an event is constant from trial to trial* (i. e. Binomial distribution), the relationships above simplifies. We obtain some of the following relationships *per definitionem*

$$
\begin{aligned}
A &\equiv n \times p(a_t) + n \times p(b_t) &&= n \times p(A_t) \\
B &\equiv n \times p(a_t) + n \times p(c_t) &&= n \times p(B_t) \\
a &\equiv n \times p(a_t) &&= n \times p(A_t \cap B_t) \\
b &\quad\; n \times p(b_t) \\
c &\quad\; n \times p(c_t) \\
d &\quad\; n \times p(d_t) \\
n &\equiv n \times p(a_t) + n \times p(b_t) &&+ n \times p(c_t) + n \times p(d_t) \\
n &\equiv n \times p(A_t) + n \times p(\underline{A}_t) &&= n \times p(B_t) + n \times p(\underline{B}_t)
\end{aligned}
\tag{2}
$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 9**). The relationships are valid even under conditions where n = 1.

Table 9. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A (risk factor)	Yes =+1	a	b	A
	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2. Index of unfairness

T*he index of unfairness* (IOU) is defined as

$$IOU \equiv \left(\left(\frac{A + B}{n}\right) - 1\right) \tag{3}$$

Definition 3. Index of independence (IOI)

The index of independence (IOI) is defined as

$$IOI \equiv \left(\left(\frac{A + \underline{B}}{n}\right) - 1\right) \tag{4}$$

Definition 4. Sufficient Condition (Conditio per Quam)

The *sufficient* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (*conditio per quam*) of a population is defined (I. Barukčić, 2019a, 2019c) as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{(a_t) + (c_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(B_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{A}_t) \\ &\equiv +1. \end{aligned} \tag{5}$$

and is used to prove the hypothesis: *if* A_t *then* B_t or is taken to express that *the occurrence of an event* A_t *is a sufficient condition for existence or occurrence of an event* B_t. Sufficient and necessary conditions are converse relations (I. Barukčić, 2019a, 2019c).

Definition 5. The X² Test of Goodness of Fit of a Sufficient Condition

Under certain circumstances, the X^2 test of goodness-of-fit is an appropriate method for testing the null hypothesis that a random sample of observations comes from a specific distribution (i.e. the distribution of a sufficient condition) against the alternative hypothesis that the data have some other distribution (I. Barukčić, 2019a, 2019c). The additive property of X^2 distribution is of special importance in this context. The applicability of using the Pearson chi-squared statistic including Yate's continuity correction (I. Barukčić, 2019a, 2019c) are widely discussed in literature. Especially, the need of incorporating Yate's continuity correction into the calculation of the X^2 value is very controversial. Thus far, only due to formal reasons, in the following, the use of *the continuity correction* is assured. The chi-square value of a conditio per quam relationship is derived (I. Barukčić, 2019a, 2019c) as

$$X^2\left((A \rightarrow B)|A\right) \equiv \frac{\left((b) - (1/2)\right)^2}{A} + 0 = 0 \tag{}$$

or alternatively as

$$X^2\left(\left(A \rightarrow B\right)|\underline{B}\right) \equiv \frac{\left(\left(b\right)-\left({}^{1}/_{2}\right)\right)^2}{\underline{B}}+0=0 \tag{6}$$

Definition 6. Necessary Condition (Conditio Sine Qua Non)

The self-organization of matter is governed by view basic natural laws among those is the necessary condition (conditio sine qua non) too. An event A_t which is necessary (or an essential) for some other event B_t to occur must be satisfied in order to obtain B_t (I. Barukčić, 2019a, 2019c). In this respect, let an event A_t with its own probability $p(A_t)$ at the (period of) time *t* be a necessary condition for another event B_t with its own probability $p(B_t)$. This is equivalent to say that it is impossible to have B_t without A_t. In other words, *without* A_t *no* B_t or the absence of A_t must guarantee the absence of B_t. The mathematical formula of the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (conditio sine qua non) of a population is defined (I. Barukčić, 2019a, 2019c) as

