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Is There a Role for Antifungal Prophylaxis in Patients Undergoing Penile Prosthesis Surgery? A Systematic Review

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Abstract
Objective: The aim of this study is to review the literature on the use of antifungal prophylaxis in penile prosthesis (PP) surgery and provide a summary on its efficacy as an adjunct to current prophylactic regimes in patients undergoing PP surgery. ***Materials and Methods:*** PubMed, Medline, and EMBASE databases were systematically searched up to May 2020. All included studies were analysed and the information extracted included author, title of study, year of publication, type of study, journal of publication, and main findings regarding post PP implantation fungal infections. ***Results:*** Nine relevant studies were included in this review, comprising retrospective single-centre studies and retrospective multicentre studies ranging from 2017 to 2020. Fungal infections were found responsible for 11.1% of all PP infections, with a greater risk in patients with diabetes, obesity, and from warmer climates. Current American Urological Association (AUA) and European Association of Urology (EAU) prophylaxis guidelines do not incorporate the use of antifungals. Trials of antifungal prophylaxis regimes combined with antibiotic prophylaxis have demonstrated a reduction in PP fungal infections. ***Conclusions:*** Fungal infections represent a significant proportion of implant infections and therefore antifungal prophylaxis is warranted. Future studies comparing the efficacy of traditional antibiotic prophylaxis as set out by AUA/EAU with novel prophylaxis regimes including the addition of an antifungal may provide more definitive guidance on this issue. Until then antifungal prophylaxis in all patients undergoing PP procedures may provide a significant cost-effect benefit.

Introduction

Penile prostheses (PPs) have been the chosen end-stage treatment for erectile dysfunction worldwide for many years, although increasingly there is now an appropriate move to discuss and offer implant surgery to patients earlier in their treatment journey so that patients can choose the treatment most acceptable to them. First performed in 1936 by Nicoli Bogoras, the surgical technique has vastly evolved and now involves the insertion of silicone and bioflex devices into the corpus cavernosa [1]. Implantation of foreign material into the body has long been associated with an increased risk of infection of prosthetic devices [2]. PPs are no different, and while the infection rate is low (<2%), the consequences of implant infection are often devastating requiring explantation of the device [3]. Studies have shown that removal of a PP due to infection costs

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healthcare providers more ($11,252) than revision for mechanical failure ($8,602) [4]. In the UK, the cost per patient requiring a new implant is £8,647, increasing by a further £2,969 if a revision procedure is necessary [5]. Continuous improvements in a surgical technique and pharmacological advances with prophylactic antibiotics and implant preparation have seen a reduction in the prosthetic infection rate [6]; however, the growing prevalence in obesity and diabetes, within the erectile dysfunction patient cohort [7], and the presence of other factors such as immunosuppression or poor hygiene represent further infection risks.

Typically, PP infections are associated with common skin flora (*Staphylococcus aureus* or *Staphylococcus epidermidis*), but a significant proportion of infections (11%) are attributed to fungal infections (*Candida* species) [8]. At present, the American Urological Association (AUA) best practice guidelines (2012) advise prophylactic administration of Aminoglycoside plus Vancomycin or a first- or second-generation Cephalosporin an hour before surgery [9]. The European Association of Urology guidelines on urological infections advise all patients undergoing PP implantation to be administered a group 2 or 3 Cephalosporin and penicillin [10]. There is currently no consensus in urological guidelines on the use of antifungal treatment alongside antibiotics to allow better coverage of non-bacterial infectious agents. The aim of this article is to review the existing literature on the use of antifungal prophylaxis in PP surgery and provide a summary on its efficacy as an adjunct to current prophylactic regimes in patients undergoing PP surgery.

Materials and Methods

This review article was conducted in agreement with the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (http://www.prisma-statement.org). The PRISMA checklist has been submitted in the online supplementary material (available at www.karger.com/doi/10.1159/000522173).

Study Eligibility Criteria

Studies reporting the incidence, and management of fungal infections following PP implantation were included. Case reports and other literature reviews were excluded from this review article.

Information Sources and Search

An extensive search of the existing literature was conducted in May 2020 using the NICE Healthcare Databases Advanced Search (https://www.evidence.nhs.uk). The following keywords were used to search databases including Medline (1946-present), PubMed (1946-present), and EMBASE (1974-present): "penile prosthesis," "infection," "fungal," and "*Candida*." Further studies were gained from the references of recent review articles, in addition to studies attained via the databases.

