



ORIGINAL RESEARCH PAPER

Nephrology

UTERINE CERVICAL CANCER AND HEMODIALYSIS

KEY WORDS: uterine, cervical, cancer, hemodialysis

**Montes de Oca
Gavilanez
Lizbeth Maritza**

Independent Author

**Salinas González
Daniela Carolina**

Independent Author

**Torres Segovia
Stalin Fernando***

Independent Author*Corresponding Author

**Cevallos Lopez
Ivan Mauricio**

Independent Author

**Velasco Mora
Sofia Alejandra**

Independent Author

**Tixilema
Chimborazo Alba
Alexandra**

Independent Author

**Macias
Rivadeneira
Edgar Alexander**

Independent Author

**Ayala Brito Rosa
Guadalupe**

Independent Author

ABSTRACT

SUMMARY: cervical cancer in Ecuador is a very frequent pathology among lower class and illiterate women, the little access to health services has caused them to arrive late for cancer treatment, so much so that they present with significant vaginal bleeding and masses tumors greater than 10cm in diameter with significant intake of parametria and therefore kidney failure, the reason for the following review is to determine the benefit of dialysis treatment in patients with locally advanced cervical cancer.

INTRODUCTION

Cervical carcinoma is currently the second leading cause of cancer death in women worldwide.

The underdeveloped or developing countries of Sub-Saharan Africa, Latin America and the Caribbean, and central regions of Southeast Asia are the ones with the largest number of cases in the world.

In underdeveloped countries about 70% of these cases present as locally advanced disease and 1: 3 of them with renal failure.

In many of these cases it is difficult to offer a definitive treatment since they present in uremia as a consequence of an obstructive uropathy, this is due to external compressions or malignant invasion of the lower ureters.

Obstructive uropathy occurs on several occasions in previously treated patients who did not have evidence of a recurrent disease, however, they developed hydronephrosis due to ureteral invasion in pelvic fibrosis.

Patients may be symptomatic or asymptomatic with elevated uric acid, urea, creatinine, and electrolytes.

Urinary diversion by percutaneous nephrostomy (PCN) is the most commonly practiced technique, not only because it restores kidney function, but also because it improves quality of life and allows most patients to receive tumor-specific palliative treatment and curative treatment in some well-defined cases.

There is no defined criterion for the use of PCN in patients with advanced cervical cancer who develop obstructive uropathy, the results are unpredictable in terms of recovering renal function and the benefits obtained by administering radiotherapy, surgery or chemotherapy.

Regarding this aggravating factor, chemotherapy management is difficult since the fundamental pillar is chemotherapy based on platinum themselves, which have been shown to present nephrotoxicity.

METHODS

A bibliographic review was carried out in English and Spanish in PUBMED, Science, Latindex, of a total of 70 bibliographic reviews, the search method was validated under the Caspe tool, 35 articles that did not comply with the characteristics of the research were rejected.

NEPHROTOXIC CISPLATINUM: Neoplastic pathologies are usually managed by chemotherapy, radiotherapy or surgical schemes.

Regarding pharmacological management, nephrotoxicity from antineoplastic treatment, regardless of the type of cancer, is a factor that limits the dose and / or its continuation. According to their mechanism of action, they are classified into 3 general groups: Cytotoxic Drugs, Hormones and others that attack specific targets.

At a general level, all antineoplastic drugs can generate adverse reactions that are explained by their antiproliferative action on normal tissues, but there are also specific adverse reactions of groups and drugs, such as nephrourological alterations.

Nephrotoxicity is a process by which the kidney is affected by toxins of chemical or natural origin, acting directly or through metabolites in the kidney, it can originate from the different routes of administration.

As a consequence, they can cause kidney failure, functional loss of kidney filtering capacity, or kidney necrosis.

This is because most cytostatics reach high concentrations in this organ.

