



Complications of percutaneous nephrostomy in a district general hospital

Rafal Turo¹ , Seth Horsu¹ , James Broome² , Sanjay Das¹ , Dev Mohan Gulur¹ , Bo Pettersson¹ , Gerard Doyle³ , Ninaad Awsare¹

Cite this article as: Turo R, Horsu S, Broome J, Das S, Gulur DM, Pettersson B, et al. Complications of percutaneous nephrostomy in a district general hospital. Turk J Urol 2018; 44(6): 478-83.

ABSTRACT

Objective: Percutaneous nephrostomy (PCN) is one of the commonest procedures performed. There are currently no European recommendations on the accepted rate of complications. The aim of the present study is to report the complication rate of PCN with the specific emphasis on sepsis and septic shock, the causative organisms, sensitivities to antibiotics, and associated risk factors.

Material and methods: Retrospectively collected data on patients undergoing acute or elective PCN at the Department of Radiology, Countess of Chester Hospital (COCH), in the UK between January 2014 and December 2016 were analyzed after the study was approved by Local Audit Department at COCH.

Results: A total of 66 patients underwent 90 acute or elective PCNs. Three patients developed major post-PCN complication (two patients developed septic shock and the third suffered a hemorrhagic episode requiring blood transfusion). Nephrostomy tube complications (blockage, leaking, fracturing and kinking of the catheter) occurred in 4 patients. Complications were more common when the PCN was performed out of working hours (71.4% [10/14], and 17.3% [9/52] for PCNs performed within, and out of working hours, respectively; $p < 0.001$). The age of the patients did not seem to correlate with the development of complications ($p < 0.001$). Of all 25 patients, in whom septicemia was diagnosed prior to PCN tube insertion, 12 developed septic shock and 13 had signs of sepsis for longer than 24 h. Fifteen patients had positive urine cultures. The most common organism isolated was *Escherichia coli*. Blood culture isolates included: *Escherichia coli*, *Eggerthella lenta*, *Enterococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

Conclusion: Our complication rates were within United States proposed target ranges. Our data may help to serve as a baseline for outcome targets in the European centres.

Keywords: Complications; infection; percutaneous nephrostomy; radiology; results.

ORCID IDs of the authors:

R.T. 0000-0001-9954-9252;
S.H. 0000-0003-3437-3983;
J.B. 0000-0003-0401-6213;
S.D. 0000-0003-4827-3094;
D.M.G. 0000-0001-7084-3167;
B.P. 0000-0001-9778-8858;
G.D. 0000-0002-8186-6716;
N.A. 0000-0002-9711-683X

¹Department of Urology,
Countess of Chester Hospital,
Chester, UK

²Department of Urology,
Leighton Hospital, Crew, UK

³Department of Radiology,
Countess of Chester Hospital,
Chester, UK

Submitted:
20.01.2018

Accepted:
18.06.2018

Correspondence:
Rafal Turo
E-mail:
rturo7@yahoo.com

©Copyright 2018 by Turkish
Association of Urology

Available online at
www.turkishjournalofurology.com

Introduction

Since the first description of percutaneous nephrostomy (PCN) in 1955 by Goodwin et al.^[1] it has become a well-established technique for providing permanent or temporary drainage of an obstructed urinary system. PCN is one of the commonest procedures performed in both major centres and district general hospitals. Several institutions from the USA have published their data on the success and complication rates pertaining to PCN. However much less data is available from centres within the

United Kingdom (UK). To date only two papers have been published from the UK, both from large tertiary referral centres.^[2,3] There are currently no European recommendations on the accepted rate of PCN-associated complications. The American College of Radiologists (ACR) recommended a threshold level of 4% for septic shock and 4% for major hemorrhage whereas the Society of Cardiovascular and Interventional Radiologists (SCVIR) quoted higher major post-PCN complication rates of 1-4% for vascular injury or hemorrhage and 1-9% for septic shock.^[4]

The aim of the present study is to report the complication rate of PCN with a specific emphasis on the rate of sepsis and septic shock, the causative organisms, antibiotic sensitivities and associated risk factors.

