Probiotics in the add-on treatment of otitis media in clinical practice

M. Gelardi[1], I. La Mantia[2], L. Drago[3], G. Meroni[3], S.E. Aragona[4], G. Cupido[5], C. Vicini[6], C. Berardi[7], G. Ciprandi[8], and the Italian Study Group on Upper Respiratory Infections*

*[1]Department of Otolaryngology, University of Foggia, Foggia, Italy; [2]Unit of Otolaryngology, Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy; [3]Microbiology Department, University of Milan, Milan, Italy; [4]Center of Regenerative Medicine, Humanitas Mater Domini, Castellanza (VA), Italy; [5]ENT Department, University of Palermo, Palermo, Italy; [6]ENT Department, Forlì-Faenza Hospital, Italy, University of Ferrara e Bologna, Italy; [7]ENT Department, Istituto Clinico Città Studi di Milano, Milan, Italy; [8]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy; *Italian Study Group on Upper Respiratory Infections, Italy*

*the Italian Study Group on Upper Respiratory Infections: G. Albanese, A. Anni, G. Antoniacomi, S. Artoni, G. Asprella, R. Azzaro, A. Azzolin, A. Balduzzi, I. Barbarino, C. Berardi, B.I. Bertetto, a. Bianchi, N. Bianco, A. Bonanno, C. Bordonaro, A.M. Brindisi, S. Bucolo, A.G. Bulzomì, G. Caligo, P. Capaccio, M. Capelli, A. Capone, S. Carboni, G. Carluccio, M. Casaula, M. Cassano, M. Cavaliere, A. Ciabattoni, A. Conti, A. Cordier, F. Cortellessa, M. Costanzo, F. Cupido, L. D'Ascanio, C. Danza, C. D'Auria, M. De Ciccio, C. De Luca, M. D'Emila, R. Dessi, A. Di Lullo, M. D'Urso, S. Falcetti, R. Falciglia, G. Fera, G. Ferrari, S.M. Ferraro, O. Fini, M. Fiorella, A. Floriddia, F. Asprea, C. Fusco, R. Fuson , A. Gallo, T. Gambardella, G. Gambardella, F. Giangregorio, G. Gramellini, M. Ierace, F. Ingria. A. La Paglia, L. Lanza, R. Lauletta, P. Lavazza, M. Leone, P. Lovotti, P. Luperto, F. Maniscalco, I. Marincolo, R. Martone, A. Melis, A. Messina, V. Milone, N. Mirra, S.C. Montanaro, F. Muià, A. Nacci, E. Nardello, L. Paderno, D. Padovani, A. Palma, M. Paoletti, I. Pedrotti, F. Petrillo, M. Piccolo, P. Pinto, M. Policarpo, M. Raguso, A. Ranieri, G. Romano, M. Rondinelli, C. Russo, L. Scotto Di Santillo, G. Sequino, E.M. Serraino, I. Spahiu, G. Spanò, C. Stabile, G. Stagni, M. Stellin, S. Tassi, G. Tomacelli, A. Tombolini, V. Valenzise, A. Zirone

Otitis media (OM) affects the middle ear and is typically characterized by earache. OM may be classified as acute (AOM) or chronic (COM), based on symptom duration. OM may be clinically suspected, but the diagnosis is usually confirmed by the otoscopy. Antibiotic therapy is frequently used in clinical practice. However, antibiotics often induce intestinal and respiratory dysbiosis associated with some clinical problems. A one-month course of a probiotic mixture (Abincol® containing *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 million living cells), and *Lactobacillus delbrueckii* LDD01 (200 million living cells), was prescribed in the Group A, and was compared with no add-on treatment, such as the Group B. Patients were evaluated at baseline (T0), at the end of antibiotic treatment (T1), at the end of probiotic course (T2), and at the end of 3-month follow-up (T3).