In the case of cisplatin, it accesses the proximal renal tubule through the use of a specific transporter, as it is a substrate for the organic cation transporter (OCT), this transporter has three subtypes, subtype 1 being the one located in the liver while subtype 2 is found in the basolateral membrane of the renal proximal tubules.

Also important is the role that the Cooper transporter acquires from now on Ctrl located in the adult kidney, specifically it is expressed in the cells of the basolateral membrane of the proximal tubule, which is responsible for maintaining homeostasis.

DIALYSIS AND CHEMOTHERAPY: Chemotherapy is a standard systemic treatment for malignant neoplasms, the efficacy of which has been reported in randomized studies in which an improvement in disease-free time and survival of this type of patients has been demonstrated; however, these clinical trials that demonstrate its efficacy, for the most part, include populations with normal renal function.

In this context, it is currently more common to observe nephropathic patients who develop cancer and vice versa.

Therefore, in recent years, the importance of involving Nephrology with Oncology has been valued.

There is a higher incidence of malignant neoplasms in HD patients compared to controls, and urogenital neoplasms have been observed to be the most prevalent in this population.

In addition, a recent epidemiological study evaluated the causes of mortality in patients with renal replacement therapy, among which cancer represents the third cause, with 20%, after cardiovascular events and infections.

Carcinogenesis in patients with hemodialysis could be explained by the increase in chronic oxidative stress—which damages cellular structures—the alteration of the cellular immune system, exposures to viral infections and to medications administered in these patients.

ANALYSIS

In patients with ESRD on replacement therapy, the administration of chemotherapy is not contraindicated;

however, these patients have been reported to have a high mortality rate from causes other than cancer compared to non-dialysis patients, as described by Funakoshi et al. in a retrospective study of 675 patients.

The multicenter CANDY (Cancer and Dialysis) study studied antineoplastic treatment in patients with chronic HD.

This study reported that 88% of the patients required specific management of the cytotoxic drug, 44% developed iatrogenic toxicity in relation to inappropriate dose adjustment due to the lack of management recommendations in this specific group of patients. that chemotherapy overdose was more frequently associated with hematological, gastric and neurological side effects. Since renal excretion plays an important role in the elimination of antineoplastic drugs, renal failure conditions the accumulation of the drug, which increases toxicity.

In contrast, some reports indicate a reduction in neurotoxicity in patients with non-Hodgkin lymphoma undergoing chemotherapy and with kidney failure who required HD.

The current challenge consists in establishing the role of the nephrologist when our patients on HD or acute renal failure have an indication for chemotherapy.

Above all, it must be borne in mind that each patient has a unique context: type of neoplasm, clinical stage, performance status and a type of drug indicated with established doses, specific pre- or post-HD administration time.

In daily practice, the clinical course of these patients is complex, given the little evidence in the literature on the management of cytotoxic drugs in patients with ESRD in HD: the optimal time of administration, dose adjustments based on the size of the molecule and pharmacokinetic behavior are poorly understood.

There is a small number of case series and expert opinions that do not reach a consensus on the subject, which is reflected in the few retrospective systemic reviews of some chemotherapeutic drugs that attempt to evaluate their pharmacokinetics and pharmacodynamics. In conclusion, this is a field under investigation and we must continue to study since having fibrosis due to infiltration of the parametria would require chemotherapy first and then management with radiotherapy after nephrectomy placement.

