CASE STUDY

CONTENTS

Relation of *Streptococcus Pyogenes* tonsillitis isolate to antimicrobial agents and its infection treatment

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ABSTRACT

We reported the case of tonsillitis treatment in a 17-years-old boy with use of chemical non-antibiotic preparations, plant derived products and antibiotic benzathine phenoxymethylpenicillin. The antimicrobial agents for treatment were selected on the basis of their activity against a disease agent, the group A *β*-hemolytic strain *Streptococcus pyogenes* BS1 isolated from a patient.

The bacterium was susceptible *in vitro* to β-lactams, with largest zones conditioned by penicillin G and benzathine phenoxymethylpenicillin discs, to fluoroquinolones and to cephems, with exception of cefazolin. Lincosamide clindamycin, macrolide spiramycin, aminoglycoside gentamicin, erythromycin, tetracycline and combination of sulfamethoxazole and trimethoprim were inactive against this bacterium. The *Streptococcus pyogenes* BS1 demonstrated intermediate susceptibility to the cephalosporin cephalexin, fluoroquinolone lomefloxacin and glycopeptide vancomycin.

Non-antibiotic preparations were evaluated against *Streptococcus pyogenes* BS1 also. Among them "Stomatidin", "Chlorophyllipt", and phages of "Pyofag" were more effective than "Decatylen", "Decasan" and "Furadonin" *in vitro*.

The antimicrobial applications of "Stomatidin", "Chlorophyllipt" and phages of "Pyofag" in the patient were less effective compared to the result of antibiotic benzathine phenoxymethylpenicillin treatment. Complete recovery of the patient was achieved with use of this antibiotic and *Calendula* flower extract as an local anti-inflammatory agent.

KEY WORDS: *Streptococcus pyogenes,* antibiotics and non-antibiotic preparations, susceptibility, resistance, tonsillitis treatment, 17-years-old boy

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INTRODUCTION

Streptococcal sore throat, strep throat also known as tonsillitis is a common bacterial infection. It is most spread in children, accounting 20%–30% sore throat visits to doctors, and less in adults, comprising 5%–15% of sore throat visits. The *β*-hemolytic *Streptococcus pyogenes* causes from 15 to 30% of all pharyngitis in children [1]. It is generally accepted that children cohorts from 5 to 15 years are most vulnerable to the disease.

β-lactams are usually applied in the treatment of strep throat infection, with macrolides being used for patients allergic to β-lactams.

However, reduced susceptibility to β-lactams [2] and resistances to penicillin [3], to cephalosporins ceftriaxone, macrolide erythromycin, lincosamide clindamycin, tetracycline, amphenicol chloramphenicol, fluoroquinolone levofloxacin [4, 5] were detected in *S. pyogenes*. Up to one-third of patients treated for group A Streptococcus pharyngitis fail to respond to antibiotic therapy [3].

Throat lozenges containing antimicrobial quaternary ammonium compound, dequalinium chloride [6], antiseptic and local anesthetic hexylresorcinol [7] demonstrated effectiveness in treatment of acute sore throat.

Some plant products are able to suppress the growth of *S. pyogenes*. Most often such activity were reported in compounds containing aromatic rings [8]. Particularly, hot water infusions from licorice root, barberry root, thyme, and oregano flowering shoots that contain such compounds may provide potential sources for developing remedies against *S. pyogenes* infections [9]. List of medicinal plants producing compounds active against *Streptococcus pyogenes* contains 82 species [10].

On human tissue *Streptococcus pyogenes* is able to form biofilms that contribute to mechanisms of the bacterium resistance to antibiotics and antibiotic treatment failure [11]. Bacteriophage-encoded endolysin PlyC diffuses through the extracellular material constituting the bacterial biofilm and lyses the *Streptococcus pyogenes* cells within the biofilm matrix [12]. In contrast

to antibiotics, bacteriophages act specifically against particular microbes and, usually, have no harmful effect on normal microbiota of humans [13].

In this article we reported about treatment of tonsillitis in 17-years old boy with use of several non-antibiotic medications (synthetic chemicals, plant derived products and phages preparation) that only alleviated symptoms, and antibiotic benzathine phenoxymethylpenicillin application, that finally lead to the complete recovery of the patient.