Study Selection and Data Collection

The abstracts were identified by the database search to determine those studies that were potentially relevant. Full-text manuscripts of these articles were then reviewed to identify those specifically related to post PP implantation fungal infections, prophylaxis used, and "at risk" groups. Conflicts in opinion were discussed between all authors until there was an agreement on manuscripts eligible for the study.

Data Extraction and Analysis

Each paper was studied to identify certain information of relevance to this review. Information was tabulated for summary and analysis. Information extracted included author, title of study, year of publication, type of study, journal of publication, and main findings regarding post PP implantation fungal infections. Hospital Episode Statistics data were analysed for 2019–2020 to determine the number of PP procedures performed in England during that period. The following procedural codes were included the following: implantation of prosthesis into penis (N29.1) and attention to prosthesis in penis (N29.2).

Results

Study Selection

A total of 109 potentially relevant studies were identified from the literature search; however, after the subsequent abstract review, 25 studies were eliminated due to duplication and a further 59 studies were excluded after abstracts were screened. Another 11 studies were excluded following full-text review due to irrelevance. Lastly, a further 5 studies were excluded as they included case reports and literature reviews. The final number of relevant studies included in this review was 9 (shown in Table 1), comprising 1 retrospective single-centre studies and 8 retrospective multicentre studies ranging from 2017 to 2020 (shown in Fig. 1).

Prevalence of Fungal Infections following PP Implantation Surgery

Studies reporting cases of infection following PP surgery demonstrated an increasing proportion of infections due to atypical organisms including more fungi. Case studies dating back to 1988 have reported PP-related *Candida Albicans* abscesses both locally within the corporal tissue and in more distant organs, e.g., renal tissue [11–13].

While it is widely accepted that the majority of infections post PP implantation are predominantly due to *Staphylococcus*, *Enterococcus*, and fungi [14], a retrospective multicentre study by Smith et al. [15] in 2014 looked to determine the difference, if any, between patients with

Table 1. Overview of the studies included in this review

Author	Title	Journal	Type of study	Findings
Gross et al. [8]	Multicentre investigation of the microorganisms involved in PP infection: an analysis of the efficacy of the AUA and EAU guidelines for PP prophylaxis	Journal of Sexual Medicine	Retrospective multicentre	153/227 positive cultures. 11.1% *Candida*, 10.5% anaerobes, 9.2% methicillin-resistant *Staphylococcus*. Guidelines did not cover organisms in 14–38% of cases
Gross et al. [17]	Multicentre investigation of the microorganisms involved in PP infection: Are the AUA and EAU guidelines appropriate for PP prophylaxis and infection management?	Journal of Sexual Medicine	Retrospective multicentre	227 intraoperative cultures at salvage/explantation. 33% no growth. 79% Gram positive. 39% Gram negative. *Candida* 11.1% of 153 positive cultures. Guidelines did not cover organisms in 14–38% of cases
Jani et al. [15]	Infection retardant coatings impact on bacterial presence in PP surgery: a multicentre study	Urology	Retrospective multicentre	84/300 patients with revision surgery that had positive cultures. Divided into 2 groups: clinically uninfected (71) and overtly infected (13). More traditional infectious profile in group 1 versus 2. *Candida* appeared in both groups
Gross et al. [18]	The relationship between infection severity, microorganisms, and surgical intervention in inflatable PP infections	Journal of Sexual Medicine	Retrospective multicentre	14/213 had fungal infections. 60% salvaged, while 40% explanted. Less successful salvage rate compared to anaerobic and Gram-positive organisms
Gross et al. [19]	New findings regarding the timeline of microorganisms, infection severity, and surgical intervention in inflatable PP infections	Journal of Urology	Retrospective multicentre	Fungal infections treated on average 5.8 months after implantation (1m–27m, median 3m). Anaerobic infections more rapid (2.6m) and Gram-negative slower (6.96m)
Gross et al. [20]	Multicentre investigation of fungal infections of inflatable penile prostheses	Journal of Sexual Medicine	Retrospective multicentre	26/217 had fungal infections. 23/26 were diabetic/overweight. 91% had antibiotic prophylaxis as per AUA
Gross et al. [21]	Multicentre investigation on the influence of climate in penile prosthetic infection	International Journal of Impotence Research	Retrospective multicentre	PP infections occurred more in June than in winter. Fungal infections positively correlate with humidity
Brennan et al. [22]	Minimizing candida infections: adding antifungal agents to the implant dip	Journal of Sexual Medicine	Retrospective single centre	Added Amphotericin B to usual Vancomycin and Gentamicin dip. 6/1,027 underwent explantations or salvage and none had *Candida* infections
Towe et al. [23]	Adherence to the AUA PP antibiotic prophylaxis guidelines in diabetic patients is associated with significantly higher risks of device infection	Journal of Sexual Medicine	Retrospective multicentre	804 patients, 30 infections, 38 explantations, 57 revisions. AUA guidelines followed in 348/804. 22 versus 8 infections, 29 versus 9 explantations. 5.8x greater risk in AUA group. Quinolones reduced both infections and explantations. Antifungals reduced explantation rate