Material and methods

Patients

All patients who underwent acute or elective primary PCN at the Department of Radiology, Countess of Chester Hospital (COCH), in UK between January 2014 and December 2016 were included in this study. The Countess of Chester Hospital is a district general hospital and provides a service to a population of approximately 445,000 people. The Clinical Improvement, Assurance and Audit Department at COCH approved this study.

Equipment

Puncture of the renal collecting system was performed using a guidewire and a 18 G/1.2 mm trocar needle (Angiotech) under the guidance of a ultrasound scanner GE Healthcare Logiq S8 with a 3.5 MHz curved transducer. Renal positioning was followed by X-ray C-arm unit "DSRX-T7345GFS" (Toshiba) and iodinated contrast medium (Omnipaque 140 mg/mL) diluted in 100 ml NaCl at a ratio of 1:2 (GE Healthcare) was injected through the puncture needle. In dilated systems, a straight 0.035" Amplatz (Angiotech) guide wire was used as standard. In all non-dilated systems a hydrophilic guide wire Radifocus® 0.035" (Terumo) was inserted.

Table 1. Indications of PCN in non-dilated systems

| | |
|-----------------------------------|---|
| Leakage from neobladder | 1 |
| Stenosis of the ureter | 1 |
| Staghorn nephrolithiasis | 1 |
| Intolerance to Foley catheter | 1 |
| Vesico-vaginal fistula | 1 |
| Leakage from ureter after surgery | 1 |
| Total | 6 |

PCN: percutaneous nephrostomy

Table 2. Complications

| Complication | SIR grade | Number of patients | (%) |
|----------------------------------|-----------|--------------------|------|
| Septic shock | D | 2 | 3 |
| Hemorrhage requiring transfusion | D | 1 | 1.5 |
| PCN tube complications | B | 4 | 6.1 |
| Total | | 7 | 10.6 |

PCN: percutaneous nephrostomy; SIR: Society of Interventional Radiology

Catheters of 7F were used as standard whereas 10F catheters were used in the presence of pyohemonephrosis, and tumour debris. Eight F and 10 F dilators were used to dilate a PCN tract before placing a 10 F catheter.

Indications

The indications for PCN in non-dilated systems are listed in Table 1. The indications for PCN in dilated systems were clinically and radiologically confirmed obstructive hydro- or pyonephrosis. Preferably, PCN tube was inserted over ureteric stent as general anesthesia was contraindicated in majority of the patients.

Preparation

Consent was obtained from all patients. A single dose of prophylactic analgesic (morphine 5-10 mg PO or paracetamol 1000 mg PO) was given to all patients 1 h before the procedure. Patients were positioned prone on the fluoroscopy table, with the right flank elevated at 15-30° and the C-arm on the contralateral side to the nephrostomy. The skin was disinfected with 10% povidone-iodine or 0.5% chlorhexidine gluconate. Local anaesthesia was performed using 10-20 mL of 1% lidocaine. A single dose of antibiotic was administered prior to the procedure (gentamicin or other antibiotic in compliance with the culture sensitivity test results).

Technique

Percutaneous nephrostomy tube insertion was either performed by an experienced radiologist or trainee under his supervision. As a primary procedure, PCN tubes were successfully inserted in all patients.

The degree of hydronephrosis was initially assessed. Then the puncture site and entry angle were determined. In the majority of the cases, to avoid vascular injury, percutaneous access through posterior calyx major in the lower pole was preferred.

First the ultrasound-guided puncture was made with a 1.2 mm trocar needle directed through the base of a renal pyramid and papillary tip. If there was a return of urine following withdrawal of the trocar then the access was considered successful.

The renal collecting system was then visualised via injection of 10 mL of iodinated contrast medium (Omnipaque 240 mg/mL). The guidewire was then introduced. After removing the trocar needle the PCN catheter was placed over the guidewire and advanced under fluoroscopic control into the renal pelvis. The catheter was then secured by locking the C-lock on the shaft of the catheter. Finally, the catheter was connected to a drainage bag with a closed system and fixed to the skin with an adhesive patch (Drain-Fix®).

