

# Clinical Use of the Antiseptic Polihexanide for Genital Tract Infections

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## Key Words

Polihexanide • Polyhexamethylene biguanide • Genital tract infection • Bacterial vaginosis • Human papilloma virus • Antisepsis • Antiseptic

## Abstract

**Background:** In clinical practice, treatment of genital tract infections is based on administration of either antibiotics or antiseptics. While antibiotics may be applied systemically or topically, antiseptics may be applied only topically. In case of bacterial vaginosis (BV), antibiotic therapy may often be limited and side effects due to systemic administration may develop. Polihexanide (PHMB) is a promising option for the topical treatment of genital tract infections, in particular BV and vaginitis. **Method:** A systematic search for publications on the use of PHMB for the treatment of genital infections in two electronic databases was performed. Titles, abstracts and citations were imported into a reference database. Duplicates were removed and two reviewers assessed each identified publication separately. **Results:** Among a total of 204 references, 3 prospective randomized trials were identified. Two trials treated BV infections with PHMB in comparison to clindamycin as antibiotic standard therapy with no

significant differences either in safety or in efficacy. The third controlled trial investigated the clinical efficacy of PHMB compared to placebo in the treatment of human papilloma virus. Patients treated with PHMB daily for up to 16-weeks showed significantly higher (52%) clearance of genital warts as compared to patients treated with placebo (4%). **Conclusion:** PHMB may be a clinically effective alternative for the treatment of BV and human papilloma virus. Although PHMB-based antiseptics are available since the late 90s, controlled trials to investigate its clinical potential for antiseptic treatment are scant. Clinical use of antiseptics for the treatment of infectious diseases should be explored and supported further.

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## Introduction

The genital tract is an ecosystem for a multiplicity of microorganisms which have to be maintained in a fragile balance. If this balance is disturbed, infection may occur. Infectious diseases of the genital tract caused by bacteria, fungi, parasites, and viruses are a worldwide issue and are highly evidenced to impair somatic functions including

reproduction [1, 2]. Additionally, the vaginal flora may be a source for surgical site infections [3], urogenital tract infections during pregnancy [4], and newborn infections including an increased risk of preterm birth [5, 6].

*Mycoplasma hominis* is known to decrease fertility in males [7], whereas *Mycoplasma genitalium* and *Chlamydia trachomatis* are responsible for infertility in males and females [8, 9]. Equally important are gonococcal infections which can cause urethritis, proctitis, cervicitis, and pelvic inflammatory disease with long-term effects such as infertility, ectopic pregnancy, and chronic pelvic pain [10]. Enterobacteriaceae like *Escherichia coli* or *Enterococcus faecalis* are the most common causes of non-sexually transmitted infections [2]. *Pseudomonas aeruginosa* as well as Gram-positive cocci that commonly colonize the male urethra can cause prostatitis and epididymitis and consecutively impair fertility [11]. *Candida albicans* was associated with male infertility because of an inhibitory effect on human sperms [12]. In the female genital tract, *C. albicans* is a common commensal but may also cause vaginitis and cervicitis [2]. Toxin-producing *Staphylococcus aureus* strains have been identified as underlying pathogens for the development of vaginal menstrual toxic shock syndrome [13–15]. Viral genital tract infections are mostly caused by herpes viruses, human papilloma viruses (HPV), and human immunodeficiency viruses (HIV) either due to the virus itself or to side effects.

Bacterial vaginosis (BV) is the most common disorder of the vaginal flora, caused by different microbial species, with a prevalence of 5–30% in adult females [16–18]. BV is associated with an increased risk of acute upper genital tract infection [19, 20]. Vaginitis is the most common gynecologic diagnosis secondary to BV [21], vulvovaginal candidiasis [22], or trichomoniasis [23].