CASE REPORT

17 years old boy experienced fever (temperatures above 38°C), sore throat, palatine tonsils enlargement to above 75% of the oropharyngeal width, the grade +4 , according to tonsil size grading by Brodsky and co-workers [14] and redness with typical tonsillar exudate, pain with swallowing and enlarged lymph nodes in the front of the neck. The blood analysis results, provided by the clinical laboratory, demonstrated an increase in lymphocytes to 46 per 100 of leucocytes (Table 1). The spleen and liver were not enlarged, suggesting no viral glandular fever.

The rapid antigen detection test (using a kit of AMEDA Labordiagnostik GmbH (Austria) was positive. The microscopy of the exudate demonstrated Gram-positive streptococci. The bacterium, cultured from exudate, was catalase-negative in catalase test [15]. It was sensitive to 0.04 IU of the bacitracin in the CLSI disc diffusion test. The β-hemolysis was observed around streptococcal colonies seeded from a throat swab and grown onto sheep blood agar at 37°C for 1 day [16]. The isolate was identified as group A β-hemolytic *Streptococcus pyogenes* and given the strain number BS1.

Susceptibility of *Streptococcus pyogenes* BS1 to antibiotics (Table 2) was studied in a disc diffusion test, using discs from HiMedia Laboratories Pvt. Limited (India) and Liofilchem Inc (USA).

To test other antimicrobials for antistreptococcal activity, sterile Whattman №1 paper discs (6 mm in diameter) were impregnated with solutions of these antimicrobial agents using 5 µL pipette to give comparable concentrations of active ingredients per disc. These discs were dried in sterile air flow each time before the next drop of the solution application. By this way the discs were prepared from preparations "Stomatidin" (chlorhexidine, 1 mg/ml), Bosnalijek d. d., (Bosnia and Herzegovina), "Chlorophyllipt" (ethanol extract of chlorophylls A and B from *Eucalyptus viminalis,* 10 mg/mL), Halychfarm (Ukraine), "Furadonin" (nitrofurantoin) tablets Olainfarm, (Latvia), "Decatylen" lozenges (0.25 mg dequalinium chloride/0.03 mg cinchocaine hydrochloride) Merckle GmbH (Germany), "Decasan" (0.02% decamethoxine solution, inhalation antiseptic) YURiA Pharm (Ukraine) (Table 3).

The *Pelargonium sidoides* roots ethanol extract Eps® 7630 (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), and Calendulae flos (*Calendula* flowers extract in 70% ethanol, 1:10) (LLC DKP Pharmaceutical factory, (Ukraine) were applied as 20 µL drops on Petri dishes medium in advance of lawns inoculation. The "Pyofag", a suspension of phages, including specific to *Streptococcus pyogenes*, "Pharmex Group" LLC (Ukraine) was applied as 20 µL drops onto the fresh seeded lawns.

All discs were placed onto lawns of *Streptococcus pyogenes* BS1 fresh-seeded on the blood-agar with broth night culture. The inhibition zones (Table 2) were evaluated after 1 day of the Petri dishes incubation at 37°C according to CLSI standards [17].

The isolate *Streptococcus pyogenes* BS1 was most sensitive to β-lactams, susceptible to all tested penicillins with largest zones conditioned by penicillin G and benzathine phenoxymethylpenicillin (Table 2). It also demonstrated good sensitivity to fluoroquinolones and to cephems, with exception of cefazolin. Lincosamide clindamycin, macrolide spiramycin and aminoglycoside gentamicin produced zones 10 mm in diameter or less and were regarded as inactive against our isolate. Application of discs containing erythromycin, tetracycline and combination of sulfonamide antibiotic sulfamethoxazole and trimethoprim, a dihydrofolate reductase inhibitor, resulted in no zones formation in the lawns evidencing resistance of isolated strain to these antibiotics. The *Streptococcus pyogenes* BS1 demonstrated intermediate susceptibility to the cephalosporin ceph-

Table 1. White blood cell distribution in blood of the patient

White blood cell line	Cells before treatment, %	Cells after treatment, %
Neutrophils	45	50
Lymphocytes	46	37
Monocytes	8	8
Eosinophils	1	4
Basophils	0	1

