Nutrition and Dietary Supplements

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REVIEW

Clinical potential for the use of probiotics in the management of respiratory conditions and cold- and influenza-like symptoms

This article was published in the following Dove Press journal:
Nutrition and Dietary Supplements
31 March 2011
Number of times this article has been viewed

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Abstract: Respiratory conditions including complaints like cough, rhinitis, sinusitis, or influenza-like symptoms are commonly summarized as acute upper respiratory tract infections (URTIs). The mechanisms of the potential beneficial effects of probiotics in the management of URTIs are not completely elucidated. Possible explanations are any or all of the following: 1) probiotics compete against other pathogens for colonization of the upper respiratory tract, 2) probiotics increase the barrier function, and 3) probiotics directly cause immunomodulatory effects. Here we review the current evidence for the use of probiotics in the clinical management of URTIs in different age groups. Animal studies and in vitro data reveal that probiotics might have clinical potential in the management of URTIs. In contrast, data from double-blind placebo-controlled clinical trials show conflicting results. Given the current level of evidence, it is therefore not appropriate to recommend probiotics as a part of standard therapy or for the management of URTIs.

Keywords: probiotics, prevention, infection, respiratory tract, asthma, children

Introduction

Respiratory complaints in the daily routine of pediatricians include symptoms like cough, rhinitis, sinusitis, or influenza-like symptoms and are commonly summarized as acute upper respiratory tract infections (URTIs). URTIs are among the most common reasons for emergency department visits and hospitalization of infants and preschool children.[1–4] Even if URTIs are usually acute events, clinical symptoms may also continue up to several weeks in some children.[5] Over recent decades rhinovirus and respiratory syncytial virus (RSV) followed by influenza have been identified as the most common pathogens.[6,7] Moreover, viral respiratory infections are the most frequent cause of acute asthma exacerbations in children.[8–12] Direct medical costs as well as indirect expenses contribute to URTIs as a significant global health burden.[7,13] Therefore, prevention of infections in children is of major importance.

Probiotics are defined as products or preparations containing viable microorganisms in numbers thought to alter the host's microflora, thereby bringing about beneficial health effects.[14] Essential criteria for bacteria to be classified as a probiotic are defined as: 1) viability during processing, transport, and storage; 2) the ability to survive gastric transport; 3) the ability to adhere and colonize the gastrointestinal tract; and 4) demonstrated clinical health outcomes. To date, no consensus exists about the optimum dosage required for probiotic supplements to induce beneficial effects. Current dosages vary substantially and range from 10^8 to 10^{11} colony forming units per day.

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Lactic acid bacteria and bifidobacteria are the most commonly used probiotics in clinical trials. This might be due to the fact that bifidocateria and lactic acid bacteria are the best characterized probiotics in terms of in vitro activities, potential health effects, and safety. Metchnikoff was the first to show the potential health effects of lactic acid bacteria.[15] He observed that rural populations in Bulgaria and Russia had a higher life expectancy. Mechtnikoff explained his observation with the extensive consumption of milk fermented with lactic acid bacteria.[15] He proposed that consumption of fermented milk would colonize the intestinal tract with beneficial lactic acid bacteria thus suppressing the growth of "proteolytic" bacteria.

Most of the conducted studies[16–27] focused on a wide range of potentially beneficial health effects of probiotics. The research on the molecular biology of lactobacilli and bifidobacteria has focused on anticancer potential, and potential as a therapeutic agent in diseases like antibiotic-associated diarrhea and gastrointestinal infections in pediatric populations, inflammatory bowel disease, irritable bowel syndrome, and allergic diseases like atopic eczema, allergic rhinitis, and bronchial asthma.[28] However, it should be noted that the reported effects are not general effects of probiotics. It is of particular importance to point out that, analogous to "antibiotics", "probiotics" are an umbrella term for different bacteriological strains and species with a broad range of various immunological and clinical abilities. Consequently, a species-specific evaluation instead of a generalized statement is mandatory to determine the clinical efficacy of probiotics. Reported effects of probiotics can only be attributed to the individual strain(s) tested. Animal models and in vitro data are useful as screening instruments to select certain probiotic strains for preventive or therapeutic use. However, the gold standard to consider the efficacy of probiotics for prevention and/or treatment of URTIs is randomized, double-blind, placebo-controlled clinical trials.