Infectious genital tract diseases are commonly treated with antibiotics such as clindamycin or metronidazole [24]. Today, antimicrobial chemotherapy is increasingly complicated by progressive antibiotic resistance [25]. Moreover, new insights into the structure and function of the colonization of the vagina help to explain why antibiotic treatment is only of limited use in infections involving microbial biofilms. The treatment of genital tract infections, in particular vaginosis and vaginitis, is therefore still a great challenge. Compared to oral antibiotic therapy, local treatment of genital tract infections shows less systemically side effects like nausea, vomiting, and taste perversion [26, 27].

Modern antiseptics are an excellent alternative to antibiotic treatment, provided that they combine a broad

antimicrobial spectrum with low toxicity, high tissue compatibility, low or missing adsorption, and good applicability. Therefore, antiseptics are the first option for the treatment of local microbial infections.

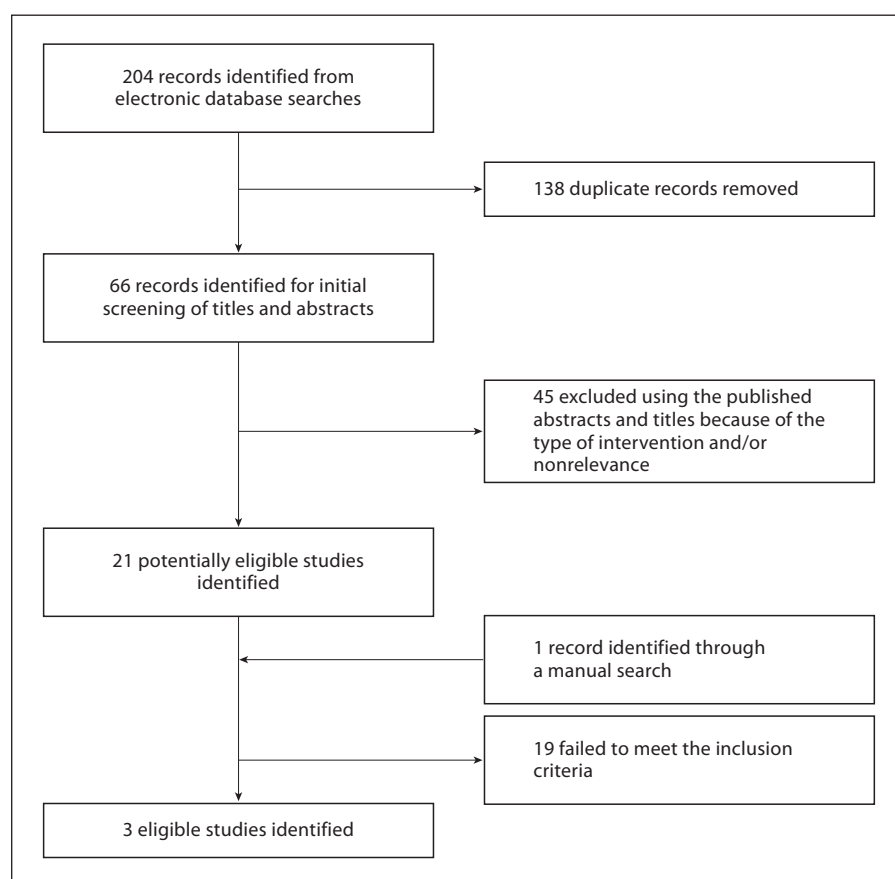
In the past, chlorhexidine digluconate (CHX) was used as a general vaginal antiseptic for over three decades [28]. However, hyperkeratosis, ulceration, dysplasia, and a significant increase in DNA damages by CHX were observed in rat experiments [29, 30]. Additionally, concentration-dependent CHX significantly inhibits wound healing and granulation [31, 32], which corresponds with the cytotoxic effect on osteoblasts and odontoblast-like cells [33, 34]. Moreover, degradation during storage may release the carcinogen 2-chloroaniline from low-grade CHX [35].