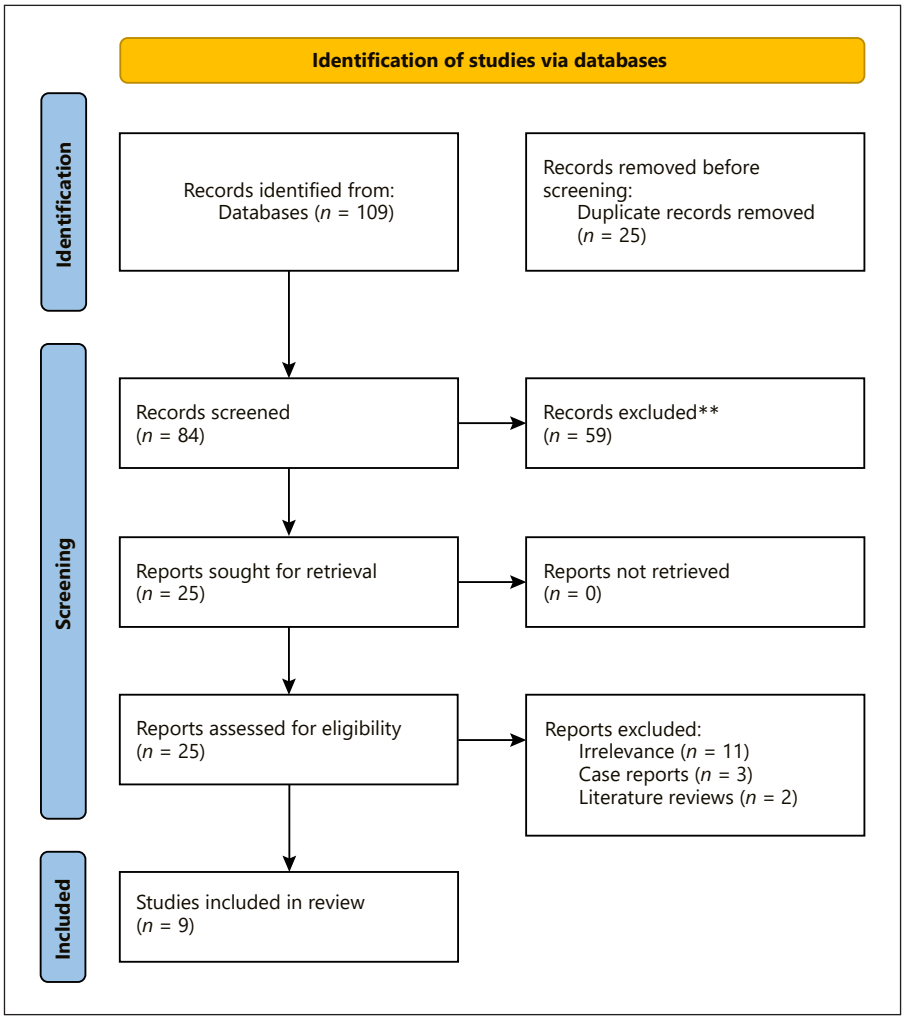

Fig. 1. PRISMA 2020 flow diagram for identification of studies via databases. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

clinically apparent or asymptomatic infection. Of their 84 patients with post PP implantation positive cultures, 71 were asymptomatic with the remaining 13 patients displaying infective symptoms. A traditional infection profile was noted in the clinically unaffected group, with *Candida* responsible for infections in 2% of positive cultures in the clinically unaffected group, while it was responsible for 6% of positive cultures in the group displaying infective symptoms. Although this reiterates the lesser contribution of fungi compared to bacterial infections, it is perhaps suggestive of fungal infections tending to present more often with clinical signs of infection [15].