This review summarizes the current evidence for the use of probiotics in the management of URTIs, which is based on recently published clinical trials. A Medline research was performed, using the terms "probiotics", "prebiotics", and "respiratory tract infection". All clinical trials published between 2000 and September 2010 were included in this review.

Use of probiotics in the prevention of URTIs: possible mechanisms

The mechanisms of action of probiotics in the management of URTIs are still unclear. One possible explanation is that there might be a competition of probiotics with other pathogens for colonization of the upper respiratory tract.[29] Alternatively, probiotics might increase the barrier function. In line with this theory, administration of lactobacilli was shown to improve gut integrity as measured by the dual-sugar permeability test in children with atopic dermatitis.[30] Moreover, certain probiotics are able to increase the expression of mucin secretion from intestinal epithelial cells. Mucin hampers the adherence of pathogenic microbes to prevent microbes invading the body.[31] Finally, probiotics might have immunomodulatory effects.[32] Specifically, the cell-mediated nonspecific immunity against different infectious agents (viral, bacterial, and fungal) is mainly mediated by natural killer (NK) cells. Clinical data have shown that numbers of NK cells are significantly decreased in infants with severe RSV infection. In line with these data, lung tissue from infants with fatal RSV demonstrated a near absence of CD8+ lymphocytes and NK cells but an extensive viral antigen load.[33] A number of studies have shown that administration of lactobacilli in mice increases NK cell activity and might therefore be protective against airway infection.[34,35] Recently, Kaiko and coworkers reported that NK cell deficiency in BALB/c mice during primary RSV infection results in the suppression of interferon (IFN)-γ production and the development of an RSV-specific Th2 response and subsequent allergic lung disease.[36] In vitro data indicate that human mononuclear cells stimulated with *Lactobacillus rhamnosus* GG (LGG) showed increased IFN-γ and interleukin (IL)-10 production compared with the negative control.[37] The observed in vitro capacity of LGG to increase the IFN-γ and IL-10 production might also contribute to an immunological health effect of probiotics in patients with URTIs. In line with these data, Harata and colleagues showed in a BALB/C mouse model that intranasal administration of LGG protects host animals from influenza virus infection.[38] LGG-treated mice had a significantly lower symptom rate. While only 20% of the control group survived, more than 60% of the LGG-treated mice outlived the infection ($P < 0.05$). In parallel, pulmonary IL-1β, tumor necrosis factor, and monocyte-chemoattractant protein 1 (MCP-1) mRNA expression were significantly higher in the LGG group. While IL-1β stimulates IL-2 production and upregulates NK cell proliferation and differentiation, the MCP-1 induces the migration and activation of NK cells in the infected tissue.[38] These data provide a conclusive model of a specific immunoregulatory effect of lactobacilli in preventing respiratory infection in mice models. However, the ultimate proof of these concepts to establish clinical recommendations are data derived from properly designed clinical trials.

Clinical evidence for the use of probiotics in the prevention of URTIs

There are a growing number of clinical trials using probiotics in the management of URTIs. However, direct comparison of the different studies is hampered by the fact that different probiotic strains are applied. Moreover, the comparability is limited by the fact that various endpoints are studied and different populations in many countries and continents with different genetic and environmental backgrounds are included. To facilitate the review of the published data, we categorized the clinical trials into studies including infants, young children, and adults.

Use of probiotics in the prevention of URTIs in infants

There are data from three clinical trials involving infants, who were supplemented with probiotics in the first months of life or even before birth (Table 1). Additional data from clinical trials are reported which primarily focused on the prevention of allergic diseases but also reported results of supplementation of probiotics on URTIs as secondary endpoint.

Rautava and colleagues recruited formula-fed infants before the age of 2 months.[16] The intervention group received formula supplemented with the probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* during the first year of life. The primary outcome measure was the incidence of early infections (<7 months) and the incidence of recurrent (>3 times) infections until the age of 12 months. In the probiotic group, significantly fewer infants received antibiotics (31% versus 60%; $P = 0.015$) or showed recurrent respiratory infections (28% versus 55%; $P = 0.022$).

