Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy

Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK

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Study question What is the relation between penicillin allergy and the development of meticillin resistant Staphylococcus aureus (MRSA) and Clostridium difficile?

Methods Using the Health Improvement Network, a UK general practice database (1995-2015), the authors studied a matched cohort of adults without previous MRSA or C difficile. Participants with incident penicillin allergy were matched with up to five penicillin users without allergy by age, sex, and date of study entry. Hazard ratios were calculated for the relation between penicillin allergy and incident MRSA and C difficile, adjusting for potential confounders. The authors also examined the use of β lactam alternative antibiotics and whether use was a mediator for incidence of MRSA and C difficile.

Study answer and limitations Among 64,141 adults with penicillin allergy and 237,258 matched comparators, 1,365 developed MRSA (442 participants with penicillin allergy and 923 comparators) and 1,688 developed C difficile (442 participants with penicillin allergy and 1,246 comparators). The adjusted hazard ratios among participants with penicillin allergy were 1.69 (95% confidence interval 1.51 to 1.90) for MRSA and 1.26 (1.12 to 1.40) for C difficile. The adjusted risk ratios for antibiotic use among participants with penicillin allergy were 4.15 (95% confidence interval 4.12 to 4.17) for macrolides, 3.89 (3.66 to 4.12) for clindamycin, and 2.10 (2.08 to 2.13) for fluoroquinolones. Increased use of β lactam alternative antibiotics accounted for 55% of the increased risk of MRSA and 35% of the increased risk of C difficile. Limitations were that the dataset could have missed MRSA and C difficile in hospital patients, outcomes were identified from records of diagnoses, and residual confounding might exist.

What this study adds Patients with a documented penicillin allergy have an increased risk of new MRSA and C difficile that is modifiable, to some degree, through changes in antibiotic prescribing.

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PAE for benign prostatic hyperplasia

ORIGINAL RESEARCH Randomised, open label, non-inferiority trial

Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia

Abt D, Hechelhammer L, Müllhaupt G, et al Cite this as: BMJ 2018;361:k2338
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Study question How does PAE compare with TURP in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH-LUTS), in terms of patient reported and functional outcomes?

Methods This prospective trial included 103 patients aged 40 years and older with refractory BPH-LUTS from a Swiss tertiary care centre, who were randomly assigned and allocated to PAE and TURP between 11 February 2014 and 24 May 2017 (48 and 51 patients reached the primary endpoint at 12 weeks’ follow-up, respectively). Primary outcome was the change in international prostate symptom score (IPSS) from baseline to 12 weeks after surgery. A difference between treatments of less than 3 IPSS points was defined as non-inferiority for PAE and tested with a one sided t-test. Secondary outcomes included further questionnaires, functional measures, magnetic resonance imaging findings, and assessment of adverse events, and were compared with two sided tests for superiority.

Patient reported outcomes did not differ significantly after TURP and PAE, clear advantages of TURP were found regarding improvement of micturition parameters, and fewer adverse events occurred after PAE.

What this study adds Our study suggests that the improvement of BPH-LUTS by PAE is close to that achieved by TURP in the short term. PAE is associated with fewer adverse events than TURP but with clear disadvantages regarding improvement of micturition parameters, which should be considered for patient selection.

Funding, competing interests, data sharing Funded by the research committee of St Gallen Cantonal Hospital. The authors declare no conflicts of interest. Data sharing is provided on request.

Study registration Clinicaltrials.gov NCT02054013.

Commentary PAE fills a therapeutic niche between medication and surgery

Prostate artery embolisation (PAE) is a new treatment for benign prostatic hyperplasia that has emerged in the past few years as a potential alternative to endoscopic surgical treatments such as transurethral resection of the prostate (TURP). The recent UK Register of Prostatic Embolisation (ROPE) study has shown its preliminary safety and efficacy in a multicentre observational evaluation, which also included an indirect comparison with TURP. After several small trials, Abt and colleagues’ larger trial adds further detail to PAE’s ongoing evaluation.

PAE involves cannulation and embolisation of the prostatic arteries via access in the groin or arm. Before the procedure, potentially eligible men receive multiparametric, magnetic resonance imaging scanning to rule out malignancy, a contrast computed tomography scan of the prostatic arteries to ensure vessel patency and no contraindications, and sometimes urodynamics to confirm bladder outlet obstruction.