In total, 1164 outpatients with OM were enrolled. Acute OM affected 1058 subjects: 563 in Group A and 495 in Group B. Chronic OM affected 106 outpatients: 49 in Group A and 57 in Group B. All of them were treated with a 7-10-day course of antibiotic therapy. The probiotic mixture reduced the duration of symptoms associated with antibiotic therapy already at the end of the antibiotic cycle. Group A patients with acute otitis media experienced significantly less fever, tiredness, headache, pain,

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Corresponding Author:
Dr Giorgio Ciprandi
Via P. Boselli 5,
16146 Genoa, Italy
e-mail: gio.cip@libero.it

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malaise, nausea ($p<0.001$ for all), and diarrhea ($p=0.023$) than patients in Group B at T1. Group A patients with chronic otitis media experienced less tiredness ($p<0.01$) and malaise ($p<0.001$) than patients in Group B at T1.

The probiotic course reduced the possible clinical relapse, and the use of additional medications in both diseases at T2 and T3. In conclusion, the present clinical experience demonstrated that a probiotic mixture containing *Lactobacillus plantarum* LP01, *Lactobacillus lactis subspecies cremoris* LLC02, and *Lactobacillus delbrueckii subspecies delbrueckii*, was able to reduce symptoms associated with antibiotic therapy in patients with both acute and chronic OM. Otitis media (OM) is an inflammation of the middle ear (1).

However, the term OM is an umbrella term that comprises three main, distinct conditions: acute OM (AOM), OM with effusion (OME), and chronic OM (COM). These conditions, even though different, are, however, closely related and can also overlap (2-4). OM is one of the most common diseases in young children (5, 6). OM is also a leading cause of medical consultation, antibiotic prescription, and surgery, mainly in young people (7-10).

On the other hand, OM may also affect adult subjects, frequently after an upper airway infection. It entails a relevant burden for healthcare resources and a negative impact on both patients and their families' quality of life. From a practical point of view, there is a need to use clear and unambiguous terms. Literature abounds with misleading terms that significantly affect the methodologic rigor and consequently, the outcomes. Moreover, it is essential to differentiate patients according to the OM type (i.e. AOM, OME, and COM).

Bacteria may infect the middle ear primitively or successively to a viral infection. OM can be a severe condition that should be promptly treated. Therefore, antibiotics are commonly used in daily practice to treat AOM or COM when a bacterial cause is suspected (11). On the other hand, antibiotic treatment is frequently associated with microbiota perturbation, such as dysbiosis. To restore the physiological balance of microbiota, probiotics are usually prescribed along with antibiotics in clinical practice.

Probiotics could improve intestinal and respiratory microbiota equilibrium, reduce respiratory symptoms, and promote general wellbeing (12). In this regard, Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (formerly *Lactobacillus pntarum*) (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 million living cells), and *Lactobacillus delbrueckii* subspecies *delbruekii* LDD01 (200 million living cells). It has been recently placed on the market. This product has been previously tested in patients with gastroenterological disorders (13-15). Therefore, the present clinical experience evaluated the potential role of probiotic add-on treatment to antibiotic therapy in patients with otitis media, recruited by a group of Italian otorhinolaryngologists (ORL) in clinical practice.

MATERIALS AND METHODS

The current experience was conducted in Italian otorhinolaryngology centres, distributed across Italy, so assuring an extensive and complete national coverage, during the fall-winter 2019-2020. ORL specialists were asked to recruit all consecutive outpatients with otitis media. Patients were consecutively recruited during the specialist visit. The inclusion criteria were to have otitis media diagnosis, both genders, adulthood, and ongoing antibiotic treatment. Exclusion criteria were to have comorbidities and concomitant medications able to interfere with the evaluation of the outcomes. All patients signed informed consent. All the procedures were conducted in a real-world setting.

