CONSENSUS REPORT

Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry

Lisa J. Heitz-Mayfield1 | Merete Aaboe2 | Mauricio Araujo3 | Juan B. Carrión4 | Raffaele Cavalcanti5 | Norbert Cionca6 | David Cochran7 | Ivan Darby8 | Eiji Funakoshi9 | Petra C. Gierthmuehlen10 | Dena Hashim6 | Leila Jahangiri11 | Yongdae Kwon12 | France Lambert13 | Danielle M. Layton14 | Eduardo R. Lorenzana15 | Gerald McKenna16 | Andrea Mombelli6 | Frauke Müller6 | Mario Roccuzzo17 | Giovanni E. Salvi18 | Martin Schimmel18 | Murali Srinivasan6 | Cristiano Tomasi19 | Alvin Yeo20

1University of Sydney, Sydney, NSW, Australia
2Private Practice, Solrod, Denmark
3State University of Maringa, Parana, Brazil
4Universidad Santiago de Compostela, Santiago, Spain
5Sapienza University of Rome, Rome, Italy
6University of Geneva, Geneva, Switzerland
7University of Texas Health Science Center, San Antonio, Texas
8University of Melbourne, Melbourne, Victoria, Australia
9Kyushu Dental University, Kitakyushu, Japan
10Heinrich Heine University, Düsseldorf, Germany
11New York University, New York, New York
12Kyung Hee University School of Dentistry, Seoul, Korea
13University of Liège, Liège, Belgium
14University of Queensland, St. Lucia, QLD, Australia
15Texas A&M College of Dentistry, Dallas, Texas
16Queens University Belfast, Belfast, UK
17University of Torino, Torino, Italy
18University of Bern, Bern, Switzerland
19University of Gothenburg, Gothenburg, Sweden
20National Dental Centre, Singapore, Singapore

Correspondence
Lisa J. A. Heitz-Mayfield, University of Western Australia, Crawley, WA, Australia.
Email: heitz.mayfield@iinet.net.au

Abstract

Objectives: The aim of Working Group 4 was to address topics related to biologic risks and complications associated with implant dentistry. Focused questions on (a) diagnosis of peri-implantitis, (b) complications associated with implants in augmented sites, (c) outcomes following treatment of peri-implantitis, and (d) implant therapy in geriatric patients and/or patients with systemic diseases were addressed.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2018 The Authors. Clinical Oral Implants Research Published by John Wiley & Sons Ltd.
INTRODUCTION

The objectives of Group 4 of the 6th ITI Consensus Conference were to provide statements and recommendations for clinicians and researchers relating to risks and biologic complications in implant dentistry. Four systematic reviews formed the basis for discussion within the working group and were prepared and reviewed prior to the consensus conference. The systematic reviews were discussed within the group, and minor modifications, as required, were made to the manuscripts. The working group formed consensus statements and clinical recommendations which were then presented and accepted following further discussion and modifications when required by the plenary. Recommendations for future research were also prepared by the working group. The four systematic reviews are listed below.

The Diagnosis of Peri-implantitis: A systematic review on the predictive value of bleeding on probing (Hashim, Cionca, Combescur, Mombelli, 2018).

Long-term biological complications of dental implants placed either in pristine or in augmented sites: A systematic review and meta-analysis (Salvi, Monje, Tomasi, 2018).


Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis (Schimmel, Srinivasan, McKenna, Müller, 2018).

1 | THE DIAGNOSIS OF PERI-IMPLANTITIS: THE PREDICTIVE VALUE OF BLEEDING ON PROBING

2.1 | Preamble

Bleeding on probing has been proposed as one of the signs of mucositis and/or peri-implantitis. This review aimed to systematically evaluate the predictive value of the presence or absence of bleeding on probing (BOP) alone for the diagnosis of peri-implantitis.

Thirty-one clinical studies reporting on the prevalence of peri-implantitis, BOP and/or suppuration (SUP) after at least 1 year of functional loading were selected. Meta-analyses were conducted to combine the proportions of peri-implantitis among BOP and/or SUP-positive subjects and implants across studies up to 18 years.
Subgroups were created and compared to investigate potential sources of heterogeneity.

For BOP-positive patients, there was a 34% probability to be diagnosed with peri-implantitis (prediction interval 10% to 69%). On average, 24% of implants which presented with BOP across these studies were diagnosed with peri-implantitis. The prediction interval ranged from 7% to 58%. Thus, we can assume that the effect size varied across populations. Longer observation periods were significantly associated with higher proportions of peri-implantitis among BOP-positive implants, reflecting increasing prevalence with time.

This review was limited in its analysis by the heterogeneity of the populations and the variable definitions of peri-implantitis.

2.2 | Consensus statements

2.2.1 | Consensus statement 1

The positive predictive value of BOP alone for the diagnosis of peri-implantitis for each implant ranges from about 7%–58%, depending on the prevalence in the population. This means, if 100 implants present with BOP, between 7 and 58 implants may have peri-implantitis. This statement is based upon the prediction interval of 6.9%–57.8% bounding the weighted mean (24.1%) calculated across 29 studies identified as part of this review.

2.2.2 | Consensus statement 2

The positive predictive value of BOP alone increases with time after loading. This probably indicates that the prevalence of peri-implantitis increases with time after loading. Shorter observation periods have lower rates of peri-implantitis, while longer observation periods have higher rates of peri-implantitis. This statement is based on the reduced positive predictive value of BOP identified across two studies with 1- to 3-year mean follow-up compared with 27 studies with more than a 3-year mean follow-up.

