

# Strep: Putting out the Fire

A Biogenetix Clinical Presentation

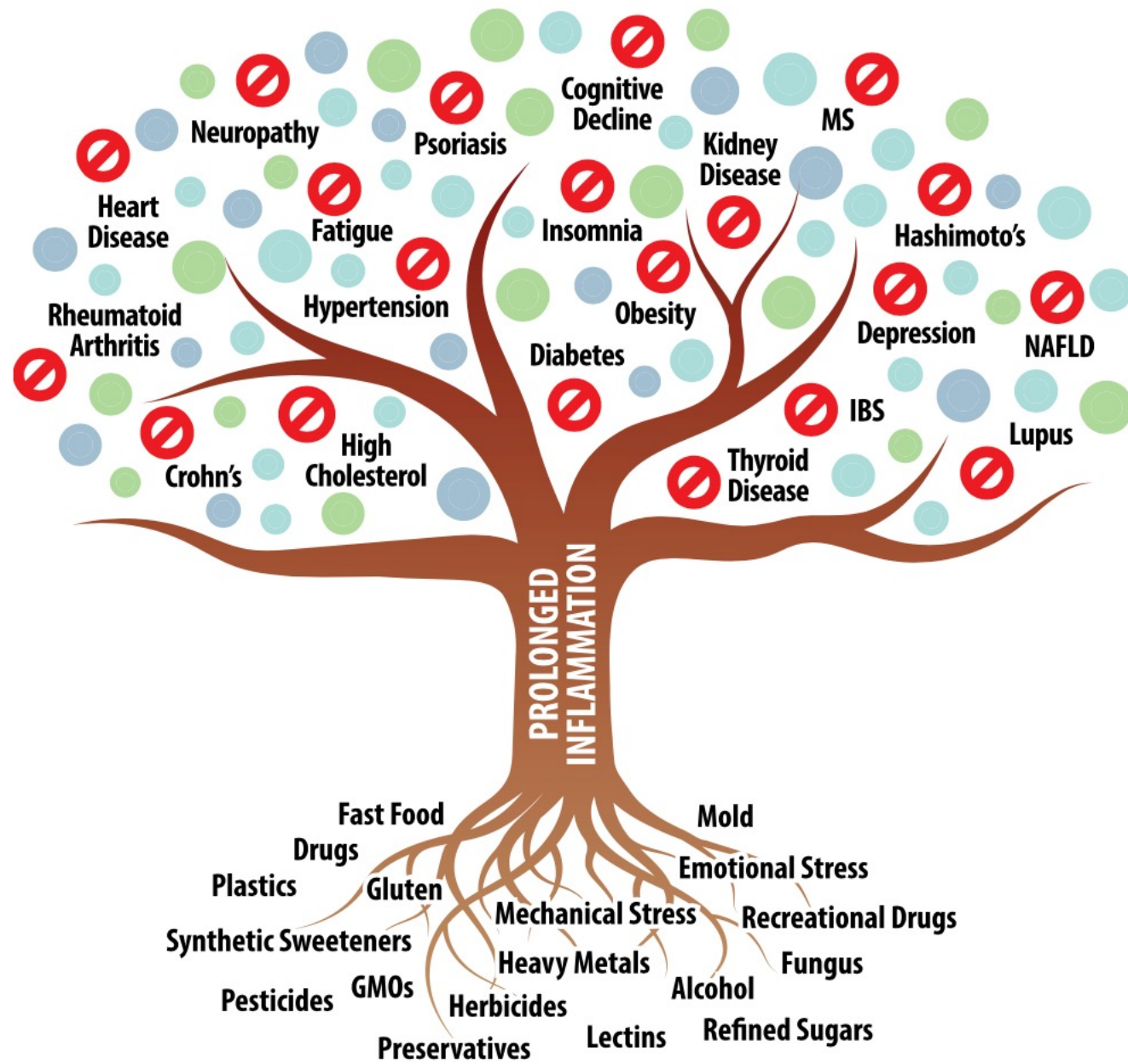
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*Streptococcus pyogenes* is a major human-specific bacterial pathogen that causes a wide array of manifestations ranging from mild localized infections to life-threatening invasive infections.[1] Ineffective treatment of *S. pyogenes* infections can result in the postinfectious sequela acute rheumatic fever and post-streptococcal glomerulonephritis. Moreover, it causes invasive infections like necrotizing fasciitis and toxic shock syndrome that is associated with and high morbidity and mortality.