Table 2. Sensitivity of *Streptococcus pyogenes* BS1 to antibiotics

Antimicrobial agent	Applied disc content	*Mean inhibition zones in bacterial lawns, mm
Penicillins		
Amoxicillin	30 µg	24 S
Amoxicillin/Clavulanic acid	20/10 µg	23 S
Ampicillin/cloxacillin	10 µg	25 S
Ampicillin/sulbactam	10 µg	24 S
Ampicillin	10 µg	25, S
Penicillin G	10 IU	27, S
Benzathine phenoxymethylpenicillin	10 µg	27, S
Macrolide		
Azithromycin	15 µg	18, S
Erythromycin	15 µg	No zone, R
Spiramycin	100 µg	7 R
Oleandomycin Oxoid	15 µg	25 S
Roxithromycin	15 µg	26 S
Cephems		
Cephotaxim	30 µg	25,S
Cefoperazone	75 µg	24, S
Cefixim	5 µg	15, S
Cefazolin	30 µg	16, R
Cephalexin	30 µg	20, I
Lincosamides		
Clindamicin	2 µg	10, R
Aminoglycoside		
Gentamycin	10 µg	10, R
Fluoroquinolones		
Lomefloxacin	10 µg	19, I
Moxifloxacin	5 µg	18, S
Norfloxacin	10 µg	20, S
Ofloxacin	5 µg	17, S
Tetracyclines		
Tetracyclin	30 µg	No zone, R
Diaminopyrimidine/sulfonamide (1:19)		
Trimethoprim/sulfametoxazole	1.25/23.75 µg	No zone, R
Glycopeptide		
Teicoplanin	30 µg	26 S
Vancomycin	30 µg	12, I
Polypeptide		
Bacitracin	0.04 IU	16 S

*Relation of isolate to antibiotics according to CLSI standards [17]: S - susceptible, I - intermediate susceptibility, R – resistant.

alexin, fluoroquinolone lomefloxacin and glycopeptide vancomycin.

The *Streptococcus pyogenes* BS1 was sensitive to antimicrobial preparations other than antibiotics also. Particularly, *in vitro* the bacterial isolate demonstrated good susceptibility to the "Stomatidin", "Chlorophyllipt", and "Pyofag" (Table 3). The "Decatylen", "Decasan" and "Furadonin" were less effective *in vitro*. They produced small inhibition zones (less than 10 mm in diameter). The "*Pelargonium sidoides* roots extract Eps® 7630", a

Table 3. Sensitivity of *Streptococcus pyogenes* BS1 in vitro to antimicrobial agents other than antibiotics

Antimicrobial agent	Applied disc content	Mean inhibition zones in bacterial lawns, mm
Stomatidin (clorhexidin) (hexetidin 0.1% solution)	20 µg	35
Decatylen lozenges (0.25 mg dequalinium chloride/0.03 mg cinchocaine hydrochloride)	25 µg/3 µg	8
Decasan (0.02% decamethoxine solution inhalation antiseptic)	20 µg	5
Furadonin (nitrofurantoin)	20 µg	9
Chlorophyllipt	20 µg	26
A prodelphinidin-rich ethanolic extract (1:9-11), from *Pelargonium sidoides* roots DC, EPs® 7630	20 µL	No zone
Calendulae flos (*Calendula* flowers extract in 70% ethanol, 1:10)	20 µL	No zone
"Pyofag", the phages suspension	20 µL	33

drug for treatment of respiratory tract infections and "Calendulae flos" the *Calendula* flowers extract in 70% ethanol, 1:10 (LLC DKP Pharmaceutical factory, Ukraine) was not active in *Streptococcus pyogenes* BS1 lawns (Table 3).