Therefore, other antiseptics like PHMB [36] and octenidine [37] have moved into the focus of antiseptic treatment. While PHMB is a structural sibling of CHX, it lacks many of its drawbacks because of the lack of 2-chloroaniline in the molecular structure of PHMB.

Polihexanide is well tolerated when used topically on skin, wounds [38], eyes [39, 40], and vaginal mucous membrane [41]. Only a negligible allergic risk, very low toxicity, and no adsorption of PHMB have been described [36]. Its tissue compatibility and biocompatibility is much better than that of CHX in vitro. Because of the additionally higher antimicrobial efficacy, PHMB achieved a better biocompatibility index than chlorhexidine and should be preferred [42]. Additionally, PHMB significantly stimulates wound healing [43] and there is no indication of any mutagenicity or carcinogenicity of PHMB in vitro or in vivo [38].

The efficacy of PHMB against infected wounds, prostheses, carcinomas, and methicillin-resistant *S. aureus* (MRSA) in vivo has been extensively studied in different controlled clinical studies. The antimicrobial activity of PHMB based on its exclusive interaction with acidic, negatively charged phospholipids in the bacterial membrane leads to increased fluidity, permeability, and loss of integrity, followed by the death of the organism [44–47]. Transferred to the cytoplasm it leads to disruption of the bacterial metabolism. Because neutral phospholipids are only slightly affected, PHMB has a low toxicity against human cells [38, 48, 49]. PHMB binds to cellular surfaces which is why it also has a sustained effect over hours [39, 50].

PHMB is commercially available in many formulations and for different indications including wound antiseptics, rinsing, and decolonization of unwanted organisms (e.g. MRSA) to name only a few. For genital treatment, PHMB is patented as a single-dose, isotonic topical



**Fig. 1.** Flow diagram outlining the literature search and review of the studies.

solution (Monogin®; Lo.Li. Pharma S.r.l., Rome, Italy). The purpose of this work is to review the existing literature on the antiseptic polihexanide (polyhexamethylene biguanide; PHMB) for the treatment of genital tract infections.

## Methods

A systematic search for manuscripts published in any language in the two electronic databases Pubmed and ISI Web of Science was performed. The following syntax for literature searches in both databases was used:

- Genital tract infection and PHMB or polihexanide or polyhexamethylene biguanide
- Vaginitis and PHMB or polihexanide or polyhexamethylene biguanide
- Vaginosis and PHMB or polihexanide or polyhexamethylene biguanide

No other limits were used. Bibliographies of manuscripts were screened for additional sources and an additional manual search was done.

Studies were included on the basis of four criteria: disease, therapy, study design, and outcome. The diseases of interest were

genital tract infections, especially vaginosis and vaginitis. The therapy of interest was treatment with PHMB. Primarily, in vivo studies and clinical studies were selected. Additionally, in vitro studies were considered to emphasize the efficacy against the disease-causing pathogen. The outcome of interest was the comparison of PHMB treatment with a placebo or standard therapy.

All relevant titles, abstracts, and citations were imported into a reference database. Duplicates were removed and two reviewers independently assessed each publication separately. Differences in opinion were discussed among all authors and the final decision was made by means of open consensus. Both reviewers independently abstracted data from all selected studies.

## Results

The search results are shown in a flow diagram (fig. 1). A total of 204 references were identified from the searches of the electronic databases. After omitting 138 duplicate references, 66 original references were further analyzed. Overall, 21 potentially eligible studies were identified. The search resulted in one further study. Nineteen references were excluded after review of the full text. The