*S. pyogenes* usually colonizes, pharynx, anus, and genital mucosa. Infections caused by *S. pyogenes* are highly contagious. Transmission can occur through airborne droplets, hand contact with nasal discharge or with objects or surfaces contaminated with bacteria, skin contact with contaminated lesions, or contaminated food sources. GAS Strains may acquire access to the skin via abrasions and skin lesions and may lead to erysipelas or cellulitis.[2] GAS can cause infection in muscle and fascia resulting in myositis and necrotizing fasciitis usually following a mild trauma and can result in toxic shock syndrome. *S. pyogenes* can cause the infection of the vaginal mucosa and uterus causing septicemia.[2] Skin lesions have been identified as the most common predisposing factor for severe *S. pyogenes* infections.[4] Crowded settings like military camps, nursing houses, and schools cause ease of transmission of the organism and result in epidemics of group A streptococci infection.



Streptococcal pharyngitis should be differentiated from throat infections due to parainfluenza virus, rhinovirus, coxsackievirus, adenovirus, etc), *Mycoplasma* species, *Corynebacterium diphtheria*, and Epstein-Barr virus.

Scarlet fever can be confused with measles and rubella. However, the absence of symptoms of upper respiratory tract infection and confluent rash in measles can help to differentiate these diseases.

Impetigo by *S. pyogenes* needs to be differentiated from impetigo infection by staphylococcus aureus. *S. pyogenes* cause non-bullous impetigo while *S. aureus* leads to bullous impetigo.

The drug of choice for treatment of bacterial pharyngitis is oral penicillin for 10 days or IM benzathine penicillin. This treatment is cost-effective and has a narrow spectrum of activity.

In patients with penicillin allergy, macrolides and first-generation cephalosporins can be used.<sup>[17][18]</sup> However, some strains of *S. pyogenes* have developed resistance to macrolides and macrolides are used as third-line of treatment for Streptococcal throat infection.<sup>[19]</sup>

Severe invasive *S. pyogenes* infections can be treated with vancomycin or clindamycin.<sup>[20]</sup> Intravenous antibiotic therapy and surgery for the removal of necrotic tissue are recommended in the case of soft tissue skin infection by *S. pyogenes*.