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv \frac{\left(a_t\right)+\left(b_t\right)+\left(d_t\right)}{N_t}=1 \\ &\equiv p\left(a_t\right)+p\left(b_t\right)+p\left(d_t\right) \\ &\equiv p\left(A_t\right)+p\left(d_t\right) \\ &\equiv p\left(a_t\right)+p\left(\underline{B_t}\right)=p\left(a_t\right)+\left(1-p\left(B_t\right)\right) \\ &\equiv +1. \end{aligned} \tag{7}$$

Definition 7. The X² Test of Goodness of Fit of a Necessary Condition

The chi-square value of a *conditio sine qua non* distribution (I. Barukčić, 2019a, 2019c) before changes to

$$X^2\left(\left(A \leftarrow B\right)|B\right) \equiv \frac{\left(\left(c\right)-\left({}^{1}/_{2}\right)\right)^2}{B}+0=0 \tag{8}$$

Depending upon the study design, another alternative and equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution (while using *the continuity correction*) is defined as

$$X^2\left(\left(A \leftarrow B\right)|\underline{A}\right) \equiv \frac{\left(\left(c\right)-\left({}^1/_2\right)\right)^2}{\underline{A}}+0=0 \tag{9}$$

Definition 8. Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (A_t excludes B_t and vice versa) of a population is defined (I. Barukčić, 2019a, 2019c) as

$$\begin{aligned} p\left(A_t|B_t\right) &\equiv \frac{\left(b_t\right)+\left(c_t\right)+\left(d_t\right)}{N_t}=1 \\ &\equiv p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right) \\ &\equiv p\left(b_t\right)+p\left(\underline{A}_t\right)=p\left(b_t\right)+\left(1-p\left(A_t\right)\right) \\ &\equiv p\left(c_t\right)+p\left(\underline{B}_t\right)=p\left(c_t\right)+\left(1-p\left(B_t\right)\right) \\ &\equiv +1. \end{aligned} \tag{10}$$

and used to prove the hypothesis: A_t *excludes* B_t and vice versa. Why should A_t exclude B_t and vice versa? Under which conditions can such a relationship be given?

Definition 9. The X^2 Test of Goodness of Fit of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated (I. Barukčić, 2019a, 2019c) as

$$X^2\left(\left(A|B\right)|A\right) \equiv \frac{\left(\left(a\right)-\left({}^1/_2\right)\right)^2}{A}+0=0 \tag{11}$$

Another equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution is defined (I. Barukčić, 2019a, 2019c) as

$$X^2\left(\left(A|B\right)|B\right) \equiv \frac{\left(\left(a\right)-\left({}^1/_2\right)\right)^2}{B}+0=0 \tag{12}$$

In particular, the chi square Goodness of Fit Test of the exclusion relationship provides evidence how well observed data compare with the expected theoretical distribution of an exclusion relationship (I. Barukčić, 2019a, 2019c).

Definition 10. Independence

In the case of independence (Kolmogoroff, 1933; Moivre, 1718) of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{13}$$

Definition 11. The Mathematical Formula of the Causal Relationship k (I. Barukčić, 2016b, 2018b, 2018a, 2019c; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) is defined *at every single event, at every single Bernoulli trial t*, as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - \left(p(A_t) \times p(B_t)\right)}{\sqrt[2]{p(A_t) \times \left(1 - p(A_t)\right) \times p(B_t) \times \left(1 - p(B_t)\right)}} \tag{14}$$

where A_t denotes the cause and B_t denotes the effect. The significance of causal relationship k can be tested by several methods. Under some certain circumstances, the chi-square distribution can be applied too. However, it is necessary to point out again that the mathematical formula of the causal relationship k has nothing to do *neither* with Pearson's concept of correlation *nor* with Pearson's concept of ϕ. Pearson's correlation methods are not identical with causation or correlation and causation must be distinguished, this has been proved (Sober, 2001) many times by different publications.

Definition 12. The 95% Confidence Interval of the Causal Relationship k

The 95% interval for the causal relationship k was calculated by the formula

$$\left\{ k(A_t, B_t) - \sqrt[2]{\frac{5}{n}} \;;\; k(A_t, B_t) + \sqrt[2]{\frac{5}{n}} \right\} \tag{15}$$

Definition 13. The Chi Square Distribution

The upper-tail critical values of chi-square distribution (Karl Pearson, 1900) with ν degrees of freedom df = 1 are visualized by **Table 10** . The P value denotes the probability of exceeding the critical value.