OM was diagnosed on a clinical ground according to validated criteria (16). The patients were subdivided into groups: Group A (active group) was treated with an oral antibiotic for 7-10 days associated with a 4-week course of Abincol®, and Group B (control group) was treated with antibiotics alone. Patients were also subdivided into two subgroups considering the acute or chronic OM diagnosis. The oral nutraceutical was taken following the specific indications, such as one stick/daily.

Patients were visited at baseline (T0), after 7-10 days (T1), such as at the end of antibiotic therapy, after four weeks (T2), such as at the end of the probiotic course in

Group A, and after a 3-month follow-up (T3). Clinical examination was performed in all patients at each visit. Doctors gave the patients a clinical diary to record clinical information. In the first period (7-10 days), patients had to report the duration (expressed in days) of symptoms, including fever, tiredness, headache, pain, malaise, diarrhea, urinary tract problems, and nausea. In the second (first month) and third (3-month follow-up) periods, patients had to report clinical relapse, use of concomitant medications, and adverse events. Statistical analysis of the data was conducted with GraphPad Prism software version 8.0.1 for Windows (GraphPad Software®, San Diego, USA, www.graphpad.com). For all tests, the accepted minimum significance limit was 0.05.

RESULTS

Globally, 1164 outpatients were enrolled. Acute OM affected 1058 subjects: 563 in Group A and 495 in Group B. Chronic OM affected 106 outpatients: 49 in Group A and 57 in Group B.

Acute OM

The intergroup analysis showed that all reported symptoms mainly diminished in Group A at T1, as reported in Fig. 1. In particular, patients in the Group A had 35% fewer days with fever, 33% fewer days with tiredness, 26% fewer days with headache, 26% fewer days with pain, 29% fewer days with malaise, 11% fewer days with diarrhea, and 13% fewer days with urinary tract infection, and 41% fewer days with nausea than Group B patients (Fig. 1).

At T2, patients in Group A had 28% fewer episodes of clinical relapse at 15 days, 31% fewer episodes of clinical relapse between 16 and 30 days, 29% less use of additional drugs at 15 days, and 23% less use of additional medications between 16 and 30 days than patients belonging to Group B (Fig. 2).