**Table 1.** Eligible studies

| Study (country)             | Type  | Setting  | Outcome   |
|-----------------------------|---|--|---|
| Gerli [41] (Italy)          | Prospective, randomized, parallel-group study                               | Among 110 BV patients, the efficacy of a single-dose PHMB vaginal gel versus a 7-day clindamycin cream treatment against BV was compared   | The efficacy of mono-dose PHMB treatment was similar to 7-days clindamycin cream treatment            |
| Marelli et al. [63] (Italy) | Prospective, double-blind, randomized, placebo trial                        | HPV patients (n = 140), who applied PHMB daily for up to 16 weeks, were cleared of warts in 52% of cases (warts clearance in the placebo group, 4%). In a 12-week treatment-free follow-up period, wart recurrence was investigated. The recurrence rate after a 12-week treatment-free follow-up period was 19% in the PHMB group and 0% in the placebo group | PHMB is effective for the treatment of genital papilloma virus infections                             |
| Minozzi et al. [57] (Italy) | Prospective, multicenter, randomized, single-blind and parallel-group study | Among 740 BV patients, the efficacy of a single-dose PHMB solution (Monogin) versus a 7-day clindamycin cream treatment against BV was compared  | There were no significant differences between the two therapy regimes either in safety or in efficacy |

three remaining references were prospective randomized trials. In two trials, BV infections were treated with PHMB in comparison to clindamycin as standard therapy. The third trial investigated HPV patients treated with PHMB or a placebo in a randomized controlled study (table 1).

#### *In vitro Studies*

The broad antimicrobial efficacy of PHMB against microorganisms frequently causing genital tract infections has been repeatedly shown in vitro. PHMB was effective against planktonic *E. coli* and *S. aureus* as well as *P. aeruginosa* in suspension and biofilms [37–42, 51–53]. In addition, PHMB was also effective against *E. faecalis* and *C. albicans* [54], as well as against intracellular bacteria such as *Chlamydia* sp. and *Neisseria* sp. [52], and protozoa such as *Acanthamoeba* [53].

The virocidal in vitro efficacy of PHMB was investigated in two references. It was shown that 0.01% PHMB is effective against herpes viruses in vitro [58]. Krebs et al. [59] found a modest antiviral efficacy against cell-free and cell-associated HIV-1. Furthermore, they found that PHMB inhibited binding and entry of the virus.

#### *Clinical Studies*

Minozzi et al. [57] compared the efficacy of a single-dose PHMB solution (Monogin) versus a 7-day clindamycin cream treatment against BV in a multi-center, randomized, single-blind and parallel-group study which en-

rolled 740 patients. Twenty-one to 30 days after the start of the study, the authors found no significant (95% CI,  $p = 0.386$ ) differences between both therapy regimes either in safety or in efficacy. Safety was investigated by monitoring treatment-emergent adverse events (e.g. urinary tract infection) throughout the study. Namely, 30.4% of all PHMB-treated patients and 26.8% of clindamycin-treated patients had an adverse event, with no statistically significant difference. The efficacy was analyzed in a per-protocol group with 347 patients. Cure of BV in the per-protocol group was evaluated by frequencies of ‘investigator cure’ (requirement for additional therapy: 89.1% of the PHMB group, 86.4% of the clindamycin group achieved cure), ‘clinical cure’ (conservative symptomatic measure: 64.3% of the PHMB group, 63.2% of the clindamycin group achieved cure), ‘Nugent cure’ (diagnostic evaluation: 56.5% of the PHMB group, 57.7% of the clindamycin group achieved cure), and ‘therapeutic cure’ (symptomatic, interpretive, and diagnostic measures: 42.1% of the PHMB group, 45.6% of the clindamycin group achieved cure). Pertaining to the results, it seems that a single dose of PHMB is statistically equivalently effective to 7 daily doses of clindamycin for the treatment of BV.

Gerli and di Renzo [41] investigated patients treated with the same regimen (PHMB,  $n = 59$ ; clindamycin,  $n = 51$ ) and concluded that mono-dose PHMB treatment should be the therapy of choice for BV.

Marelli et al. [63] showed in a prospective, double-blind, randomized placebo trial that PHMB is effective

for the treatment of genital papilloma virus infections. Patients who applied PHMB daily for up to 16 weeks were significantly ( $p < 0.0001$ ) more frequently cleared of warts (52%) as compared to patients in the placebo group (4%). In a 12-week treatment-free follow-up period, wart recurrence was investigated. The recurrence rate after the 12-week treatment-free follow-up period was 19% in the PHMB group and 0% in the placebo group.