The boy's parents insisted on non-antibiotic treatment first. Thus, "Stomatidin" (hexetidine 0.1% solution) was recommended to boy to rinse the mouth and gargle with 15 ml of undiluted solution for half of minute two times a day (after breakfast and supper) and "Chlorophyllipt" was used as a spray after dinner. The treatment lasted 3 days and resulted in some decrease in body temperature (to around 37.5°C) and alleviation of pain sensations as results of size of tonsils decrease to about 62% of the oropharyngeal width, the grade +3 by [14], some decrease in redness of tonsils and surrounding area and in reduction of whitish exudation from palatine tonsils. However, symptoms were not improved on the 4th day. Particularly, neck lymph nodes and tonsils remain enlarged and body temperature still elevated (around 37.5°C).

Then, this treatment was substituted with application of the "Pyofag". The 5 mL portions of the phages suspension was administered via compressor nebulizer "Ulaizer Home" Vega Technologies Inc. (Taiwan) inhalation during 10 min after supper for 3 consequtive days. The elevated body temperature decreased further to around 37°C. The pain with swallowing was somewhat alleviated, because size of tonsils decreased more, to about 43% of the oropharyngeal width, a grade +2. However, symptoms of enlarged lymph nodes, the redness of the tonsils and surrounding throat areas and tonsillar exudate improved a little only.

Regarding the health state of the patient after 6 days of non-antibiotic treatment as not better enough, it was decided to treat the boy with 1 g/day of benzathine phenoxymethylpenicillin in preparation OSPEN® ("Biochemie GmbH", Germany) administered orally as water suspension in four 5 mL spoons each containing 250 mg (400000 IU) of the antibiotic with interval intake of 6 hours. Additionally, as an anti-inflammation treatment, one teaspoon of *Calendula* flower extract was diluted in 150 ml of warm boiled water and used for rinsing of the throat. This was done 4 times per day after the antibiotic intake. The health of the boy significantly improved on day 4th of the antibiotic and *Calendula* extract use. Particularly, body temperature normalized, tonsillar exudation ceased completely. The redness of the tonsils and surrounding throat areas decreased further. The boy received this treatment for the 6 following days to fulfill the WHO's recommendation of 10 days for longevity of the antibiotic use. On day 7 of such a therapy the redness of the tonsils and surrounding throat areas almost completely disappeared and tonsils and neck nodes significantly decreased in size. Particularly, tonsils decreased in size to the grade +1 (they were just outside of the tonsillar fossa and occupied about 20% of the oropharyngeal width).

The blood analysis following treatment demonstrated 37% of lymphocytes among leukocytes (Table 1). Thus, the lymphocytes decreased in number to normal levels for adults.

Regarding the reports about development of reduced susceptibility to β-lactams resistance to other antibiotics of choice, such as clindamycin and macrolides in *Streptococcus pyogenes* [4, 5, 18, 19], the negative effect on microbiome of patients [20] and possible complications in patient's organism after the antibiotics use [22, 23], parents together with doctors have the right to decide whether to use these antimicrobials for their children treatment or not.

The parents of the boy insisted on non-antibiotic therapy first. We started it with "Stomatidin" and "Chlorophyllipt". They provided only partial alleviation of symptoms.

The "Stomatidin" is an antiseptic agent for topical use, particularly during streptococcal pharyngitis [24]. Its weak analgesic effect explains some pain relief in a boy's throat with swallowing at the start of his treatment. It has non-specific antimicrobial action and must be used with care not to affect the normal flora of the throat. Its application was intermitted with "Chlorophyllipt" spray. Together these preparations provided some improvement in the patient's health.

The "Decatylen", "Decasan" and "Furadonin" we not used in treatment, because they were less effective on *S. pyogenes* BS1 lawns, than "Stomatidin" and "Chlorophyllipt" prepared discs or "Pyofag".

The dequalinium chloride was reported as effective in curing of sore throat infection [6, 25]. However, in our case this and other quaternary ammonium compound, the decamethoxine, were not chosen as the treatment, because of their lower activity against *Streptococcus pyogenes* BS1 *in vitro*, compared to stomatidin, chlorophyllipt or bacteriophage (Table 3). Recently, Sydorchuk et al. [26] reported the decrease in sensitivity to decamethoxine over 50 years of its use by 5.42-3.63 times in clinical strains of *S. pyogenes*.