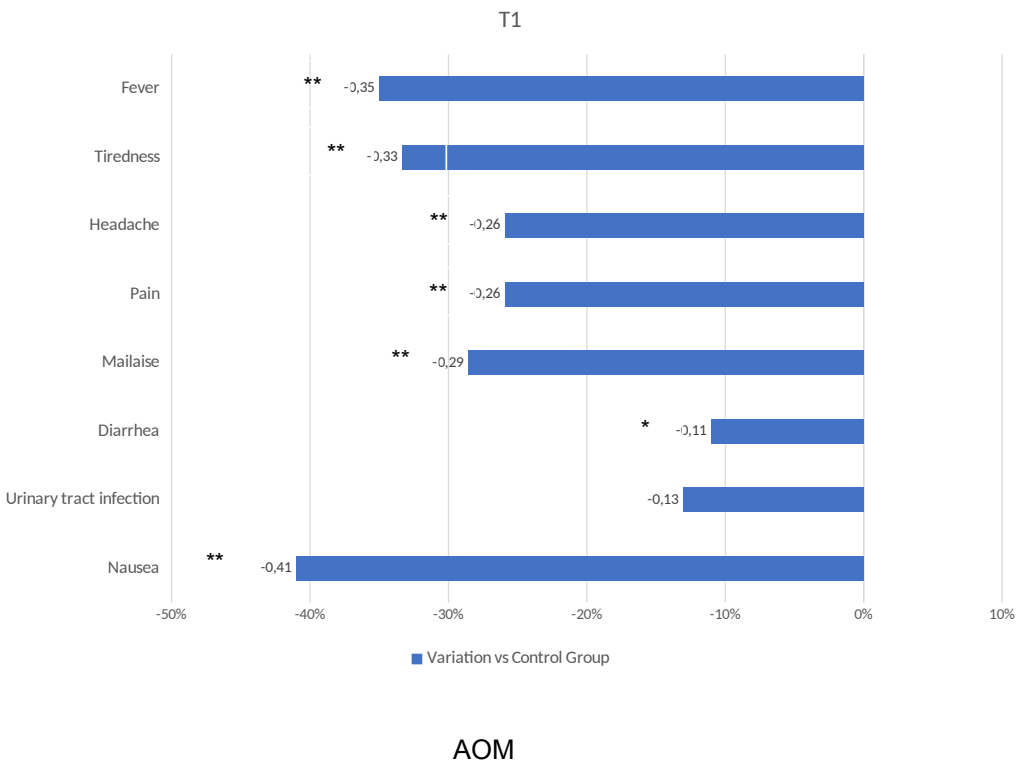

Fig. 1. *Percentage of difference between Group A and Group B concerning the evaluated symptoms in patients with acute otitis media at T1.*

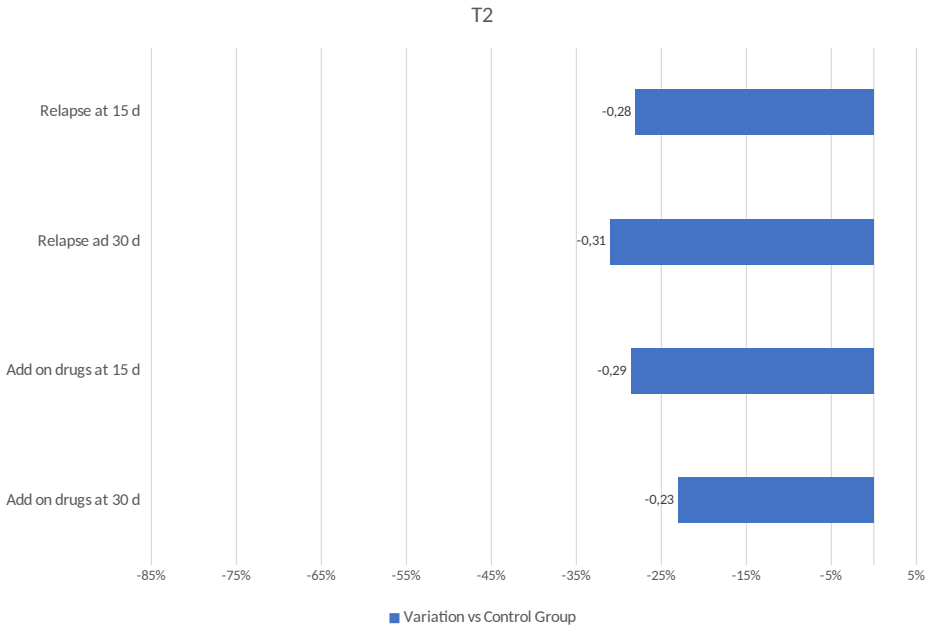

Fig. 2. *Percentage of difference between Group A and Group B concerning the clinical relapse and additional medications in patients with acute otitis media at T2.*