Complications

Complications were defined according to the Society of Interventional Radiology (SIR)^[4,5] as follows: minor complications (A) no therapy, no consequences, or (B) nominal therapy, no consequenc-

Table 3. Isolated organisms from urine and blood cultures

| No | Dilated system | Cause of obstruction | Urine culture isolate | Blood culture |
|----|----------------|----------------------|---|-------------------------------|
| 1 | Yes | Bladder cancer | <i>Escherichia coli</i> | No growth |
| 2 | Yes | Prostate cancer | <i>Escherichia coli</i> | No growth |
| 3 | Yes | Ureteric obstruction | <i>Escherichia coli</i> | No growth |
| 4 | Yes | Ureteric obstruction | <i>Escherichia coli</i> | No growth |
| 5 | Yes | Stone | <i>Escherichia coli, Klebsiella</i> | <i>Escherichia coli</i> |
| 6 | Yes | Rectal cancer | <i>Enterococcus faecalis</i> | No growth |
| 7 | Yes | Stone | <i>Enterococcus faecalis, Klebsiella pneumoniae</i> | No growth |
| 8 | Yes | Bladder cancer | <i>Klebsiella pneumoniae</i> | <i>Enterococcus</i> |
| 9 | Yes | Colon cancer | <i>Klebsiella pneumoniae</i> | No growth |
| 10 | No | Bladder cancer | Mixed growth | No growth |
| 11 | Yes | Stone | <i>Klebsiella oxytoca, Proteus mirabilis</i> | No growth |
| 12 | Yes | Stone | <i>Proteus mirabilis</i> | No growth |
| 13 | Yes | Stone | <i>Proteus mirabilis</i> | <i>Proteus mirabilis</i> |
| 14 | Yes | Stone | <i>Pseudomonas aeruginosa</i> | <i>Pseudomonas aeruginosa</i> |
| 15 | Yes | Stone | <i>Pseudomonas aeruginosa</i> | No growth |

es. Major complications (C): complications requiring therapy and minor hospitalisation (<48h), (D) major therapy, and associated with unplanned increase in level of care, prolonged hospitalisation (>48 h), (E) permanent adverse sequel, or (F) resulting in death.

Sepsis

Sepsis was defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee and guidelines of the European Association of Urology.^[6,7] Urine cultures of all patients were routinely performed at first signs of sepsis and the first access urine was sent for culture at the time of PCN tube insertion.

Statistical analyses

Data were retrieved retrospectively from electronic patient files. PCN data were collected and analysed in a database Excel from Microsoft Office in Windows 7. The rate of major complications was compared to a maximum rate of 4% recommended by SIR.^[5,6] Minor complications were compared to threshold rate of 15%. Where appropriate, categorical data were compared for statistical significance using a commercially available statistics program (GraphPad Software, San Diego, CA, USA, www.graphpad.com) and p=0.05 was taken to be the level of statistical significance. In our study comparisons between major complication rates were made using Fisher's exact test (www.graphpad.com/quickcalcs/index.cfm).

Results

Forty males aged 38-92, and 26 females 25-91 years were included in the study.

A total of 90 PCNs were performed in 84 kidneys with dilated systems and in 6 kidneys with non-dilated systems. A total of 23 PCNs on the right, 19 PCNs on the left kidney were performed, and 24 patients had bilateral procedures (48 PCNs). The main indications for nephrostomy tube insertion were obstructive uropathy due to malignant disease (46%), benign disease (3%), pyonephrosis (8%) and renal stones (43%).

The complications seen are listed in Table 2. Over the study period 90 PCNs were performed on 66 patients, of which 14 (21%) were performed out of working hours between 8:00 AM and 05:00 PM. Three patients (4.5%) developed major post-PCN complications. Two patients developed septic shock with rigors and hypotension despite prophylactic antibiotics and required further treatment, including intravenous antibiotics and fluids. These patients had no evidence of sepsis prior to PCN tube insertion. One patient had blood loss with a reduction in hemoglobin from 10 g/dL to 7.3 g/dL after nephrostomy tube insertion and was given blood transfusions. He was anticoagulated for atrial fibrillation with an INR of 1.4 at the time of procedure. We did not observe any delayed bleeding during study period. Nephrostomy tube complications, such as catheter blockage, leaking, fracturing and kinking of the catheter occurred in 4 patients (6.1%).