Earlier Kayser O. and Kolodziej H. [27] demonstrated antibacterial activity of extracts and constituents of *Pelargonium sidoides* and *Pelargonium reniforme* against β-hemolytic streptococci. However, in our case study, a prodelphinidin-rich ethanolic extract (1:9-11) from *Pelargonium sidoides* roots DC, EPs® 7630, was inactive against *Streptococcus pyogenes* BS1 in Petri dishes. Earlier Uslu H. and co-workers [28] reported about resistance of *Streptococcus pyogenes* to this plant extract also. The *Calendula* flowers extract has no antimicrobial action against our *S. pyogenes* isolate. The extract was used as a gargle to decrease local inflammation. The "*Calendulae flos*", a *Calendula* flowers extract, was inactive against *Streptococcus pyogenes in vitro*, however, demonstrated good anti-inflammatory properties, when applied in time between benzathine phenoxymethylpenicillin intakes. The extract was approved [29] as an anti-inflammatory agent for the throat. Possibly, this herbal preparation can have more wide use in strep throat treatment.

The "Pyofag" suspension contains phages that kill *S. pyogenes* and produce a large zone of cell lysis in the *Streptococcus pyogenes* BS1 lawn. However, few colonies were growing in such zones, the evidence that some streptococcal cells were resistant to the phage. The application of phages resulted in somewhat alleviated symptoms within 2 days, but symptoms not demonstrated further decrease on day 3rd of phage inhalation. This suggests that some cells of streptococci in patient were resistant to the phage or phage particles had no access to the part of the bacterium cells, possibly, to those, present in tonsillar crypts and harboring in other anatomical gaps or in depressions of the tissues as the films. Thus, phage was unable to attack all cells of *Streptococcus pyogenes* in the throat of the boy. Enlarged lymph nodes, the redness of the tonsils and surrounding throat areas and tonsillar exudate presence suggested that some bacteria were protected from the phage by human organism relief or able to resist phage action.

The benzathine phenoxymethylpenicillin for treatment of *Streptococcus pyogenes* tonsillitis is recommended in Ukraine, particularly, by the clinical guideline approved by an extended meeting of state experts and Orders of the Ministry of Health [30].

Several remedies, with different mechanisms of action onto disease agent were moderate in efficiency treatment of *Streptococcus pyogenes* tonsillitis in our case: the "Stomatidin", an antiseptic with broad antimicrobial spectrum and analgetic effect; the phages of "Pyofag" with specific action against streptococci; and "Chlorophyllipt" an antimicrobial extract from *Eucalyptus viminalis* leaves. They are, possibly, unable to provide fast recovery from the disease.

The treatments with non-antibiotic antimicrobial agents lasted for 6 days. As they were not effective enough in our patient, we then turned to antibiotic benzathine phenoxymethylpenicillin use. This antibiotic and *Calendula* extract were applied for 10 days. The complete disappearance of symptoms was observed on day 7 of antibiotic use. All together, our patient treatment lasted longer (16 days) than treatments with immediate use of antibiotics (10 days or less).

CONCLUSIONS

Thus, we used several antimicrobial preparations for this case of 'strept throat' treatment. Some non-antibiotic agents, such as "Stomatidin" and "Chlorophyllipt" or "Pyofag" manifested antimicrobial activity *in vitro* comparable to that of antibiotics. The activity *in vitro* of chosen drugs (selected by best activity *in vitro*) correlated with positive effects on patient health. However, in our case non-antibiotic remedies were less effective for fighting of streptococcal tonsillitis infection in human organism than antibiotic benzathine phenoxymethylpenicillin. The better effect of the antibiotic, possibly, is due to its better penetration into the patient tissues.

The *Streptococcus pyogenes* BS1 *in vitro* is susceptible to β-lactams, to cephalosporins and to fluoroquinolones, however, resistant to erythromycin, spiramycin, cefazolin, clindamycin, gentamicin, tetracycline, trimethoprim/sulfamethoxazole. This evidencing the resistance

spread to these antibiotics in the local *Streptococcus pyogenes* population.

Regarding possible side effects of the antibiotics use, *in vitro* active non-antibiotic preparations can be applied first for treatment of streptococcal tonsillitis. If not active enough in patients, they can be carefully substituted or supplemented by antibiotic therapy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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