Advances in PP surgery including antibiotic coating of implants, revision washout surgery and alcohol skin preparation all lower the rate of infection; however, the profile of infectious microorganisms responsible appears to be changing, with less traditional *Staphylococcus* and more fungal infections being found on cultures. Perhaps this reflects that these methods aimed at reducing infection were less effective against fungal organisms [16].

In 2017, Gross et al. were able to show that *Candida* was responsible for 11.1% of 153 positive cultures post PP insertion [8, 17], and had much lower salvage rates (60%) than both anaerobes (71%) or Gram-positive (64%) organisms [18]. Patients with fungal infections were also shown to present relatively quickly for treatment after implantation (5.8 months). This was found to be sooner than those with Gram-negative infections (6.96 months) and much later compared to infections due to anaerobes (2.6 months) [19]. In addition, Gross et al. [20] demonstrated that the majority of patients (88%) that developed fungal infections had a background of diabetes or obesity.

Climate has previously been reported to impact on the probability of developing a fungal infection following PP insertion, with more infections found to occur during the spring months. June was found to be the month with the

highest number of PP infection, while March had the least. When increased relative humidity (>55%) was present, there were almost 3 times as many cases of PP infection than with reduced relative humidity (<55%) [21].

Efficacy of Current Prophylaxis Guidance on Fungal Infections following PP Implantation Surgery

Current guidelines on fungal infection prevention during PP implantation are lacking. In the largest study to date, Gross et al. (2017) retrospectively reviewed 227 patients from 25 institutions undergoing salvage procedures or explantation. Over a 14-year period, patients with a clear source of penile or scrotal infection were offered a salvage procedure, while those with more complex infection, visible necrosis, or device erosion underwent explantation of their PP. In all cases, they aimed to identify the antibiotic regime given as prophylaxis. They found that in 77% of cases, this was done in adherence to the AUA guidelines, which recommend prophylactic administration of Aminoglycoside plus Vancomycin or a first- or second-generation Cephalosporin 1 h before surgery. In addition, they documented that *Candida* was responsible for PP infection in 11.1% of cases, the 3rd most prevalent after *Escherichia coli* (18.3%) and *Staphylococcus* (15%). Although they postulated that *Candida* infections were opportunistic and possibly brought about by the eradication of other competing microorganisms, they were unable to find evidence to corroborate this theory. The authors suggested administering broad-spectrum antibiotics and antifungals to cover MRSA, oxacillin-resistant Gram-positive, and Gram-negative bacteria including *Pseudomonas aeruginosa*, anaerobic bacteria, and *Candida* species. The suggested regime included Vancomycin, Piperacillin-Tazobactam, and Fluconazole for a duration based on clinical judgement, which covered 100% of the organisms cultured in their series. No post-operative antifungals on discharge were recommended unless cultures were positive for *Candida* due to high likelihood of eradication of fungal infections during surgery [8].

Following this work, another research group led by Brennan et al. [22] employed the use of Amphotericin B in addition to Gentamicin and Vancomycin to diminish the risk of *Candida* infections in PP surgery. Their solution was used to coat the penile implant and to irrigate the wound bed. Subsequently, a retrospective review of all 1,027 patients treated in this manner over 2 years found that only 6 patients underwent explantation or salvage surgery for PP infections, none of which were due to *Candida*. They concluded that Amphotericin B was an inexpensive, easy, and effective method of eliminating *Candida* infections in PP implantation surgery when added to the traditional antibiotic dip and irrigation solution [22].

Most recently, Towe et al. conducted a retrospective multicentre study to investigate the infection rates in patients with diabetes undergoing PP implantation with different antibiotic prophylaxis regimes. Complete data were analysed for 804 patients from 18 centres over a 15-year time frame. The addition of an antifungal to the AUA recommended that antibiotic prophylaxis regime reduced the infection rate from 6.3% to 0%; however, the authors did not comment on the reduction of fungal infections in particular [23].