Table 10. The upper-tail critical values of chi-square distribution

(degrees of freedom: 1)

	P value	Upper tail X^2
The chi square distribution	0.1000000000	2.705543454
	0.0500000000	**3.841458821**
	0.0400000000	4.217884588
	0.0300000000	4.709292247
	0.0200000000	5.411894431
	0.0100000000	6.634896601
	0.0010000000	10.82756617
	0.0001000000	15.13670523
	0.0000100000	19.51142096
	0.0000010000	23.92812698
	0.0000001000	28.37398736
	0.0000000100	32.84125335
	0.0000000010	37.32489311
	0.0000000001	41.82145620

Data analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016b, 2016c, 2017, 2018a, 2019c; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) was used to proof the data for a causal relationship while the significance was tested by the hypergeometric distribution (HGD) and the chi-square distribution (Karl Pearson, 1900). The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* HCMV infection of renal tissues *no* IgAN. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* HCMV infection of renal tissues *then* IgAN. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, (*without* HCMV infection of renal tissues *no* IgAN) **and** (*if* HCMV infection of renal tissues *then* IgAN). The index of unfairness (I. Barukčić, 2019b) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

Results

THEOREM 1. WITHOUT HCMV INFECTION OF RENAL TISSUES NO IGA NEPHROPATHY

CLAIM.

Null-Hypothesis: HCMV infection of renal tissues is a necessary condition of IgAN.

Alternative Hypothesis: HCMV infection of renal tissues is not a necessary condition of IgAN.

PROOF.

Several studies considered for a re-analysis were able to provide a convincing evidence (Nahm, 2017) of a necessary condition relationship between HCMV and IgAN. Among these studies are the studies of Müller et al. (Müller et al., 1991), Müller et al. (Müller et al., 1992) and Gregory et al. (Gregory et al., 1988). The sample size was more or less small. The Chi square values were calculated too but the decision was based on the hypergeometric distribution. The P value of the studies analyzed (**Table 2, Table 3, Table 4, Table 5**) was less than P value < 0.02. The conclusion is justified: the null-hypothesis cannot be rejected. *Without* a HCMV infection of renal tissues *no* IgAN (P value < 0.02).

QUOD ERAT DEMONSTRANDUM.

THEOREM 2. IF HCMV INFECTION OF RENAL TISSUES THEN IGA NEPHROPATHY

CLAIM.

Null-Hypothesis: HCMV infection is a sufficient condition of IgAN.

Alternative Hypothesis: HCMV infection is not a sufficient condition of IgAN.

PROOF.

The studies re-analysis provided evidence of a sufficient condition relationship between HCMV and IgAN. Among these studies are the studies of Müller et al. (Müller et al., 1991), Müller et al. (Müller et al., 1992), Gregory et al. (Gregory et al., 1988) and Liu et al. (Liu, 1992). The sample size was, as already pointed out, more or less small. Even if the Chi square values were calculated, the decision again was based on the hypergeometric distribution. The P value of the studies analyzed (**Table 2, Table 3, Table 4, Table 5**) was again less than P value < 0.02. The conclusion is justified: the null-hypothesis cannot be rejected. *If* HCMV infection of renal tissues *then* IgAN (P value < 0.02).

QUOD ERAT DEMONSTRANDUM.

THEOREM 3. HCVM INFECTION OF RENAL TISSUES IS A NECESSARY AND SUFFICIENT CONDITION OF IGA NEPHROPATHY

CLAIM.

Null-Hypothesis: HCMV infection of renal tissues is a necessary and sufficient condition of IgA Nephropathy.

Alternative-Hypothesis: HCMV infection of renal tissues is not a necessary and sufficient condition of IgA Nephropathy.

PROOF.

The studies of Müller et al. (Müller et al., 1991), Müller et al. (Müller et al., 1992), Gregory et al. (Gregory et al., 1988) were able to provide striking evidence of a necessary and sufficient condition relationship between HCMV and IgAN. The study Liu et al. (Liu, 1992) failed on this point. In point of fact, as the sample size was very small, the hypergeometric distribution was used to make the decision. The P value of the studies analyzed (**Table 2, Table 3, Table 4**) was less than P value < 0.02. The conclusion is justified: the null-hypothesis cannot be rejected. A HCMV infection of renal tissues is a necessary and sufficient condition of IgAN (P value < 0.02).