Weizman and colleagues investigated in a double-blind placebo-controlled (DBPC) study the effect of two probiotics (*Bifidobacterium lactis* and *Lactobacillus reuteri*) in preventing infections in 201 infants (age 4–10 months) attending child care centers.[17] Primary endpoints were the number of days and number of episodes with fever (>38°C) as well as number of days and number of episodes with diarrhea or respiratory illness. Again, significant differences in favor of the probiotic group were observed: The probiotic group had significantly less febrile and diarrhea episodes, and a significant decrease in the number of clinic visits, child care absences, and antibiotic prescriptions. However, rate and duration of respiratory illnesses did not differ significantly between groups.

Kukkonen recruited a large cohort of 925 pregnant mothers carrying infants at high risk for allergy.[28] Participants were randomly assigned to receive a mixture of prebiotics and four probiotic species (*Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve*, and *Propionibacterium freudenreichii* ssp. *shermanii*) or a placebo for 4 weeks before delivery and 6 months after birth. During the 6-month intervention, antibiotics were significantly less prescribed in the symbiotic group compared with the placebo group (23% versus 28%), but no difference in the occurrence of respiratory infections (66% versus 68%) was observed. During the follow-up period (6–24 months), respiratory infections were less frequent in the symbiotic group

Table 1 Clinical evidence for the use of probiotics in the prevention of URTIs in infants

	Number, age, study	Intervention	Duration	Main results
Rautava 2009[26]	72 children DBPC	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*	12 months	Significantly fewer infants in the probiotic group received antibiotics (31% versus 60%; $P = 0.015$) and showed recurrent respiratory infections (28% versus 55%; $P = 0.022$). Comment: Small sample size.
Weizman 2005[27]	201 infants (age 4–10 months) DBPC	*Bifidobacterium lactis* and *Lactobacillus reuteri*	12 weeks	Significantly fewer febrile and diarrhea episodes, a significant decrease in number of clinic visits, child care absences, and antibiotic prescriptions. Rate and duration of respiratory illnesses did not differ significantly between groups. Comment: Short follow-up period.
Kukkonen 2008[28]	925 neonates, followed over 2 years DBPC	*Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii*	6 months	Intervention: no difference in the occurrence of respiratory infections (66% versus 68%). Follow-up: respiratory infections were less frequent in the symbiotic group (93%) than in the placebo group (97%; OR: 0.49; 95% CI: 0.27–0.92). Comment: Mixture of different pro- and prebiotics.

Abbreviations: CI, confidence interval; DBPC, double-blind placebo-controlled clinic trial; OR, odds ratio; URTI, upper respiratory tract infection.

compared with the placebo group (odds ratio [OR]: 0.49; 95% confidence interval [CI]: 0.27–0.92). The authors concluded that supplementation of symbiotics to newborns at high risk for allergy is safe and tends to increase the resistance to respiratory infections during the first 24 months of life.

There are some additional data from clinical trials which primarily focused on the prevention of allergic diseases. Some of these studies reported the incidence of respiratory symptoms during the observation period. A large Australian population (n = 178) failed to demonstrate a preventive effect of *Lactobacillus acidophilus* on atopic disease.[19] Significantly more children in the probiotic group developed wheezing during the first 6 months of life.[19] This finding also corresponds with data from a German population, where a significantly higher proportion of children in the LGG group had recurrent wheezing bronchitis during the first 2 years (26%) compared with placebo (9%; $P = 0.03$).[20]

Taken together, two of three clinical trials which were designed to study effects of probiotics on URTIs in infants showed no preventive effect. However, looking at secondary endpoints (fever and prescription of antibiotics), differences between the groups were observed in favor of administration of probiotics.