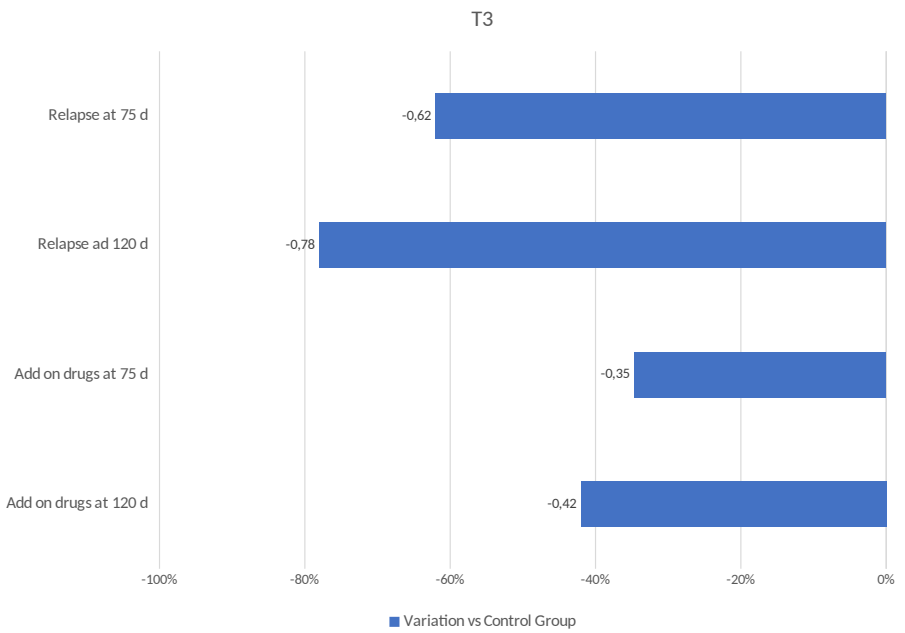

Fig. 3. *Percentage of difference between Group A and Group B concerning the clinical relapse and additional medications in patients with acute otitis media at T3.*

At T3, patients in Group A had 62% fewer episodes of clinical relapse between 30 and 75 days, 78% fewer episodes of clinical relapse between 75 and 120 days, 35% less use of additional drugs between 30 and 75 days, and 42% less use of additional medications between 75 and 120 days than patients belonging to Group B (Fig. 3).

The intergroup analysis showed that the Group A had a significantly greater reduction of fever ($p<0.001$), tiredness ($p<0.001$), headache ($p<0.001$), pain ($p<0.001$), malaise ($p<0.001$), diarrhea ($p=0.023$), and nausea ($p<0.001$) than Group B at T1.

Chronic OM

The intergroup analysis showed that all reported symptoms mainly diminished in Group A at T1, as reported in Fig. 4. In particular, patients in the Group A had 9% fewer days with fever, 16% fewer days with tiredness, 10% fewer days with headache, 13% fewer days with pain, 39% fewer days with malaise, 9% fewer days with diarrhea, 2% fewer days with urinary tract infection, and 22% fewer days with nausea than Group B patients (Fig. 4).

At T2, patients in Group A had 31% fewer episodes of clinical relapse at 15 days, 45% fewer episodes of clinical relapse between 16 and 30 days, 13% less use of additional drugs at 15 days, and 9% less use of additional medications between 16 and 30 days than patients belonging to Group B (Fig. 5).

At T3, patients in Group A had 61% fewer episodes of clinical relapse between 30 and 75 days, 73% fewer episodes of clinical relapse between 75 and 120 days, 49% less use of additional drugs between 30 and 75 days, and 60% less use of additional medications between 75 and 120 days than patients belonging to Group B (Fig 6). The intergroup analysis showed that the Group A had a significantly greater reduction of tiredness ($p<0.01$), and malaise ($p<0.001$) than Group B at T1. The nutraceutical compound was well-tolerated in all subjects.