QUOD ERAT DEMONSTRANDUM.

THEOREM 4. HCMV IS THE CAUSE OF IGA NEPHROPATHY

CLAIM.

Null-Hypothesis: HCMV infection of renal tissues is not the cause of IgAN (k = 0).

Alternative Hypothesis: HCMV infection of renal tissues is the cause of IgAN (k ≠ 0).

PROOF.

The studies (**Table 2, Table 3, Table 4, Table 5**) of Müller et al. (Müller et al., 1991), Müller et al. (Müller et al., 1992), Gregory et al. (Gregory et al., 1988) and Liu et al. (Liu, 1992) were able to provide evidence of statistically significant cause-effect relationship between HCMV and IgAN. Especially the studies (**Table 2, Table 3, Table 4**) of Müller et al. (Müller et al., 1991), Müller et al. (Müller et al., 1992), Gregory et al. (Gregory et al., 1988) were very impressive on this point. Based on the studies analyzed, there is a (highly) significant causal relationship k between HCMV and IgAN. In point of fact, the conclusion is inescapable: ***HCMV infection of renal tissues is the cause of IgAN***.

QUOD ERAT DEMONSTRANDUM.

Discussion

Many times, it is almost impossible to study the entire population (Nayak, 2010) to find a solution to a particular medical problem. Most investigations rely on studies which are performed on limited subjects drawn from a certain population known as “sample population”. Determining the optimal sample size for a study by appropriate sample size calculation (Kadam

& Bhalerao, 2010) methods is of great importance because the sample size of a study can have influence on the research outcomes. In general, the minimum power of a study required is 80% (Suresh & Chandrashekara, 2012) and it is known that the power of the study increases with an increase in sample size. However, very large samples may transform clinically insignificant small differences into statistically significant differences (Faber & Fonseca, 2014) which can imply a total waste of (taxpayer) money. A sample smaller than the ideal increases the chance of assuming as true a false premise. Thus far, a sample should not be excessive and, contrary to what one might think, should not be small. An adequate and optimal sample size is able to minimize the random error. The sample size of the studies re-analyzed is small and due to this fact, one might think that the studies are not able to answer the research question or are of questionable validity or provided only an imprecise answer. Furthermore, the polymerase-chain reaction (PCR) technology used was not standardized, the specificity of the primers used in PCR was different. Differences in the specimens and the degradation of small amounts of DNA by the fixation procedures may have influenced the results. However, and besides of some of the difficulties mentioned, the evidence (**Table 2, Table 3, Table 4, Table 5**) provided by the studies considered for re-analyses cannot be ignored.

The role of cytomegalovirus in the pathogenesis of this case of IgA nephropathy is supported indirectly by several drug studies. Ortmanns et al. (Ortmanns et al., 1998) reported a case of IgA nephropathy associated with a cytomegalovirus infection. The renal function improved during immunosuppressive CMV therapy. Following discontinuation of antiviral CMV therapy a rapid deterioration of renal function reoccurred again. The antiviral CMV therapy was restarted and, again, serum creatinine fell quickly. IgA nephropathy patients treated by Lou et al. (Lou et al., 2006) with *Leflunomide* achieved a complete remission rate of about 62.1% while proteinuria significantly decreased. Rong and Liou (Rong & Liu, 2007) investigated the effects of *Leflunomide* therapy for refractory IgA nephropathy and provided evidence that *Leflunomide* therapy significantly improved proteinuria. IgAN is a slowly progressive disease with variable course. We et al. (Wu et al., 2016) provided evidence that *Leflunomide*, a drug effective against HCMV (Avery et al., 2010; Gokarn et al., 2019; John et al., 2004; Sudarsanam et al., 2006) too, is decreasing proteinuria in certain IgAN patients. Min et al. (Min et al., 2017) investigated biopsy-proved primary IgA nephropathy patients treated with *Leflunomide* and documented a greater reduction of proteinuria during long-term follow-up in *Leflunomide* treated patients than in patients treated with corticosteroids. The results of this review and meta-analysis are encouraging. Due to the small sample size of the studies analyzed, the results should be treated as preliminary, as a pre-test or a kind of a pilot study which justifies a greater and major randomized study.