Among all 25 patients, in whom septicemia was diagnosed prior to PCN tube insertion, 12 patients developed septic shock and 13 had signs of sepsis for longer than 24 hours. These patients with signs of sepsis prior to PCN tube insertion were not included in the analysis of post procedural complication rates.

Department protocols were adhered to. All patients had appropriate pre-procedure hematological investigations. Physiological parameters such as pulse rate, blood pressure and oxygen saturation were monitored throughout the procedure and the doses of analgesics used were recorded in the notes. However the antibiotic policy was not strictly followed and three of 66 patients did not receive any antibiotics. Two of these three patients who did not receive antibiotic prophylaxis had clinical evidence of infection and both developed post-PCN septic shock.

Complications were more common when the PCN was performed out of working hours. Ten of fourteen (71.4%) patients who underwent PCNs after normal working hours suffered from complications compared with nine of fifty two (17.3%) patients whose PCNs were performed within working hours ($p=0.0002$; Fisher's test). Nine patients died within 30 days of PCN tube insertion resulting in a 30-day-mortality rate of 13.6%. None of these were procedure related. Two patients died of pre-existing septicemia and seven patients as a result of underlying malignancy. The age of the patients did not seem to correlate with the development of post-PCN complications ($p=0.46$).

Overall, there were 15 patients with positive urine cultures. The most common organism isolated was *Escherichia coli*. Table 3 represents other organisms isolated. Of all patients ($n=12$) who developed post-PCN septic shock, 3 had positive urine cultures. The organisms isolated from blood included: *Escherichia coli*, *Eggerthella lenta*, *Enterococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Streptococcus pneumonia*.

Discussion

In this retrospective study we report our success and complication rates for PCN tube insertion over a two-year period at our institution. Previously, published data mainly retrospective in nature were derived from centres within the USA. Only 2 of these studies were performed in the UK.

The rates of PCN-related major complications vary from 0 to 7% in the literature. Guidelines suggest an upper limit of 4% for major complications.^[5,8] One of the largest reported series of 454 PCNs by Farrell et al.^[9] the incidence of major complications was 5.2%. From that series 3.6% of the patients had suffered hemorrhage which required blood transfusion.

Our results reveal that our primary technical success rate, minor and major complications are comparable with those of the other published series.^[9-14] Significant hemorrhage, septicemia and inadvertent perforation of the intra-abdominal organs such as colon, spleen, liver or pleura are among the major complica-

tions reported in the literature. The single case in our series of postprocedural blood transfusion was performed on an anticoagulated patient with a preoperative INR of 1.4. He did not suffer any untoward sequela after transfusion. Our incidence of significant postoperative hemorrhage (1.5%) is comparable with other series. In a study performed by Kaskarelis et al.^[15] the major complication rate was as low as 0.29%. However, not only PCNs but also ureteric stent insertions and exchange of PCNs had been also included in their assessments. When adjustments were made for PCN only, the major complication rate might be 0.7% with postoperative bleeding at the rate of 0.4%. Another possible factor contributing to the observed low complication rate could possibly be the presence of a high degree of dilatation of the renal collection system in the studied patients. We performed PCNs for 6 kidneys with non-dilated collecting systems. Results of PCNs performed in grades II-IV hydronephrotic kidneys did not reveal any major complications as described by Carrafiello et al.^[16] However, these results are not directly comparable to ours due to lack of inclusion of non-dilated systems in their series. In more recent, large series of 500 PCNs performed on both dilated and non-dilated kidneys, described by Montvilas et al.^[17] major complications occurred in 0.45% of the cases. In the literature a number of factors have been identified as being strongly associated with an increased risk of postoperative bleeding. The pre-existence of blood coagulopathies was found to increase the risk for postoperative bleeding. Farrell et al.^[9] found that patients with a platelet count of 100,000/dL or lower had a higher transfusion rate after PCN tube insertion. In addition, the adherence to the fundamental anatomical principles during PCN tube insertion, in other words a correct needle entry between the anterior and posterior arterial divisions (Brödel's line) is of paramount importance.^[18] Interestingly, the size of the needle or the catheter inserted seemed not to correlate with the rate of hemorrhage. In one study small-bore access sheath systems were not found to be safer than larger 18G catheters.^[19]