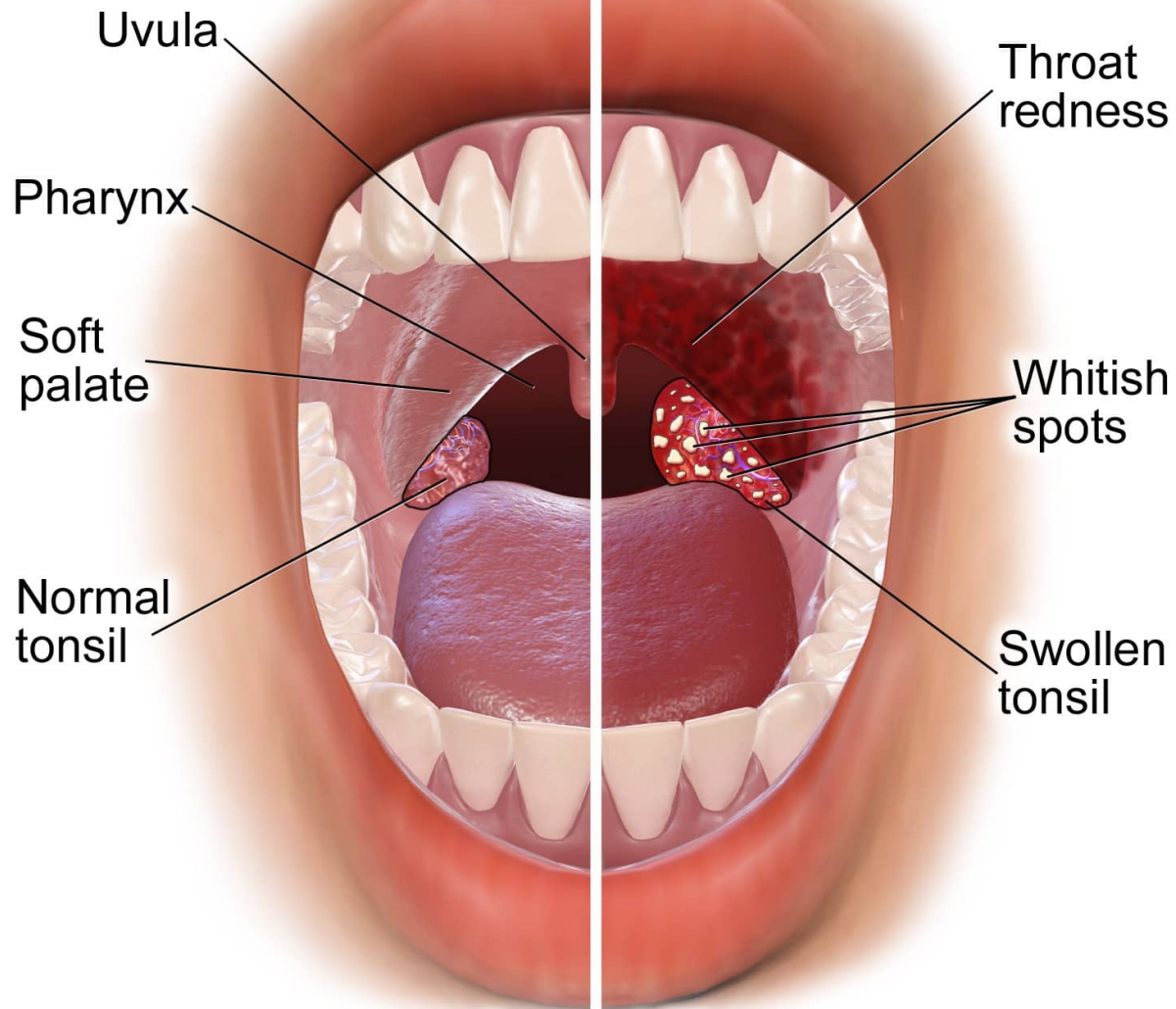
# Mayo's signs and symptoms of strep throat:

- Throat pain that usually comes on quickly
- Painful swallowing
- Red and swollen tonsils, sometimes with white patches or streaks of pus
- Tiny red spots on the area at the back of the roof of the mouth (soft or hard palate)
- Swollen, tender lymph nodes in your neck
- Fever
- Headache
- Rash
- Nausea or vomiting, especially in younger children
- Body aches



Normal

Abnormal



Tonsils and Throat









## Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media

To date, the use of probiotic strains has almost exclusively focused on the gastrointestinal benefits of ingestion of selected bacteria obtained from intestinal sources.<sup>1</sup> However, the potential for probiotic intervention at nonintestinal body sites suggests possible application of effector strains of species selected from alternative target tissues in order to obtain more specific and durable benefits.<sup>2</sup> *Streptococcus salivarius* K12, also known as BLIS (bacteriocin-like inhibitory substance) K12, was isolated in New Zealand from the mouth of a healthy child.<sup>3</sup> It is known to release two lantibiotic bacteriocins named salivaricin A2 and salivaricin B, with high efficiency.<sup>4</sup> Via these two lantibiotics, encoded by a 190 kb megaplasmid,<sup>5</sup> BLIS K12 can effectively counteract the growth of  $\beta$ -hemolytic (group A) *Streptococcus pyogenes*, a common cause of pharyngitis, tonsillitis, and acute otitis media.<sup>6</sup> This inhibitory action is strongly linked to the release of lantibiotics because BLIS K12 P(-), the same strain without the 190 kb plasmid, does not show any antagonism of growth of *Streptococcus pyogenes*.<sup>7</sup>

In addition to its action against *S. pyogenes*, BLIS K12 can also inhibit growth of *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Micrococcus luteus*, *Streptococcus anginosus*, *Eubacterium saburreum*, and *Micromonas micros*.<sup>8</sup> Many of these are potential pathogens in the ear and oral cavity, causing acute otitis media<sup>9</sup> and halitosis.<sup>10</sup> Preliminary investigations have shown that BLIS K12 colonizes the upper respiratory tract of infants (oral cavity, nasopharyngeal and adenoid tissues)<sup>11</sup> and with good persistence, given that after only 3 days of administration, it can still be detected 32 days later.<sup>12</sup> Therefore, because of its good colonization capability and very high safety profile,<sup>13,14</sup> combined with its reputed ability to counteract oral pathology,<sup>15</sup> we decided to evaluate the preventive role of BLIS K12 when administered to children having a history of recurrent streptococcal pharyngitis and/or tonsillitis. Our main endpoint was the number of episodes of streptococcal infections and acute otitis media.

## Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media

[Francesco Di Pierro](#),<sup>1</sup> [Guido Donato](#),<sup>2</sup> [Federico Fomia](#),<sup>3</sup> [Teresa Adami](#),<sup>4</sup> [Domenico Careddu](#),<sup>5</sup> [Claudia Cassandro](#),<sup>6</sup> and [Roberto Albera](#)<sup>6</sup>

Statistically significant results were seen during the 90 days of treatment with BLIS K12 ([Table 2](#)) in terms of episodes of streptococcal pharyngitis and/or tonsillitis in the 41 children having had more than three episodes of streptococcal pharyngitis and/or tonsillitis in the previous year. These 41 children had had 152 episodes in 12 months, and during the 90 days of treatment, only three episodes of oral streptococcal infection were diagnosed, with the calculated incidence per month per child dropping from 0.3109 to 0.024.

The control group, (children enrolled with a diagnosis of recurrent oral streptococcal disease but not-treated) showed an increase in terms of episodes of streptococcal pharyngitis and/or tonsillitis in comparison with the previous year, as shown by the incidence per month per child ([Table 3](#)). This increase, from 0.325 to 0.45, is likely due to seasonal reasons being the first value calculated, considering also warm months where the incidence normally decreases, while the second value calculated is only considered during the three winter months.



**Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media**

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The 41 children who completed the 90-day course of Bactoblis showed a reduction in their episodes of streptococcal pharyngeal infection (about 90%) and/or acute otitis media (about 40%), calculated by comparing infection rates in the previous year. The 90-day treatment also reduced the reported incidence of pharyngeal and ear infections by about 65% in the 6-month follow-up period during which the product was not administered. Subjects tolerated the product well, with no side effects or dropouts reported.



## Use of *Streptococcus salivarius* K12 in the prevention of streptococcal and viral pharyngotonsillitis in children

[Francesco Di Pierro](#),<sup>1</sup> [Maria Colombo](#),<sup>2</sup> [Alberto Zanvit](#),<sup>3</sup> [Paolo Riso](#),<sup>4</sup> and [Amilcare S Rottoli](#)<sup>5</sup>

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*Streptococcus salivarius* K12 is an oral probiotic strain releasing two lantibiotics (salivaricin A2 and salivaricin B) that antagonize the growth of *S. pyogenes*, the most important bacterial cause of pharyngeal infections in humans also affected by episodes of acute otitis media. *S. salivarius* K12 successfully colonizes the oral cavity, and is endowed with an excellent safety profile. We tested its preventive role in reducing the incidence of both streptococcal and viral pharyngitis and/or tonsillitis in children.



## Pilot study to explore the prophylactic efficacy of oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngo-tonsillar episodes in pediatric patients

[Giulia Marin](#)

▶ [Author info](#)

**Background:** In the pediatric population, acute pharyngo-tonsillitis represents one of the most frequent causes of access to outpatient treatment and use of antibiotics. In frequent tonsillitis, the pharmacological approach is no longer effective, and, therefore, surgery becomes the treatment of choice.

**Methods:** This study compares the prophylactic efficacy of *Streptococcus salivarius* K12 (Bactoblis®) in children with recurrent pharyngo-tonsillitis treated vs untreated, with a 12-month follow-up. The primary objectives are: The incidence of recurrence of pharyngo-tonsillar episodes and the concomitant use of other drugs. Secondary objectives are: tolerability of the treatment, the effectiveness in terms of clinical improvement, days of absence from school, reduction of the use of standard therapies, and cancellation from the surgical planning list.

**Results:** Patients belonging to group A (treated with K12 for 90 days) were 24 males and 26 females, mean age 6.6 years (SD=1.57), those belonging to group B (untreated) were 23 males and 27 females, average age 6.8 years (SD=1.72). In the follow-up, group A reported 26 inflammatory pharyngo-tonsillary episodes in the first trimester, unlike group B, who reported 72 in the second trimester. This has shown a lower incidence (3.38%) of the disease compared to group B (6.66%), for a total of 169 inflammatory pharyngo-tonsillary episodes in group A against 333 in group B. A reduction in days of school absence of 429 days in group A and 927 days in the control group ( $P<0.01$ ) was also noted. Finally, 14 children of group A (28%) underwent adenotonsillectomy, against the whole group B. No adverse events were reported.