Conclusion

In summary, the results of this study demand us to accept that *a human cytomegalovirus infection of renal tissues is the cause of IgA Nephropathy*.

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References

Avery, R. K., Mossad, S. B., Poggio, E., Lard, M., Budev, M., Bolwell, B., … Yen-Lieberman, B. "Utility of leflunomide in the treatment of complex cytomegalovirus syndromes." *Transplantation* 90.4 (2010): 419–426. https://doi.org/10.1097/TP.0b013e3181e94106. [PMID: 20683281]

Barukčić, I. Die Kausalität. 1. Aufl. Hamburg: Wiss.-Verl.

Barukčić, I. Die Kausalität. 2., völlig überarb. Aufl. Wilhelmshaven: Scientia.

Barukčić, I. Die Kausalität. Reprint of first Edition 1989. Norderstedt: Books on Demand.

Barukčić, I. "Epstein-barr virus is the cause of multiple sclerosis." *International Journal of Current Medical and Pharmaceutical Research* 4.9 (A) (2018): 3674–3682. https://doi.org/10.24327/23956429.ijcmpr20180538.

Barukčić, I. "Helicobacter Pylori is the Cause of Gastric Cancer." *Modern Health Science* 1.1 (2018): 43–50. https://doi.org/10.30560/mhs.v1n1p43.

Barukčić, I. "Human papillomavirus is the cause of human prostate cancer." *Journal of Drug Delivery and Therapeutics* 9.4-s (2019): 577–588. https://doi.org/10.22270/jddt.v9i4-s.3385.

Barukčić, I. "Human Papillomavirus—The Cause of Human Cervical Cancer." *Journal of Biosciences and Medicines* 06.04 (2018d): 106–125. https://doi.org/10.4236/jbm.2018.64009.

Barukčić, I. "Index of Unfairness." *Modern Health Science* 2.1 (2019): p22. https://doi.org/10.30560/mhs.v2n1p22.

Barukčić, I. "Smoking of tobacco is the cause of human lung cancer." *Journal of Drug Delivery and Therapeutics* 9.1-s (2019): 148–160. https://doi.org/10.22270/jddt.v9i1-s.2273.

Barukčić, I. "The Geometrization of the Electromagnetic Field." *Journal of Applied Mathematics and Physics* 04.12 (2016): 2135–2171. https://doi.org/10.4236/jamp.2016.412211.

Barukčić, I. “The Mathematical Formula of the Causal Relationship k.” *International Journal of Applied Physics and Mathematics* 6.2 (2016): 45–65. https://doi.org/10.17706/ijapm.2016.6.2.45-65.

Barukčić, I. “Unified Field Theory.” *Journal of Applied Mathematics and Physics* 04.08 (2016): 1379–1438. https://doi.org/10.4236/jamp.2016.48147.

Barukčić, K., & Barukčić, I. “Epstein Barr Virus—The Cause of Multiple Sclerosis.” *Journal of Applied Mathematics and Physics* 04.06 (2016): 1042–1053. https://doi.org/10.4236/jamp.2016.46109.

Barukčić, K., Barukčić, J. P., & Barukčić, I. “Epstein-Barr virus is the cause of rheumatoid arthritis.” *Romanian journal of rheumatology* 27.4 (2018): 148–163. Retrieved from https://view.publitas.com/amph/rjr_2018_4_art-02/page/1.