Use of probiotics in the prevention of URTIs in children

The results of the clinical trials on the use of probiotics in the prevention of URTIs in children are summarized in Table 2. Hatakka and colleagues were one of the first who conducted a DBPC clinical trial over a 7-month winter period in 571 healthy children aged 1–6 years attending a day care center.[21] He observed no significant difference between children who consumed milk supplemented with *Lactobacillus rhamnosus* GG versus the placebo group with regard to the number of days with respiratory or gastrointestinal symptoms. The overall analysis revealed that children in the LGG group had 15% fewer days of absence because of illness, and the time without respiratory symptoms was longer in the LGG group (5; 4.1–5.9 weeks) compared with placebo (4; 3.5–4.6). However, adjustment for age reduced the difference between the groups to a nonsignificant level. The authors conclude that LGG may modestly reduce respiratory infections and their severity among children in day care settings. Indeed, the reported data consistently show effects in the same direction; however, the age-adjusted results failed to prove any significant difference between the LGG and the placebo group. Therefore, this paper is rather hypothesis generating than an ultimate proof of the beneficial effects of probiotics.

Recently, Hojsak and colleagues published data from a DBPC trial performed in Zagreb.[22] They enrolled 281 children who attended day care centers and received either 100 mL of a fermented milk product supplemented with *Lactobacillus rhamnosus* GG or placebo during a 3-month intervention period. They observed that children in the LGG group had a significantly reduced risk of upper respiratory tract infections (risk ratio [RR]: 0.66; 95% CI: 0.52–0.82, number needed to treat [NNT] 5; 95% CI: 4–10), a reduced risk of respiratory tract infections lasting longer than 3 days (RR: 0.57; 95% CI: 0.41–0.78, NNT 5; 95% CI: 4–11), and a significantly lower number of days with respiratory symptoms ($P < 0.001$). No difference was observed with respect to the number of lower respiratory tract infections or gastrointestinal infections.

Looking at a different population, the same group reported data from a DBPC clinical trial of 742 hospitalized children from Zagreb, who were randomly assigned to receive either *Lactobacillus rhamnosus* GG or placebo in 100 mL of a fermented milk product.[23] Even if the two groups did not differ in hospitalization duration, the authors observed a significantly reduced risk for gastrointestinal and respiratory tract infections in the LGG group (RR: 0.38 [95% CI: 0.18–0.85]; NNT: 30) and episodes of respiratory tract infections that lasted >3 days (RR: 0.4 [95% CI: 0.2–0.9]). The authors recommend treatment with LGG as a valid option for the prevention of hospital acquired infections in children's facilities. However, there are some limitations, which should be discussed. First, infants who are of particular risk for severe nosocomial infections were not recruited because the study product contained 100 mL of fermented whole cow milk. The mean age of the study population was 9.9 and 10.6 years in the LGG and placebo group, respectively. Second, the number needed to treat was high. Therefore, treating 30 children with LGG for preventing one respiratory tract infection might not be justified. Finally, as outlined by the authors of this paper, most of the nosocomial infections were of short duration and of unproven cause.[23] More clinical trials in children with high risk for nosocomial infections are needed.

Rose and colleagues included 131 children (6–24 months old) with at least two wheezing episodes and a first-degree family history of atopic disease in a DBPC trial.[24] Children received either *Lactobacillus rhamnosus* or placebo for 6 months and were then followed for an additional 6 months. No significant differences between the groups were observed with respect to asthma-related events (need of inhalation, symptom-free days) and the development of atopic dermatitis throughout the intervention and 6-month

Table 2 Clinical evidence for the use of probiotics in the prevention of URTIs in children

	Number, age, study	Intervention	Duration	Main results
Hatakka 2001[31]	571 children 1–6 year DBPC	*Lactobacillus rhamnosus* GG	7 months	No significant difference in the absence because of illness and the time without respiratory symptoms after adjustment for age
Hojsak 2010[33]	742 hospitalized children DBPC	*Lactobacillus rhamnosus* GG	3 months	Reduced risk for respiratory tract infections (RR: 0.38 [95% CI: 0.18–0.85]). Decrease in episodes of respiratory tract infections that lasted >3 days (RR: 0.4 [95% CI: 0.2–0.9]).
Hojsak 2010[32]	281 children (day care center) DBPC	*Lactobacillus rhamnosus* GG	3 months	No effect on number of lower respiratory tract infections. Risk of upper respiratory tract infections decreased (RR: 0.66, 95% CI 0.52–0.82). Risk of respiratory tract infections lasting longer than 3 days decreased (RR: 0.57, 95% CI 0.41–0.78). Number of days with respiratory symptoms decreased.
Rose 2010[34]	131 children with at least 2 wheezing episodes 6–24 months DBPC	*Lactobacillus rhamnosus*	6 months	No significant differences in asthma-related events (eg, need of inhalation, symptom-free days) and the development of atopic dermatitis throughout the intervention and 6-month follow-up. Fewer sensitizations in the intervention group towards aeroallergens after 6 and 12 months.
Leyer 2009[36]	326 children aged 3–5 years DBPC	*Lactobacillus acidophilus* or a combination of *Lactobacillus acidophilus* and *Bifidobacterium lactis*	6 months	Significant reduction of fever, cough, antibiotic use, and duration of symptoms in the intervention group.
Hatakka 2007[37]	309 children (10 months–6 years) DBPC	*Lactobacillus rhamnosus* GG, LC705, *Bifidobacterium breve* 99, *Propionibacterium freudenreichii*	6 months	No effect of probiotic treatment in the occurrence, the median duration, or the recurrence (three) of acute otits media episodes.