**Conclusion:** The efficacy of K12 on the prevention of pharyngo-tonsillar infections, the decrease in the use of antibiotics and the improvement of the overall quality-of-life was confirmed, with a decreased number of absences from school and fewer patients undergoing surgery.



## Oropharyngeal Probiotic ENT-K12 as an Effective Dietary Intervention for Children With Recurrent Respiratory Tract Infections During Cold Season

[Hongyan Guo](#),<sup>1,†</sup> [Xiaochen Xiang](#),<sup>2,†</sup> [Xuan Lin](#),<sup>✉3,\*</sup> [Qiang Wang](#),<sup>✉2,\*</sup> [Si Qin](#),<sup>4</sup> [Xinyan Lu](#),<sup>1</sup> [Jiawei Xu](#),<sup>1</sup> [Ying Fang](#),<sup>2</sup> [Yang Liu](#),<sup>2</sup> [Jing Cui](#),<sup>2</sup> and [Zhi Li](#)<sup>2</sup>

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Recurrent respiratory tract infections (RRTi) cause a high burden of disease and lead to negative impact on quality of life, frequent school/work absenteeism, and doctor visits, which remain a great challenge to pediatricians because RRTi can increase the risk of various complications including antibiotic overuse and resistance, which is one of the biggest threats to global health, and there is no confirmed effective treatment. In this study, we aimed to assess the clinical efficacy and safety of oropharyngeal probiotic ENT-K12 as a dietary intervention or a complementary treatment along with standard medical treatment during acute respiratory infections among children with RRTi during cold season. The results of this study show that when comparing to practicing of standard medical treatment only, the complementary intake of oropharyngeal probiotic ENT-K12 can effectively reduce episodes of both acute and RRTi in school children, shorten the course of respiratory symptoms onset, reduce the use of antibiotics and antiviral drugs, and reduce the absence days from both children's school and parents' work. Using oropharyngeal probiotics as a complementary dietary intervention to stabilize oropharyngeal microflora, specifically inhibiting respiratory pathogens and enhancing host immunity, could possibly be a promising approach to reduce RRTi burden and combating antibiotic resistance in long term, more clinical studies will be needed to further confirm the clinical practicing guide to ensure its clinical benefit.



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There were 47 children, 22 male and 25 female children, with an average age of 5.71 years (SD = 1.99) in the probiotic group finishing the study, and 50 children, 32 male and 18 female children, in the control group with an average age of 6.12 years (SD = 1.98) finishing the study. During the 30-day period of oropharyngeal probiotic intake, children in the probiotic group totally had 7 episodes of upper respiratory tract infections, while children in the control group totally had 17 episodes of upper respiratory tract infections, indicating that the incidence of upper respiratory tract infection in the probiotic group (14.89%) was significantly lower than that in the control group (34.00%) during the intervention period. The days of using antibiotics and antiviral drugs in the probiotic group were significantly lower than that in the control group, and the course of respiratory symptoms onset was shorter and more moderate in the probiotic group than that in the control group; in addition, compared with the control group, both the days of children absent from school and parents' absence from work in the probiotic group were significantly lower. Children treated with oropharyngeal probiotic ENT-K12 had excellent tolerability with no side effects reported, hence confirmed safety of applying oropharyngeal probiotic ENT-K12 as a prophylactic use or an effective dietary intervention along with standard medication during respiratory infections onset.





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Intake of oropharyngeal probiotic ENT-K12 as a dietary intervention can effectively reduce episodes of upper respiratory tract infections in school children with RRTi during high peak season, reduce the days of using antibiotics and antiviral drugs, and reduce children's sick leave days, parents' absence days from work, and shorten the course of respiratory infections; the safety of oropharyngeal probiotic ENT-K12 has been confirmed with no side effects reported, excellent tolerability, and easy acceptance. Notably, this study opens up a new research idea in the field of microbe promoting human health by supplying direct proof to support its efficiency and safety.