Béné, M. C., Tang, J. Q., & Faure, G. C. “Absence of cytomegalovirus DNA in kidneys in IgA nephropathy.” *Lancet (London, England)* 335.8693 (1990): 868. https://doi.org/10.1016/0140-6736(90)90993-f. [PMID: 1969602]

Berger, J., & Hinglais, N. “Les depôts intercapillaires d’IgA-IgG (English: Intercapillary deposits of IgA-IgG).” *Journal D’urologie Et De Nephrologie* 74.9 (1968): 694–695. [PMID: 4180586]

Donadio, J. V., & Grande, J. P. “IgA nephropathy.” *The New England Journal of Medicine* 347.10 (2002): 738–748. https://doi.org/10.1056/NEJMra020109. [PMID: 12213946]

Dueymes, M., Mignon-Conté, M., Dueymes, J. M., Vernier, I., & Conte, J. J. “Mesangial staining with cytomegalovirus antibodies in IgA nephropathy.” *Lancet (London, England)* 1.8638 (1989): 619. https://doi.org/10.1016/s0140-6736(89)91648-6. [PMID: 2466185]

Einsele, H., Steidle, M., Vallbracht, A., Saal, J. G., Ehninger, G., & Müller, C. A. “Early occurrence of human cytomegalovirus infection after bone marrow transplantation as demonstrated by the polymerase chain reaction technique.” *Blood* 77.5 (1991): 1104–1110. [PMID: 1847311]

Einstein, A. “Die Grundlage der allgemeinen Relativitätstheorie.” *Annalen der Physik* 354 (1916): 769–822. https://doi.org/10.1002/andp.19163540702.

Einstein, Albert. “Kosmologische Betrachtungen zur allgemeinen Relativitätstheorie.” *Sitzungsberichte der Königlich Preußischen Akademie der Wissenschaften (Berlin), Seite 142-152.* (1917). Retrieved from http://adsabs.harvard.edu/abs/1917SPAW.....142E.

Faber, J., & Fonseca, L. M. "How sample size influences research outcomes." *Dental Press Journal of Orthodontics* 19.4 (2014): 27–29. https://doi.org/10.1590/2176-9451.19.4.027-029.ebo. [PMID: 25279518] [PMCID: PMC4296634]

Feehally, J., & Cameron, J. S. "IgA nephropathy: progress before and since Berger." *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation* 58.2 (2011): 310–319. https://doi.org/10.1053/j.ajkd.2011.03.024. [PMID: 21705126]

Gokarn, A., Toshniwal, A., Pathak, A., Arora, S., Bonda, A., Punatar, S., … Khattry, N. "Use of Leflunomide for Treatment of Cytomegalovirus Infection in Recipients of Allogeneic Stem Cell Transplant." *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation* (2019). https://doi.org/10.1016/j.bbmt.2019.04.028. [PMID: 31054984]

Gregory, M. C., Hammond, M. E., & Brewer, E. D. "Renal deposition of cytomegalovirus antigen in immunoglobulin - A nephropathy." *Lancet (London, England)* 1.8575–6 (1988): 11–14. https://doi.org/10.1016/s0140-6736(88)91000-8. [PMID: 2891887]

Haas, M. "Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases." *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation* 29.6 (1997): 829–842. https://doi.org/10.1016/s0272-6386(97)90456-x. [PMID: 9186068]

Hessen, J. Das Kausalprinzip. Augsburg: Filser.

Hung, K. Y., Chen, W. Y., Yen, T. S., Yang, C. S., Ferng, S. H., & Kao, C. L. "Adult primary IgA nephropathy and common viral infections." *The Journal of Infection* 32.3 (1996): 227–230. [PMID: 8793713]

John, G. T., Manivannan, J., Chandy, S., Peter, S., & Jacob, C. K. "Leflunomide therapy for cytomegalovirus disease in renal allograft recepients." *Transplantation* 77.9 (2004): 1460–1461. https://doi.org/10.1097/01.tp.0000122185.64004.89. [PMID: 15167608]

Kadam, P., & Bhalerao, S. "Sample size calculation." *International Journal of Ayurveda Research* 1.1 (2010): 55–57. https://doi.org/10.4103/0974-7788.59946. [PMID: 20532100] [PMCID: PMC2876926]

Kadereit, S., Michelson, S., Mougenot, B., Thibault, P., Verroust, P. J., Mignon, F., … Ronco, P. M. "Polymerase chain reaction detection of cytomegalovirus genome in renal biopsies." *Kidney International* 42.4 (1992): 1012–1016. https://doi.org/10.1038/ki.1992.381. [PMID: 1333545]

Kolmogoroff, A. Grundbegriffe der Wahrscheinlichkeitsrechnung. https://doi.org/10.1007/978-3-642-49888-6.