REFERENCES

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7-30. [PubMed] [Google Scholar]
- [2] Lee YS, Hsu CC, Weng SF, et al. Cancer incidence in physicians: a Taiwan national population-based cohort study. *Medicine (Baltimore)* 2015;94:e2079. [PMC free article] [PubMed] [Google Scholar]
- [3] Wang PH, Yen MS, Chao KC, et al. Outstanding female cancer research paper awards of the 2015 Taiwan Association of Obstetrics and Gynecology and Hsu Chien-Tien Cancer Foundation. *Taiwan J Obstet Gynecol* 2016;55:757-9. [PubMed] [Google Scholar]
- [4] Wang PH, Chen CP, Kuo TC. Outstanding female cancer research paper awards of the 2016 Taiwanese Association of Obstetrics and Gynecology and Hsu Chien Cancer Foundation. *Taiwan J Obstet Gynecol* 2017;56:581-2. [PubMed] [Google Scholar]
- [5] Wang PH, Chen CP, Kuo TC. Outstanding female cancer research paper awards of the Taiwanese Association of Obstetrics and Gynecology. *Taiwan J Obstet Gynecol* 2018;57:179-80. [Google Scholar]
- [6] Tanaka A, Inaguma D, Watanabe Y, et al. Relationship between mortality and cancer-bearing status in patients with chronic kidney disease who attended an educational program. *Ther Apher Dial* 2018;22:49-57. [PubMed] [Google Scholar]
- [7] Pisano A, Cernaro V, Gembillo G, et al. Xanthine oxidase inhibitors for improving renal function in chronic kidney disease patients: an updated systematic review and meta-analysis. *Int J Mol Sci* 2017;18:E2283. [PMC free article] [PubMed] [Google Scholar]
- [8] Vart P, van Zon SKR, Gansevoort RT, et al. SES, chronic kidney disease, and race in the U.S.: a systematic review and meta-analysis. *Am J Prev Med* 2017;53:730-9. [PubMed] [Google Scholar]
- [9] Bae E, Cha RH, Kim YC, et al. Circulating TNF receptors predict cardiovascular disease in patients with chronic kidney disease. *Medicine (Baltimore)* 2017;96:e6666. [PMC free article] [PubMed] [Google Scholar]
- [10] Cheng Z, Limbu MH, Wang Z, et al. MMP-2 and 9 in chronic kidney disease. *Int J Mol Sci* 2017;18:pii:E776. [Google Scholar]

[11] Tanaka A, Inaguma D, Shinjo H, et al. Relationship between mortality and cancer-bearing status at time of dialysis initiation. *Ther Apher Dial* 2017;21:345-53. [PubMed] [Google Scholar]

[12] Parrish AR. Advances in chronic kidney disease. *Int J Mol Sci* 2016;17:pii: E1314. [Google Scholar]

[13] Huang BS, Chang WH, Wang KC, et al. Endometriosis might be inversely associated with developing chronic kidney disease: a population-based cohort study in Taiwan. *Int J Mol Sci* 2016;17:pii: E1079. [PMC free article] [PubMed] [Google Scholar]

[14] Tain YL, Hsu CN. Developmental origins of chronic kidney disease: should we focus on early life. *Int J Mol Sci* 2017;18:pii: E381. [PMC free article] [PubMed] [Google Scholar]

[15] Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;88:950-7. [PMC free article] [PubMed] [Google Scholar]

[16] GBD 2013 Mortality and Cause of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death; 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117-71. [PMC free article] [PubMed] [Google Scholar]

[17] Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013;158:825-30. [PubMed] [Google Scholar]

[18] Grams ME, Yang W, Rebholz CM, et al. CRIC Study Investigators. Risks of adverse events in advanced CKD: the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2017;70:337-46. [PMC free article] [PubMed] [Google Scholar]

[19] Sahutoglu T, Sakaci T, Hasbal NB, et al. Serum VEGF-C levels as a candidate biomarker of hypervolemia in chronic kidney disease. *Medicine (Baltimore)* 2017;96:e6543. [PMC free article] [PubMed] [Google Scholar]

[20] Chien CC, Han MM, Chiu YH, et al. Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. *J Cancer* 2017;8:9-18. [PMC free article] [PubMed] [Google Scholar]

[21] Wong G, Hayward JS, McArthur E, et al. Patterns and predictors of screening for breast and cervical cancer in women with CKD. *Clin J Am Soc Nephrol* 2017;12:95-104. [PMC free article] [PubMed] [Google Scholar]