The total rate of minor complications in our series was 6.1% which is comparable with other studies and below the established RCR standard of 15%.^[20] All our minor complications were catheter-related problems most frequently catheter dislodgement. Carrafiello et al.^[16] reported 43 [43/299 (14.4%)] cases of dislodgements, which did not seem to correlate with a type of nephrostomy tube fixating system.^[16] Other commonly reported minor complications include transient hematuria and catheter site infection/inflammation.^[9,15,16] None of these were observed in our study population. One patient (1.5%) in our study group experienced catheter blockage requiring replacement. This rate seems to correspond with incidence rates of 0.4-4.1%. Described in the literature:^[3,15] The comparisons of minor complications among published studies proved to be very difficult due to variability of definitions used. In 2007, the suggested standard set by

the RCR in the UK was $\leq 15\%$. The UK group of investigators proved this to be an achievable target and demonstrated the rate of minor complications to be as low as 12%.^[20]

The most commonly described complications were sepsis and infectious complications among many others. The reviewed incidence of such complications was highly variable due to the fact that different studies used different definitions of sepsis, septicemia, post-interventional fever and septic shock. These terms have been also commonly used interchangeably. According to the definitions of sepsis used in the literature the majority of infections causing systemic response might be classified as sepsis.^[6,21] For the purposes of our study we have used more stringent criteria recommended by the Third International Consensus Definitions for Sepsis and Septic Shock.^[22] The most significant major complications included severe sepsis and septic shock. Interestingly none of the studies described infectious complications in great detail. To our knowledge our study was the first to look at the causative organisms and to determine the presence of urinary tract infections prior to PCN tube insertion. The commonly used recommendation of the ACR and SIR for the maximal rate of post-PCN septic shock only distinguishes these rates by the presence or absence of pyonephrosis before PCN tube insertion. The accepted rates for septic shock with and without pyonephrosis were 10, and 4%, respectively. When this definition was applied, studies reported sepsis as a major complication in 0.7-3.6% of cases.^[8,17,18] Thirty-eight percent (n=25) of our patients were diagnosed with septicemia prior the PCN tube insertion and 15 of them had positive urine cultures. The most commonly isolated organism from urine culture was *Escherichia coli* followed by *Klebsiella pneumonia* and *Proteus mirabilis*. Interestingly 4 patients had confirmed bacteremia and only 2 of them had evident pyonephrosis at the time of PCN tube insertion. We therefore think it is absolutely imperative to perform urine and blood cultures on all patients prior to PCN tube insertion.

One of the limitations of our study is relatively small numbers of patients included in our research. We were not able to evaluate the effect of tube size, level of hydronephrosis and radiologist experience concerning complication rates.

In conclusion, PCN is a commonly used technique, with a high success and low rates of complications. Our complication rates were within the accepted target ranges proposed in the North American literature. Our data may help to serve as a baseline for the establishment of outcome targets in European centres.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Local Audit Department at Countess of Chester Hospital.

Informed Consent: Anonymised patients' data collection permission was obtained from Audit Department at Countess of Chester Hospital, Chester, UK

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.T., S.H., N.A., G.D.; Design – R.T., S.H., N.A., G.D.; Supervision – B.P., N.A., D.M.G., S.D.; Resources – B.P., N.A., D.M.G., S.D.; Materials – R.T., S.H., N.A.; Data Collection and/or Processing – R.T., S.H., N.A., G.D.; Analysis and/or Interpretation – R.T., S.H., N.A., G.D.; Literature Search – R.T.; Writing Manuscript – R.T.; Critical Review – B.P., N.A., D.M.G., S.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that they have not received no financial support.