Korch, H. Das Problem der Kausalität. Berlin: Dt. Verlag der Wissenschaften.

Kunimoto, M., Hayashi, Y., Kuki, K., Mune, M., Yamada, Y., Tamura, S., … Samukawa, T. "Analysis of viral infection in patients with IgA nephropathy." *Acta Oto-Laryngologica. Supplementum* 508 (1993): 11–18. [PMID: 8285037]

Lai, F. M., Tam, J. S., Lo, S. T., & Lai, K. N. "Cytomegalovirus antigens in IgA nephropathy: fact or artefacts?" *Nephron* 55.1 (1990): 87–88. https://doi.org/10.1159/000185928. [PMID: 2162010]

Liu, Z. "Cytomegalovirus-DNA in serum and renal tissue of patients with IgA nephropathy (Article in Chinese)." *Zhonghua Yi Xue Za Zhi* 72.4 (1992): 198–200, 253. [PMID: 1327445]

Lou, T., Wang, C., Chen, Z., Shi, C., Tang, H., Liu, X., … Yu, X. "Randomised controlled trial of leflunomide in the treatment of immunoglobulin A nephropathy." *Nephrology (Carlton, Vic.)* 11.2 (2006): 113–116. https://doi.org/10.1111/j.1440-1797.2006.00547.x. [PMID: 16669971]

McGrogan, A., Franssen, C. F. M., & de Vries, C. S. "The incidence of primary glomerulonephritis worldwide: a systematic review of the literature." *Nephrology Dialysis Transplantation* 26.2 (2011): 414–430. https://doi.org/10.1093/ndt/gfq665.

Min, L., Wang, Q., Cao, L., Zhou, W., Yuan, J., Zhang, M., … Ni, Z. "Comparison of combined leflunomide and low-dose corticosteroid therapy with full-dose corticosteroid monotherapy for progressive IgA nephropathy." *Oncotarget* 8.29 (2017): 48375–48384. https://doi.org/10.18632/oncotarget.16468. [PMID: 28415636] [PMCID: PMC5564655]

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." *Annals of internal medicine* 151.4 (2009): 264–964. [PMID: 19622511]

Moivre, A. de [1667-1754]. The Doctrine of Chances or a Method of Calculating the Probability of Events in Play. https://doi.org/10.3931/e-rara-10420.

Müller, G. A., Kühn, W., Müller, C. A., Risler, T., Bohle, A., & Markovic-Lipkovski, J. "Detection of human cytomegalovirus-DNA in IgA nephropathy." *Nephron* 57.3 (1991): 383–384. https://doi.org/10.1159/000186298. [PMID: 1850119]

Müller, G. A., Müller, C. A., Engler-Blum, G., Kühn, W., Risler, T., Bohle, A., & Markovic-Lipkovski, J. "Human cytomegalovirus in immunoglobulin A nephropathy: detection by

polymerase chain reaction." *Nephron* 62.4 (1992): 389–393. https://doi.org/10.1159/000187086. [PMID: 1338641]

Nagy, J., Haikin, H., Sarov, B., Háber, A., Kun, L., & Sarov, I. "Altered humoral immunity against cytomegalovirus and Epstein-Barr virus without detectable virus antigens and virus-DNA in the glomeruli of patients with IGA nephropathy in remission phase." *Acta Microbiologica Et Immunologica Hungarica* 42.2 (1995): 179–187. [PMID: 7551711]

Nahm, F. S. "What the P values really tell us." *The Korean Journal of Pain* 30.4 (2017): 241–242. https://doi.org/10.3344/kjp.2017.30.4.241. [PMID: 29123617] [PMCID: PMC5665734]

Najafi, S., Ghane, M., Poortahmasebi, V., Jazayeri, S. M., & Yousefzadeh-Chabok, S. "Prevalence of Cytomegalovirus in Patients With Multiple Sclerosis: A Case-Control Study in Northern Iran." *Jundishapur Journal of Microbiology* 9.7 (2016): e36582. https://doi.org/10.5812/jjm.36582. [PMID: 27679707] [PMCID: PMC5035392]

Nayak, B. K. "Understanding the relevance of sample size calculation." *Indian Journal of Ophthalmology* 58.6 (2010): 469–470. https://doi.org/10.4103/0301-4738.71673. [PMID: 20952828] [PMCID: PMC2993974]