[22] Crews DC, Khaliq W. Screening women with CKD for the emperor of all maladies. *Clin J Am Soc Nephrol* 2017;12:5-6. [PMC free article] [PubMed] [Google Scholar]

[23] Wang SM, Lai MN, Chen PC, et al. Increased upper and lower tract urothelial carcinoma in patients with end-stage renal disease: a nationwide cohort study in Taiwan during 1997-2008. *Biomed Res Int* 2014;2014:149750. [PMC free article] [PubMed] [Google Scholar]

[24] Wang SM, Lai MN, Chen PC, et al. Increased risk of urothelial cancer in young and middle aged patients with end-stage renal disease. *J Formos Med Assoc* 2015;114:52-7. [PubMed] [Google Scholar]

[25] Butler AM, Olishan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. *Am J Kidney Dis* 2015;65:763-72. [PMC free article] [PubMed] [Google Scholar]

[26] Christenson A, Savage C, Sjoberg DD, et al. Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years. *Int J Cancer* 2013;133:1452-8. [PMC free article] [PubMed] [Google Scholar]

[27] Dugué PA, Rebolj M, Garred P, et al. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther* 2013;13:29-42. [PubMed] [Google Scholar]

[28] Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999;354:93-9. [PubMed] [Google Scholar]

[29] Stewart JH, Buccianti C, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003;14:197-207. [PubMed] [Google Scholar]

[30] Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. *JAMA* 2006;296:2823-31. [PubMed] [Google Scholar]

[31] Liang JA, Sun LM, Yeh JJ, et al. The association between malignancy and end-stage renal disease in Taiwan. *Jpn J Clin Oncol* 2011;41:752-7. [PubMed] [Google Scholar]

[32] Yu HC, Su NY, Huang JY, et al. Trends in the prevalence of periodontitis in Taiwan from 1997 to 2013: a nationwide population-based retrospective study. *Medicine (Baltimore)* 2017;96:e8585. [PMC free article] [PubMed] [Google Scholar]

[33] Lai SW, Lin CL, Liao KF. Population-based cohort study investigating the correlation of diabetes mellitus with pleural empyema in adults in Taiwan. *Medicine (Baltimore)* 2017;96:e7763. [PMC free article] [PubMed] [Google Scholar]

[34] Chiang JK, Lee YC, Kao YH. Trend analysis of end-of-life care between hospice and nonhospice groups of cancer patients in Taiwan for 2002-11. *Medicine (Baltimore)* 2017;96:e7825. [PMC free article] [PubMed] [Google Scholar]

[35] Lin SC, Lin HW, Chiang BL. Association of croup with asthma in children: a cohort study. *Medicine (Baltimore)* 2017;96:e7667. [PMC free article] [PubMed] [Google Scholar]

[36] Kao LT, Huang CY, Lin HC, et al. No increased risk of fracture in patients receiving antimuscarinics for overactive bladder syndrome: a retrospective cohort study. *J Clin Pharmacol* 2018; [Epub ahead of print]. [PubMed] [Google Scholar]

[37] Wang YF, Chen YT, Luo JC, et al. Proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population: a nationwide population-based study. *Am J Gastroenterol* 2017;112:1084-93. [PubMed] [Google Scholar]

[38] Hsiao KC, Huang JY, Lee CT, et al. Different impact of aspirin on renal progression in patients with predialysis advanced chronic kidney disease with or without previous stroke. *Eur J Intern Med* 2017;39:63-8. [PubMed] [Google Scholar]

[39] Chou CY, Wang SM, Liang CC, et al. Peritoneal dialysis is associated with a better survival in cirrhotic patients with chronic kidney disease. *Medicine (Baltimore)* 2016;95:e2465. [PMC free article] [PubMed] [Google Scholar]