References

1. Goodwin WE, Casey WC, Woolf W. Percutaneous trocar (needle) nephrostomy in hydronephrosis. J Am Med Assoc 1955;157:891-4. [\[CrossRef\]](#)
2. Patel RD, Newland C, Rees Y. Major complications after percutaneous nephrostomy-lessons from a department audit. Clin Radiol 2004;59:766. [\[CrossRef\]](#)
3. Wah TM, Weston MJ, Irving HC. Percutaneous nephrostomy insertion: outcome data from a prospective multi-operator study at a UK training centre. Clin Radiol 2004;59:255-61. [\[CrossRef\]](#)
4. Ramchandani P, Cardella JF, Grassi CJ, Roberts AC, Sacks D, Schwartzberg MS, et al. Quality improvement guidelines for percutaneous nephrostomy. J Vasc Interv Radiol 2001;12:1247-51. [\[CrossRef\]](#)
5. Available from: <http://www.acr.org>. American College of Radiology (ACR) and the Standards of Practice Committee of the Society of Interventional Radiology (SIR) Practice guideline for the performance of percutaneous nephrostomy. 2016.
6. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55. [\[CrossRef\]](#)
7. Available from: <http://www.uroweb.org>. European Association of Urology Definition and clinical manifestation of sepsis in urology. 2013.
8. Agostini S, Dedola GL, Gabbriellini S, Masi A. A new percutaneous nephrostomy technique in the treatment of obstructive uropathy. Radiol Med 2003;105:454-61.
9. Farrell TA, Hicks ME. A review of radiologically guided percutaneous nephrostomies in 303 patients. J Vasc Interv Radiol 1997;8:769-74. [\[CrossRef\]](#)
10. Fowler JE, Jr., Meares EM, Jr., Goldin AR. Percutaneous nephrostomy: techniques, indications, and results. Urology 1975;6:428-34. [\[CrossRef\]](#)

11. Stables DP, Ginsberg NJ, Johnson ML. Percutaneous nephrostomy: a series and review of the literature. *AJR Am J Roentgenol* 1978;130:75-82. [[CrossRef](#)]
12. Kehinde EO, Newland CJ, Terry TR, Watkin EM, Butt Z. Percutaneous nephrostomies. *Br J Urol* 1993;71:664-6. [[CrossRef](#)]
13. Nielsen OS, Grossmann E. Ultrasonically guided percutaneous nephrostomy. *Scand J Urol Nephrol* 1990;24:219-21. [[CrossRef](#)]
14. Vehmas T, Kivisaari L, Mankinen P, Tierala E, Somer K, Lehtonen T, et al. Results and complications of percutaneous nephrostomy. *Ann Clin Res* 1988;20:423-7.
15. Kaskarelis IS, Papadaki MG, Malliaraki NE, Robotis ED, Malagari KS, Piperopoulos PN. Complications of percutaneous nephrostomy, percutaneous insertion of ureteral endoprosthesis, and replacement procedures. *Cardiovasc Intervent Radiol* 2001;24:224-8. [[CrossRef](#)]
16. Carrafiello G, Lagana D, Mangini M, Lumia D, Recaldini C, Bacuzzi A, et al. Complications of percutaneous nephrostomy in the treatment of malignant ureteral obstructions: single-centre review. *Radiol Med* 2006;111:562-71. [[CrossRef](#)]
17. Montvilas P, Solvig J, Johansen TE. Single-centre review of radiologically guided percutaneous nephrostomy using "mixed" technique: success and complication rates. *Eur J Radiol* 2011;80:553-8. [[CrossRef](#)]
18. Lewis S, Patel U. Major complications after percutaneous nephrostomy-lessons from a department audit. *Clin Radiol* 2004;59:171-9. [[CrossRef](#)]
19. Clark TW, Abraham RJ, Flemming BK. Is routine micropuncture access necessary for percutaneous nephrostomy? A randomized trial. *Can Assoc Radiol J* 2002;53:87-91.
20. Chalmers N, Jones K, Drinkwater K, Uberoi R, Tawn J. The UK nephrostomy audit. Can a voluntary registry produce robust performance data? *Clin Radiol* 2008;63:888-94. [[CrossRef](#)]
21. Urology. EAoUDacmosi. 2013. Available from: <http://www.uroweb.org>.
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10. [[CrossRef](#)]