## Discussion

Genital tract infections are a serious challenge in gynecology as well as in urology. In the last decade it has become increasingly clear that antimicrobial chemotherapy is limited by an increasingly prevalent antibiotic resistance. Additionally, frequent and inappropriate use of antibiotics promotes resistance even further. With the availability of new antiseptic compounds with a broad antimicrobial spectrum, provided in easy-to-use and well-tolerated formulations, local treatment is expected to become more and more important in genital tract therapy of localized limited infections.

PHMB is a modern antiseptic that combines a broad antimicrobial spectrum with low toxicity and without long-term risks, and with high tissue compatibility, no reported adsorption, and good applicability as solution, gel, ointment, or foam [37]. The modes of action make the development of resistance to PHMB highly unlikely. Actually, no bacterial resistance has been described in vitro or from clinical or environmental samples [69]. The antimicrobial efficacy of PHMB is not impaired by protein and blood [71]. The most interesting feature of PHMB is its outstanding relation between antimicrobial efficacy and low cytotoxicity and exceptional tissue compatibility that has been repeatedly described by independent researchers in vitro, in animal models, and in controlled clinical studies and case reports. At low concentrations, PHMB even seems not only to be nontoxic but also to have a positive effect on the proliferation of human keratinocytes that promotes wound healing [60–62]. It is actually one of the most promising antiseptic substances and has been used in medicine for many indications for over 20 years.

Although the efficacy of PHMB against typical genital tract pathogens has been repeatedly demonstrated, the number of actual clinical studies published on the topic is limited because the introduction of PHMB in clinical practice (except in wound antisepsis) only started in the last decade. Identified studies show the clinical effective-

ness of PHMB and go along well with results from in vivo studies and clinical data from other indications, e.g. wound infections and treatment of acanthamoeba keratitis [36]. Minozzi et al. [57] and Gerli et al. [41] compared the efficacy of a single-dose PHMB solution (Monogin) versus 7-day clindamycin cream treatment against BV and found no significant differences between the two therapy regimes in either safety or efficacy. The mechanism of action of clindamycin is based on the inhibition of protein synthesis by binding to the 50S subunit of the bacterial ribosome, resulting in a mostly bacteriostatic effect. Therefore, the efficacy depends mainly on the period of time during which the effective concentration is above the minimum inhibitory concentration of the pathogen. Because both agents were self-administered by the patients, the efficacy depends also on the compliance, which is commonly better in cases of single treatment with PHMB.

Even the antiviral efficacy against genital papilloma-virus could be demonstrated in a clinical trial [63]. In the past, CHX or antibiotics were often used for the treatment of genital tract infections. The evidence available today, though limited, indicates that even a single dose of PHMB is comparable to a 7-day antibiotic course but has no unwanted effects like induction of antimicrobial resistance.

Until now, a final evaluation of PHMB in comparison to other genital tract antiseptics, e.g. CHX, has not been possible because no studies comparing both substances are available. Due to the better tissue compatibility of PHMB compared with CHX, the in vitro effectiveness of PHMB in the presence of a bio-burden, the primary decreased susceptibility of enterococci strains against CHX [64], and the R-plasmid-coded CHX resistance in vitro [65–67] with possible cross-resistance against antibiotics [68], such studies would be highly appreciated as final evidence for the superiority of treatment of genital tract infections by PHMB as previously shown for other indications.

## Conclusion

PHMB may be a clinically effective alternative for the treatment of BV and HPV. Although PHMB-based antiseptics have been available since the late 90s, controlled trials to investigate its clinical potential for antiseptic treatment are scant. Clinical use of antiseptics for the treatment of infectious diseases should be explored and supported further.

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## Disclosure Statement

The authors have no conflicts of interest that are directly relevant to the content of this study.

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