Comparable improvement in symptoms

In this randomised, open label non-inferiority trial comparing PAE with TURP in men with moderate prostatic hyperplasia, both treatments led to comparable reductions in symptom scores (PAE 9.2 IPSS points 9 TURP 10.8 points), although the authors were unable to confirm non-inferiority for this outcome. Changes in other functional outcomes, however, were significantly better after TURP than after PAE, including maximum flow rate, residual volume, prostate volume reduction, and relief of obstruction on urodynamic studies. Patient reported outcomes did not differ between the groups. There was no detrimental effect on erectile function in either group, but the rate of ejaculatory dysfunction was unexpectedly high after PAE (56% of those assessed), possibly owing to the specific technique used in this trial. PAE was associated with less blood loss and fewer adverse events than TURP, but longer procedural time and more men reported pain after the procedure (56% after PAE vs 32% after TURP). Specific complications related to PAE included one patient with postembolisation syndrome, one with groin haematoma, and one with bladder necrosis requiring endoscopic debridement.

Is PAE a good option for men with voiding lower urinary tract symptoms who have not responded to medical treatment? The procedure improves urinary symptoms, avoids surgery and its inherent risks (at least for the medium term), and could preserve normal ejaculation more than TURP. But it is impossible to know the true risk of recurrence from this 12 week trial. Recurrence rate is a key outcome in future studies to clarify the long-term benefits and risks of PAE.
PAE for benign prostatic hyperplasia

**COMMENTARY**

PAE fills a therapeutic niche between medication and surgery. Patients choosing this option can be reassured that the procedure is important while we wait for more definitive evidence of the longer term benefits and risks of PAE. Patients choosing this option can be reassured that the procedure is unlikely to compromise a TURP or holmium laser enucleation of the prostate (HoLEP) if required in the future.

Other potential advantages worthy of further study include improved cost effectiveness relative to TURP, suitability of PAE for higher risk patients, reduced blood loss, and the option for outpatient treatment without hospital admission.

Future studies should also help characterise those men likely to benefit most from PAE. It is possibly best for those men with severe urinary symptoms (high IPSS), with no middle lobe, and who have not improved with medical treatment and wish to avoid surgery. PAE is a technically challenging procedure currently limited to specialised centres. It is likely to be here to stay, has been approved by the National Institute for Health and Care Excellence this year, and fills a therapeutic niche between medication and bladder outflow surgery for eligible men.

**AUTHOR'S PERSPECTIVE**

Dominik Abt

**Prostatic artery embolisation: time to improve collaboration**

Given the demographic shift towards a more elderly population, lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH-LUTS) will become more and more prevalent.

Although established surgical techniques, such as transurethral resection of the prostate (TURP), have matured over decades, they are still associated with considerable side effects.

Prostatic artery embolisation (PAE) in the treatment of BPH-LUTS seems to have some obvious advantages, including performance under local anaesthesia, a favourable side effect profile, and no need for postoperative physical rest. It is therefore not surprising that the main difficulty in conducting our randomised controlled trial comparing PAE and TURP in patients with refractory BPH-LUTS was not finding patients who were willing to undergo an intervention still considered experimental and not mentioned in any guidelines, but to convince them to participate in a randomised trial with a 50% chance of being assigned to TURP.

Our study provides data that may help to clarify the evidence currently available for PAE. The findings largely confirm the general assumption that PAE is a safe procedure that improves BPH-LUTS in most patients.

The discussion regarding the use of PAE to treat BPH-LUTS is still controversial and is influenced by political interests, since interventional radiologists are encroaching on what has so far been a fundamental domain of the urologist. Nevertheless, based on the evidence available, NICE recently recommended PAE as a treatment option for BPH symptoms.

It seems, therefore, that the question is no longer whether PAE has a role in the treatment of BPH-LUTS, but rather how long do the beneficial effects persist? What are the ideal patients and indications? When should classic surgery be preferred? Should PAE be seen as an alternative to medical rather than surgical treatment?

These questions can only be answered by large, robust trials. Now is the time to find the most appropriate spectrum of indications for PAE.

1 DA is a consultant urologist in the Department of Urology of St Gallen Cantonal Hospital, Switzerland.
**Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies**

Given JE, Loane M, Garne E, et al

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Study question Does exposure to metformin in the first trimester of pregnancy, for diabetes or other indications, increase the risk of all or specific congenital anomalies?