[40] Li K, Yin R, Li Q, et al. Analysis of HPV distribution in patients with cervical precancerous lesions in Western China. *Medicine (Baltimore)* 2017;96:e7304. [PMC free article] [PubMed] [Google Scholar]

[41] Yang-Chun F, Zhen-Zhen C, Yan-Chun H, et al. Association between PD-L1 and HPV status and the prognostic value for HPV treatment in premalignant cervical lesion patients. *Medicine (Baltimore)* 2017;96:e7270. [PMC free article] [PubMed] [Google Scholar]

[42] Yang-Chun F, Yuan Z, Cheng-Ming L, et al. Increased HPV L1 gene methylation and multiple infection status lead to the difference of cervical epithelial cell lesion in different ethnic women of Xinjiang, China. *Medicine (Baltimore)* 2017;96:e6409. [PMC free article] [PubMed] [Google Scholar]

[43] Chertow GM, Paltiel AD, Owen WF, Jr, et al. Cost-effectiveness of cancer screening in end-stage renal disease. *Arch Intern Med* 1996;156:1345-50. [PubMed] [Google Scholar]

[44] Tsai HW, Huang MT, Wang PH, et al. DcR3 promotes cell adhesion and enhances endometriosis development. *J Pathol* 2018;244:189-202. [PubMed] [Google Scholar]

[45] Liu CH, Chang Y, Wang PH. Poly(ADP-ribose) polymerase (PARP) inhibitors and ovarian cancer. *Taiwan J Obstet Gynecol* 2017;56:713-4. [PubMed] [Google Scholar]

[46] Sung PL, Wen KC, Chen YJ, et al. The frequency of cancer predisposition gene mutations in hereditary breast and ovarian cancer patients in Taiwan: from BRCA1/2 to multi-gene panels. *PLoS One* 2017;12:e0185615. [PMC free article] [PubMed] [Google Scholar]

[47] Wen KC, Sung PL, Hsieh SL, et al. α 2,3-sialyltransferase type I regulates migration and peritoneal dissemination of ovarian cancer cells. *Oncotarget* 2017;8:29013-27. [PMC free article] [PubMed] [Google Scholar]

[48] Chang CM, Chiou SH, Yang MJ, et al. Gene set-based integrative analysis of ovarian clear cell carcinoma. *Taiwan J Obstet Gynecol* 2016;55:552-7. [PubMed] [Google Scholar]

[49] Teng SW, Horng HC, Ho CH, et al. Taiwan Association of Gynecology Systematic Review Group. Women with endometriosis have higher comorbidities: analysis of domestic data in Taiwan. *J Chin Med Assoc* 2016;79:577-82. [PubMed] [Google Scholar]

[50] Huang CY, Yang YC, Wang KL, et al. Possible surrogate marker for an effective dose-dense chemotherapy in treating ovarian cancer. *Taiwan J Obstet Gynecol* 2016;55:405-9. [PubMed] [Google Scholar]

[51] Chavan DM, Huang Z, Song K, et al. Incidence of venous thromboembolism following the neoadjuvant chemotherapy regimen for epithelial type of ovarian cancer. *Medicine (Baltimore)* 2017;96:e7935. [PMC free article] [PubMed] [Google Scholar]

[52] Sung PL, Jan YH, Lin SC, et al. Periostin in tumor microenvironment is associated with poor prognosis and platinum resistance in epithelial ovarian carcinoma. *Oncotarget* 2016;7:4036-47. [PMC free article] [PubMed] [Google Scholar]

[53] Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. *N Engl J Med* 2009;361:170-7. [PubMed] [Google Scholar]

[54] Moyer VA. U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2012;157:900-4. [PubMed] [Google Scholar]

[55] Reade CJ, Riva JJ, Busse JW, et al. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. *Gynecol Oncol* 2013;130:674-81. [PubMed] [Google Scholar]

[56] Murdoch J, Oram D, Rabideau DJ, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016;387:945-56. [PMC free article] [PubMed] [Google Scholar]