Abbreviations: CI, confidence interval; DBPC, double-blind placebo-controlled clinic trial; RR, risk ratio; URTI, upper respiratory tract infection.

follow-up. However, the authors noted fewer sensitizations in the intervention group towards aeroallergens after 6 and 12 months, respectively ($P = 0.027$ and $P = 0.03$). The authors summarized that in children susceptible for atopy with recurrent wheezing episodes, probiotics had no clinical effect on atopic dermatitis or asthma-related events, and only mild effects on allergic sensitization. The latter results should be interpreted with caution, because this trial was not designed to detect differences in the prevalence of allergic sensitization. Moreover, in contrast to Rose, Soh observed no effect of daily probiotic supplementation (*Bifidobacterium longum* (BL999) and *Lactobacillus rhamnosus*) daily for the first 6 months on the incidence of eczema, the total immunoglobulin E concentration, and the prevalence of allergic sensitization in 253 infants with a family history of allergic disease.[25]

Leyer and colleagues reported data from 326 children aged 3–5 years who were randomly assigned to a placebo group, a group receiving *Lactobacillus acidophilus* or a combination of *Lactobacillus acidophilus* and *Bifidobacterium lactis* for 6 months during winter season in Shanghai.[26] They observed a significant reduction of fever, cough, antibiotic use, and duration of symptoms in the intervention group. The authors concluded that daily consumption of probiotics significantly reduce the incidence and duration of respiratory tract infection symptoms in children.

Hatakka examined whether probiotics would reduce acute otitis media (AOM) in 309 children (10 months–6 years).[27] They were supplemented either with a combination of *Lactobacillus rhamnosus* GG, LC705, *Bifidobacterium breve* 99, and *Propionibacterium freudenreichii* or placebo. However, they found no effect of probiotic treatment with respect to the occurrence, the median duration, or the recurrence of AOM episodes. Therefore, the authors stated that probiotics did not prevent the occurrence of AOM or the nasopharyngeal carriage of otitis pathogens in children. They observed also a tendency of a nonsignificant reduction in recurrent respiratory infections but postulated that these

effects require confirmation in further studies. In parallel with these results, Kukkonen also observed no effect of symbiotic on the incidence of middle-ear infections.[18]

In conclusion, only two of four clinical trials which were specifically designed to study effects of probiotics on URTIs in young children and were conducted in Zagreb[22] and Shanghai[36] showed a preventive effect (Table 2).

Use of probiotics in the prevention of URTIs in adults

Tiollier and colleagues examined the effect of a probiotics supplementation on respiratory tract infection and immunological changes in 47 cadets during 3 weeks French Commando training. They observed no difference in the overall incidence of respiratory tract infection between groups. In contrast, rhinopharyngitis was significantly more prevalent in the probiotic group ($P < 0.05$). Immunoglobulin A decreased after the training course only in the placebo group ($P < 0.01$), but the difference between the two groups was not significant.[39]