Methods This was a population based case-control study using malformed controls. Cases of 29 specific subgroups of non-genetic congenital anomalies, and all non-genetic congenital anomalies combined, were compared with controls (all other non-genetic anomalies or genetic syndromes) in terms of metformin exposure. Eleven EUROmediCAT congenital anomaly registries surveying 1 892 482 births in Europe 2006-13 contributed data. The analysis included 50 167 babies affected by congenital anomaly, including five births, fetal deaths from 20 weeks’ gestation, and terminations of pregnancy for fetal anomaly, of which 168 were exposed to metformin. Odds ratios for the risk of each case congenital anomaly subgroup related to metformin exposure were calculated with adjustment for the confounding factors maternal age, registry, multiple birth, and maternal pregestational/gestational diabetes.

Study answer and limitations No evidence was found of an increased risk of all non-genetic congenital anomalies combined following first trimester exposure (adjusted odds ratio 0.84, 95% confidence interval 0.55 to 1.30, compared with genetic controls), and the one significant association for a cardiac defect was no more than would be expected by chance. Despite the large study population, the statistical power to detect increased risk of rarer specific anomalies was limited.

What this study adds This study, with an estimated eight times the number of metformin exposures previously available in the literature, is the first to be able to explore the risk of specific congenital anomalies after exposure to metformin in the first trimester.

Funding, competing interests, data sharing Grants from the Economic and Social Research Council and European Union Framework 7 supported the study. Data sharing can be requested as per the ENCePP Code of Conduct—Implementation Guidance for Sharing of Study Data. See full paper on bmj.com for more information.

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**Prospective external validation of the PROOF-BP strategy for triaging ambulatory monitoring in the diagnosis and management of hypertension**

Sheppard JP, Martin U, Gill P, et al on behalf of the PROOF-BP investigators

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Study question What is the accuracy of triaging patients for ambulatory blood pressure monitoring (ABPM) in routine clinical practice?

Methods This study used a prospective observational cohort design, recruiting patients from 10 primary care practices and one hospital in the United Kingdom. Consecutive adults aged 18 years or more referred for ABPM in routine clinical practice were enrolled. All participants underwent ABPM and had the new triage algorithm, Predicting Out-of-Office Blood Pressure (PROOF-BP), applied. The proportion correctly classified with hypertension using the triaging strategy was estimated and compared with the reference standard of daytime ABPM. Secondary outcomes included sensitivity, specificity, and area under the receiver operator characteristic curve (AUROC) for detecting hypertension.

Study answer and limitations In a population of 887 patients referred for ABPM, the new triaging approach accurately classified hypertensive status in 801 (90%, 95% confidence interval 88% to 92%) and had a sensitivity of 97% (95% confidence interval 96% to 99%) and specificity of 76% (95% confidence interval 71% to 81%) for hypertension. Use of triaging, rather than uniform referral for ABPM in routine clinical practice would have resulted in 435 patients referred, 69 (8%, 6% to 10%) would have received treatment deemed unnecessary had they received ABPM.

What this study adds The new triaging strategy accurately classified an individual’s hypertensive status with half the utilisation of ABPM compared with usual care. The algorithm can therefore be recommended for diagnosis or management of hypertension in patients in whom ABPM is being considered, particularly in settings with limited resources.

Funding, competing interests, data sharing This work was funded by a Medical Research Council fellowship (MR/K022032/1). The authors declare no other conflicts of interest. Patient level data are available upon request.

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**Accuracy of triaging approach. Values are percentages (95% confidence intervals) unless stated otherwise**

<table>
<thead>
<tr>
<th>Population</th>
<th>Total population</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>887 (100)</td>
<td>0.86 (0.84 to 0.89)</td>
<td>97.2 (95.8 to 98.5)</td>
<td>75.9 (70.9 to 80.6)</td>
<td>89.4 (87.1 to 91.8)</td>
<td>92.7 (89.4 to 96.1)</td>
</tr>
<tr>
<td>For diagnosis*</td>
<td>268 (30)</td>
<td>0.90 (0.86 to 0.94)</td>
<td>95.1 (91.8 to 98.6)</td>
<td>84.6 (77.7 to 91.5)</td>
<td>90.7 (86.4 to 95.0)</td>
<td>91.7 (86.1 to 97.2)</td>
</tr>
<tr>
<td>For management†</td>
<td>619 (70)</td>
<td>0.84 (0.81 to 0.88)</td>
<td>97.9 (96.6 to 99.3)</td>
<td>70.9 (64.3 to 77.5)</td>
<td>89.0 (86.2 to 91.8)</td>
<td>93.5 (89.4 to 97.6)</td>
</tr>
</tbody>
</table>

AUROC = area under the receiver operating characteristic curve.

* Patients without a history of hypertension.
† Patients with a history of hypertension.