[57] Suh-Burgmann E, Kinney W. Potential harms outweigh benefits of indefinite monitoring of stable adnexal masses. *Am J Obstet Gynecol* 2015;213:816.e1-4. [PubMed] [Google Scholar]

[58] Chiang YC, Chen CA, Chiang CJ, et al. Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan. *J Gynecol Oncol* 2013;24:342-51. [PMC free article] [PubMed] [Google Scholar]

[59] Chang WH, Wang KC, Lee WL, et al. Endometriosis and the subsequent risk of epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2014;53:530-5. [PubMed] [Google Scholar]

[60] Lee WL, Chang WH, Wang KC, et al. The risk of epithelial ovarian cancer of women with endometriosis may be varied greatly if diagnostic criteria are different: a nationwide population-based cohort study. *Medicine (Baltimore)* 2015;94:e1633. [PMC free article] [PubMed] [Google Scholar]

[61] Wang KC, Chang WH, Lee WL, et al. An increased risk of epithelial ovarian cancer in Taiwanese women with a new surgico-pathological diagnosis of endometriosis. *BMC Cancer* 2014;14:831. [PMC free article] [PubMed] [Google Scholar]

[62] Minlikeeva AN, Freudenheim JL, Eng KH, et al. Ovarian Cancer Association Consortium; Australian Ovarian Cancer Study Group. History of comorbidities and survival of ovarian cancer patients, results from the Ovarian Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev* 2017;26:1470-3. [PMC free article] [PubMed] [Google Scholar]

[63] Doherty JA, Jensen A, Kelemen LE, et al. Epidemiology Working Group Steering Committee, Ovarian Cancer Association Consortium Members of the EWG SC, in alphabetical order. Current gaps in ovarian cancer epidemiology: the need for new population-based research. *J Natl Cancer Inst* 2017;109: doi: 10.1093/jnci/djx144. [PMC free article] [PubMed] [Google Scholar]

[64] Lai JC, Chen HH, Chu KH, et al. Nationwide trends and in-hospital complications of trachelectomy for surgically resectable cervical cancer in Taiwanese women: a population-based study, 1998-2013. *Taiwan J Obstet Gynecol* 2017;56:449-55. [PubMed] [Google Scholar]

[65] Huang CC, Huang YT, Chueh PJ, et al. The laparoscopic approach is more preferred among nurses for benign gynecologic conditions than among nonmedical working women: a nationwide study in Taiwan. *Taiwan J Obstet Gynecol* 2016;55:229-34. [PubMed] [Google Scholar]

[66] Chou CH, Lee JT, Lin CC, et al. Septicemia is associated with increased risk for dementia: a population-based longitudinal study. *Oncotarget*

- 2017;8:84300–8. [PMC free article] [PubMed] [Google Scholar]
- [67] Chang SS, Sung FC, Lin CL, et al. Association between hemorrhoid and risk of coronary heart disease: a nationwide population-based cohort study. *Medicine (Baltimore)* 2017;96:e7662. [PMC free article] [PubMed] [Google Scholar]
- [68] Hsieh MS, Chiu CS, How CK, et al. Contrast medium exposure during computed tomography and risk of development of end-stage renal disease in patients with chronic kidney disease: a nationwide population-based, propensity score-matched, longitudinal follow-up study. *Medicine (Baltimore)* 2016;95:e3388. [PMC free article] [PubMed] [Google Scholar]
- [69] Chen JS, Lu CL, Huang LC, et al. Chronic kidney disease is associated with upper tract urothelial carcinoma: a nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)* 2016;95:e3255. [PMC free article] [PubMed] [Google Scholar]
- [70] Chen CY, Dai CS, Lee CC, et al. Association between macular degeneration and mild to moderate chronic kidney disease: a nationwide population-based study. *Medicine (Baltimore)* 2017;96:e6405. [PMC free article] [PubMed] [Google Scholar]