De Vrese and colleagues enrolled 479 healthy adults (aged 18–67) in a DBPC trial and investigated the combined effect of vitamins and minerals with or without the probiotic bacteria (*Lactobacillus gasseri*, *Bifidobacterium longum*, and *B. bifidum*) on the incidence, duration, and the severity of symptoms of the common cold. The duration of common cold episodes and days with fever during an episode were lower in the probiotic group. In a subgroup of participants, immunological data were obtained. Here the authors observed a significantly higher enhancement of cytotoxic plus T suppressor cells (CD8+) and a higher enhancement of T helper cells (CD4+) in the probiotic group. The authors concluded that the intake of probiotic bacteria during at least 3 months significantly shortened common cold episodes by almost 2 days and reduced the severity of symptoms.[40]

Similarly, Winkler et al reported that consumption of a dietary supplement containing probiotic bacteria plus vitamins and minerals affects the duration, frequency, and severity of symptoms of common cold infections as well as cellular immune parameters.[41] They enrolled a population of 477 healthy adults who daily received the probiotic multivitamin and mineral supplement or a placebo for 3 or 5.5 months. The authors showed that the incidence of viral respiratory tract infections was 13.6% lower in the intervention group compared with the placebo group ($P = 0.07$). Common cold and influenza-like symptoms tended to be lower in the verum group; however, the difference was only statistically significant for the number of days with fever (reduction of 54%; $P = 0.03$). No difference was observed in the duration of infections. Based on their data, the authors emphasize that supplementation of probiotic bacteria plus vitamins and minerals during a period of at least 3 months may reduce the incidence and the severity of symptoms in common cold infections.[41]

In a DBPC study of Guillemard, the beneficial effect of a *Lactobacillus casei* on common infectious diseases (CIDs) of the airways of elderly was examined. Over all, 1072 volunteers (median age = 76.0 years) were randomized and supplemented with probiotics or placebo over 3 months. A significant reduction in both episode and cumulative durations was observed for URTIs ($P < 0.001$) and rhinopharyngitis ($P < 0.001$). Considering all CIDs, the cumulative number of CIDs was not different between groups, but in the probiotic group the average duration per episode of CID was shorter.[42]

Ventilator-associated pneumonia (VAP) is frequent in intubated adult intensive care unit patients. Although VAP is not within the focus of this review, the results of a recently published meta-analysis of Siempos et al should be briefly discussed.[43] They included five randomized clinical trials demonstrating that *Lactobacillus* species or combinations of different strains that include at least one *Lactobacillus* species reduce the prevalence of VAP in adults. The studies revealed that there is a nonsignificant trend in mortality, favoring probiotics (OR 0.75; 95% CI: 0.47–1.21), and a significant reduction in the prevalence of VAP (OR 0.61; 95% CI: 0.41–0.91).[43] However, there is an ongoing debate about the methodological limitations of this meta-analysis.[44,45] In conclusion, these data do not allow a firm conclusion that probiotics may reduce VAP in mechanically ventilated patients.

Conclusion

There is evidence from animal studies as well as in vitro data that probiotics might have potential benefit in the clinical management of respiratory conditions and cold- and influenza-like symptoms. However, data from DBPC clinical trials are less convincing. While some studies showed positive effects, others failed to demonstrate that probiotics are efficient in reducing the rate of URTIs. Direct comparison of clinical trials is hampered by the fact that different probiotics are used and that clinical trials comprise different populations and different study designs with various clinical endpoints. Given the current level of evidence, it is not appropriate to recommend probiotics or symbiotics as a part of standard therapy or as a preventive option for URTIs. Therefore, analogous to other indications, the health effect of probiotics should be reviewed in large clinical trials and coordinated through an international consortium. Moreover, a tandem of clinical trials and detailed mechanistic studies are necessary

to verify the current concepts of the immunological properties of probiotics. Finally, the selection of the most beneficial probiotic strain or the composition of different probiotics and/or prebiotics, the timing of supplementation, the optimal dose, and method of delivery still need to be determined. In view of the variabilities in selective immune responses towards specific probiotics in different age groups (immaturity of the immune system in infants, immunological aging in the elderly) and different patient populations (comorbidities and habits, eg, smoker versus nonsmoker), large well designed trials with detailed phenotyping of cohorts are needed to draw conclusions.

Disclosure

Conflict of interest: MVK was head of the investigator-initiated clinical trial "Lactobacillus GG and prevention of atopic dermatitis", which was partially supported by Infectopharm, Heppenheim, Germany.

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