Okamura, M., Kanayama, Y., Negoro, N., Takeda, T., & Inoue, T. "Failure to detect cytomegalovirus-DNA in IgA nephropathy by in-situ hybridisation." *Lancet (London, England)* 1.8649 (1989): 1265. https://doi.org/10.1016/s0140-6736(89)92358-1. [PMID: 2566805]

Ortmanns, A., Ittel, T. H., Schnitzler, N., Handt, S., Helmchen, U., & Sieberth, G. "Remission of IgA nephropathy following treatment of cytomegalovirus infection with ganciclovir." *Clinical Nephrology* 49.6 (1998): 379–384. [PMID: 9696435]

Palevsky, P. M., Liu, K. D., Brophy, P. D., Chawla, L. S., Parikh, C. R., Thakar, C. V., … Weisbord, S. D. "KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury." *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation* 61.5 (2013): 649–672. https://doi.org/10.1053/j.ajkd.2013.02.349. [PMID: 23499048]

Park, J. S., Song, J. H., Yang, W. S., Kim, S. B., Kim, Y. K., & Hong, C. D. "Cytomegalovirus is not specifically associated with immunoglobulin A nephropathy." *Journal of the American Society of Nephrology: JASN* 4.8 (1994): 1623–1626. [PMID: 8025236]

Pearson, K. On the theory of contingency and its relation to association and normal correlation. London: Dulau and Co.

Pearson, Karl. “X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling.” *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 50.302 (1900): 157–175.

Priel, E., Wohl, A., Teperberg, M., Nass, D., & Cohen, Z. R. “Human cytomegalovirus viral load in tumor and peripheral blood samples of patients with malignant gliomas.” *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia* 22.2 (2015): 326–330. https://doi.org/10.1016/j.jocn.2014.06.099. [PMID: 25443081]

Roberts, I. S. D. “Pathology of IgA nephropathy.” *Nature Reviews. Nephrology* 10.8 (2014): 445–454. https://doi.org/10.1038/nrneph.2014.92. [PMID: 24861083]

Rong, L., & Liu, Z. “Effects of leflunomide combined with hormone therapy for refractory IgA nephropathy (Article in Chinese).” *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University* 27.6 (2007): 893–894. [PMID: 17584664]

Sober, E. “Venetian Sea Levels, British Bread Prices, and the Principle of the Common Cause.” *The British Journal for the Philosophy of Science* 52.2 (2001): 331–346.

Sudarsanam, T. D., Sahni, R. D., & John, G. T. “Leflunomide: a possible alternative for gangciclovir sensitive and resistant cytomegalovirus infections.” *Postgraduate Medical Journal* 82.967 (2006): 313–314. https://doi.org/10.1136/pgmj.2005.038521. [PMID: 16679469] [PMCID: PMC2563786]

Suresh, K., & Chandrashekara, S. “Sample size estimation and power analysis for clinical research studies.” *Journal of Human Reproductive Sciences* 5.1 (2012): 7–13. https://doi.org/10.4103/0974-1208.97779. [PMID: 22870008] [PMCID: PMC3409926]

Tomino, Y., Yagame, M., Suga, T., Miura, M., Endoh, M., Nomoto, Y., & Sakai, H. “Detection of viral antigens in patients with IgA nephropathy.” *Japanese Journal of Medicine* 28.2 (1989): 159–164. [PMID: 2543852]

Wu, J., Duan, S.-W., Sun, X.-F., Li, W.-G., Wang, Y.-P., Liu, W.-H., … Chen, X.-M. “Efficacy of Leflunomide, Telmisartan, and Clopidogrel for Immunoglobulin A Nephropathy: A Randomized Controlled Trial.” *Chinese Medical Journal* 129.16 (2016): 1894–1903. https://doi.org/10.4103/0366-6999.187848. [PMID: 27503012] [PMCID: PMC4989418]

Yi, F., Zhao, J., Luckheeram, R. V., Lei, Y., Wang, C., Huang, S., … Xia, B. “The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan, Central China.” *Virology Journal* 10.1 (2013): 43. https://doi.org/10.1186/1743-422X-10-43.