DISCUSSION

Even though otitis media frequently affects

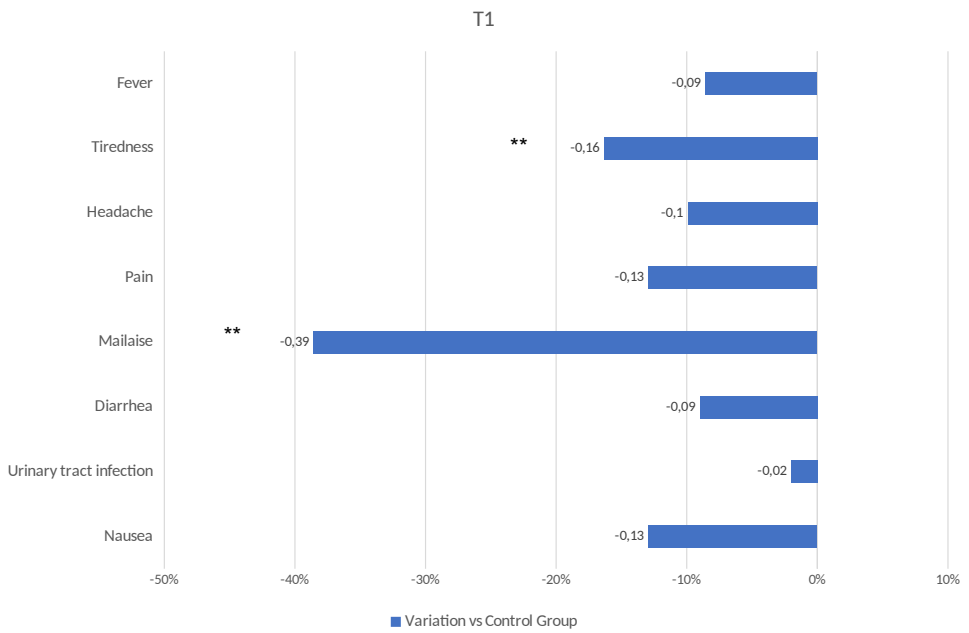

Fig. 4. *Percentage of difference between Group A and Group B concerning the evaluated symptoms in patients with chronic otitis media at T1.*

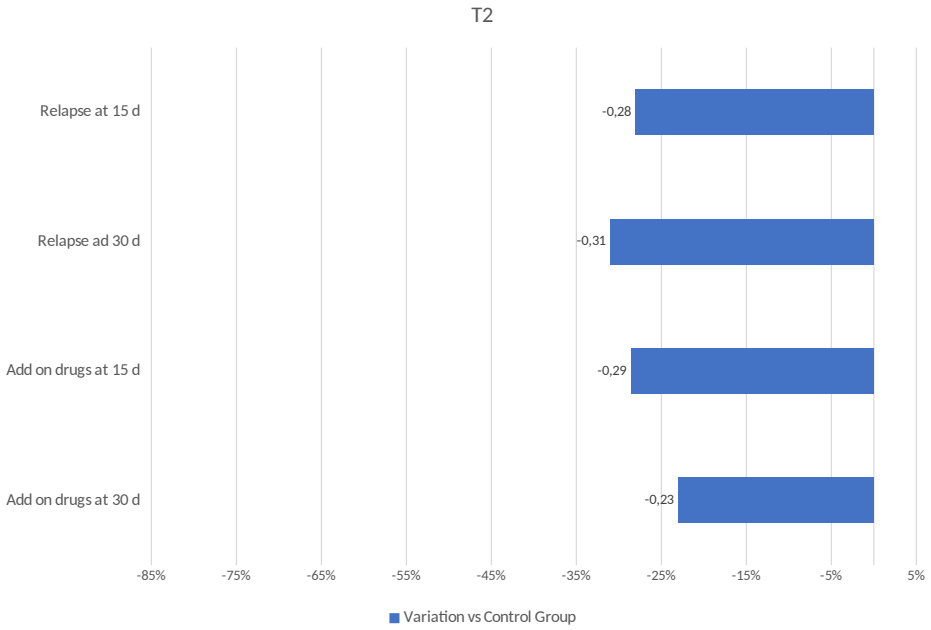

Fig. 5. *Percentage of difference between Group A and Group B concerning the clinical relapse and additional medications in patients with chronic otitis media at T2.*