Financial Cost of Incorporating Antifungal Prophylaxis in Patients Undergoing PP Implantation Surgery

The Hospital Episode Statistics data for the financial year of 2019-2020 demonstrate that a total of 488 PP implantation procedures were performed in England last year. It is important to note that the COVID-19 pandemic is unlikely to affect these data as the UK lockdown came into effect in week 51 of the financial year. The total PP implantation procedures were further divided into 466 elective cases and 22 emergency cases [24]. BAUS reports that the overall risk of PP infection following primary implantation is 2% allowing us to estimate ~10 cases last year [25]. According to Gross et al. [8], only 1 case (11%) would have been attributed to a fungal infection. The cost of a single vial of Amphotericin B is £3.88 [26], equating to an annual cost of £1 893.44 if all patients undergoing PP implantation received a prophylactic dose, far less than the cost of a single revision procedure as a consequence of implant infection.

Discussion

Infections following PP surgery have been well documented in the literature. It has been commonly cited as a post-operative complication; however, traditionally the microorganisms thought to be most attributed to these infections were bacterial. For this reason, many advisory bodies such as AUA and European Association of Urology have developed guidelines to help prevent this significant complication with the use of antibiotic prophylaxis. This currently comprises the use of an Aminoglycoside plus Vancomycin or a first- or second-generation Cephalosporin 1 h before surgery.

This review has shown that there is evidence in the literature suggesting a change in microorganisms being found at the time of PP implantation revision surgery, with less *Staphylococcus* and more fungi, *E. coli*, and *En-*

terococcus [16] infections. Interestingly, fungal infections were reported in up to 11.1% of all infections in some studies [8]. This change in trend over the years could be related to the improvements in surgical technique, antibiotic prophylaxis, and alcohol skin preparation [16]. The eradication of previously common microorganisms, such as *Staphylococcus*, could naturally allow other organisms not covered by prophylactic regimes to flourish and lead to a greater proportion of PP infections.

As the literature reported an increased incidence of fungal PP infections, various research groups have investigated the efficacy of introducing an antifungal agent in combination with the current antibiotic prophylaxis given. Studies have shown that the addition of antifungals such as Fluconazole [8] and Amphotericin B [22] reduces the incidence of post PP implantation fungal infections [23].

It is difficult to extrapolate tangible findings given the sparsity of studies investigating fungal infections following PP implantation surgery, and the quality of the evidence provided by the studies identified is a limiting factor; however, they do facilitate a basic financial calculation revealing the minimal cost of additional antifungal prophylaxis. Using the recent Hospital Episode Statistics data, it can be demonstrated that given the number of PP implants performed annually in the UK, only a very small proportion are likely to develop the devastating complication of a fungal infection requiring revision surgery, most likely explantation and delayed reimplantation. With antifungal prophylaxis with Amphotericin B being so cheap, the routine addition of such an antifungal with traditional antibiotic prophylaxis is likely to be cost effective if it prevents a single revision episode over a 4- to- 5-year period. To date, there are no randomized controlled trials available studying the efficacy of antifungal prophylaxis on patients undergoing PP implantation. The majority of fungal infections in patients undergoing PP surgery occur in isolated cases reports. However, in the last 3 years, there has been an emergence of larger multicentre retrospective studies, providing more robust data.

Currently, there are no studies that have looked into the long-term effects of combined antifungal and antibiotic prophylaxis, including side-effect profile. It is possible that over time we may see further changes in the profile of microorganisms resulting in PP infections. The literature suggests that patients suffering with diabetes and obesity [20, 23], as well as those living in warmer, more humid climates [21] are at a much higher risk of developing a fungal infection following PP implantation, thus opening up the potential for focused antifungal prophylaxis if widespread usage is resisted.

Conclusion

Fungal infections are responsible for a growing proportion of post-penile implant infection. The literature has reported a reduction in fungal infections when prophylactic antifungal agents are employed. Two of the more popular agents, Fluconazole and Amphotericin B, have shown particular promise in efficacy and low cost. Future studies able to directly compare the efficacy of traditional antibiotic prophylaxis versus novel antifungal prophylaxis and study the long-term consequences of such regimes may provide more definitive guidance on this issue but will require huge numbers to illustrate statistical significance. Until robust evidence allowing for a guideline change is available to the contrary, we suggest the widespread adoption of routine antifungal prophylaxis for all patients undergoing PP surgery.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors (Z.S., I.P., and V.M.) were involved in performing the literature review to select relevant papers for inclusion in the systematic review. Z.S. wrote the initial draft with I.P. and V.M. editing this to produce the final draft for submission.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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