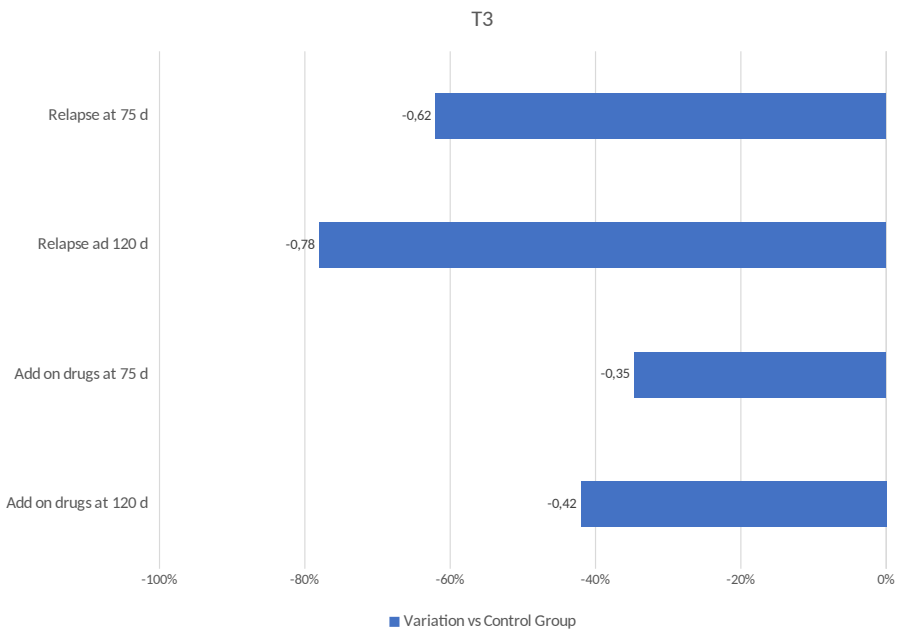

Fig. 6. *Percentage of difference between Group A and Group B concerning the clinical relapse and additional medications in patients with chronic otitis media at T3.*

young people, it is quite common also in adults. AOM represents a common problem facing general practitioners, paediatricians, and otolaryngologists. Acute OM usually follows an acute respiratory infection, mainly caused by viral or bacterial pathogens (17). AOM places a large burden on health care systems worldwide. Although symptomatic relief could be enough for some patients, other cases require antibiotics, especially if complications are suspected.

COM is also a common problem facing general practitioners and otolaryngologists (18). COM most commonly presents with painless otorrhoea and hearing loss. Treatment options vary according to the activity and type of disease encountered. COM carries significant patient morbidity and is characterized by an inflammatory process potentially associated with an infectious episode (18).

In both acute and chronic OM, the diagnosis is based on clinical features and otoscopic outcomes. When an infection is suspected, clinicians prescribe antibiotic treatment. However, antibiotics may frequently cause dysbiosis, both at the intestinal and respiratory levels. Consequently, the use of probiotics has become a common practice to contrast dysbiosis.

In the vast panorama of probiotic products, existing on the market, Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 million living cells), and *Lactobacillus delbrueckii subspecies delbrueckii* LDD01 (200 million living cells). Some clinical studies showed that Abincol® improved symptom severity in patients with different intestinal problems (13-15). The current experience was conducted on a large group of patients with acute or chronic OM. The outcomes showed that the probiotic mixture reduced the intensity of symptoms during the antibiotic treatment (7-10 days), the probiotic course (one month), and the 90-day follow-up. Patients with both acute and chronic OM had an improvement. Moreover, the probiotic mixture reduced the frequency of clinical relapse and additional medications for both acute and chronic OM.

The current experience has some limitations, and the most relevant was the open design. However, the strength of the present experience was many randomly recruited outpatients, mainly concerning the acute pharyngotonsillitis. Further rigorous studies, such as placebo-controlled, should be conducted to confirm these preliminary findings. In conclusion, the present clinical experience demonstrated that a probiotic mixture containing *Lactobacillus plantarum* LP01, *Lactobacillus lactis subspecies cremoris* LLC02, and *Lactobacillus delbrueckii subspecies delbrueckii*, was able to reduce symptoms associated with antibiotic therapy in patients with both acute and chronic OM.

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