2.3 | Clinical recommendations

2.3.1 | What are the key criteria to diagnose the presence of peri-implantitis?

BOP alone is insufficient for the diagnosis of peri-implantitis. The diagnosis of peri-implantitis requires the evaluation of inflammation/infection and progressive bone loss that can vary between implants and patients.

2.3.2 | What does the predictive value of a diagnostic test mean in clinical practice?

If a site bleeds after probing, there is a chance that the implant may have peri-implantitis. The probability that this is the case is called the positive predictive value. Clinicians should be aware that the positive predictive value of a diagnostic test may vary and is related to the prevalence of the disease within the specific patient population.

In specific patient populations where the prevalence of peri-implantitis may be increased, the predictive value may be higher than in a general patient population.

2.4 | Recommendations for future research

- To investigate the presence of BOP as a risk factor for the development of peri-implantitis, specifically designed longitudinal studies are required.
- Biological conditions of human BOP-positive and negative peri-implant tissues should be investigated, on a histological and molecular level, to better understand the underlying causes of bleeding upon probing.
- The documented relationship between probing force and frequency of BOP at healthy teeth suggests that tissue trauma due to probing with an inappropriate force may occasionally be the reason for bleeding at implants. However, recommendations for ideal probing forces at implants can presently not be made due to lack of evidence. There is a need for clinical studies determining the impact of various factors affecting outcomes of peri-implant probing.
- Future research should investigate the utility of different assessments of bleeding, such as a bleeding index, rather than using a dichotomous evaluation of BOP.
- Research should explore the possibility of combining other diagnostic tools with BOP to increase the predictive value.

3 | Long-term biological complications of dental implants placed either in pristine or in augmented sites

3.1 | Preamble

Placement of dental implants in conjunction with augmentation procedures is well documented and has been shown to yield high predictability in terms of implant survival rates and volume stability. However, a comparison between the long-term prevalence of biological complications at implants placed in pristine sites (sites not requiring augmentation prior to or in conjunction with implant placement) versus augmented sites is lacking.

This systematic review investigated and compared the prevalence of biological complications and failure (loss) of implants placed in pristine versus augmented sites after a mean observation period of at least 10 years. The following focused questions were addressed:

- In patients with osseointegrated dental implants, are there differences in biological complications at implants placed in pristine versus augmented sites?
- In patients with osseointegrated dental implants, are there differences in failure rates of implants placed in pristine versus augmented sites?
The systematic review included 8 investigations (1 RCT, 1 case–control study, 1 cross-sectional study, 5 case series). The mean number of patients included across the studies was 56.9 (range: 15–96 patients), while the mean number of implants was 113.5 (range: 15–153 implants) with a mean follow-up of 11.1 years (range: 10–15 years).

Various augmentation techniques (e.g., lateral and/or vertical augmentation, augmentation prior to or at the time of implant placement, and alveolar ridge preservation procedures prior to implant placement), as well as a range of augmentation materials (e.g., autogenous bone and bone substitutes) and barrier membranes (e.g., resorbable and nonresorbable) were included in the four studies reporting on implant placement in augmented sites. All included studies reported that patients were enrolled in supportive care following implant therapy.

No statistically significant differences were observed between implants placed in pristine versus augmented sites for any outcome variable both at patient and implant level. High heterogeneity concerning patient sampling, case definitions of biological complications and eligibility criteria were observed.

Sufficient data were available to perform meta-analyses for the primary outcome (biological complications) and secondary outcome (implant failure).

### 3.2 | Consensus statements

#### 3.2.1 | Consensus statement 1

There is evidence that patients receiving implants in augmented sites may display a comparable prevalence of peri-implant mucositis compared with patients receiving implants in pristine sites. Patients with implants placed in pristine sites have a prevalence of peri-implant mucositis of 22.4% (95% CI: 6%–38%) compared with a prevalence of 19.6% (95% CI: 0%–40%) for patients with implants in augmented sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

#### 3.2.2 | Consensus statement 2

There is evidence that the long-term prevalence of peri-implantitis in patients with implants in pristine sites and augmented sites is low. The prevalence of peri-implantitis in patients with implants in augmented sites is more variable and less predictable compared with the prevalence in patients with implants in pristine sites. The weighted mean prevalence of peri-implantitis in patients with implants in augmented sites was 17.8% (95% CI: 0%–37%) compared with that of 10.3% (95% CI: 4%–17%) in patients with implants in pristine sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

#### 3.2.3 | Consensus statement 3

There is some evidence that the long-term prevalence of implant failure (loss) in patients with implants in pristine sites and augmented sites is low.

The weighted mean prevalence of implant failure (loss) in patients with implants in augmented sites was 3.6% (95% CI: 0%–8%) compared with that of 2.5% (95% CI: 1%–4%) in patients with implants in pristine sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

#### 3.2.4 | Consensus statement 4

In patients with a history of treated periodontitis (moderate and severe) receiving implant therapy in pristine sites, compliance with regular supportive care yields lower long-term implant failure (loss) compared with patients not complying with regular supportive care.

This statement is based on 1 study.

#### 3.2.5 | Consensus statement 5

There is limited evidence concerning the effect of regular supportive care in patients with a history of treated periodontitis receiving implants in augmented sites.

This statement is based on 1 study.

### 3.3 | Clinical recommendations

#### 3.3.1 | For the long-term monitoring of biological complications, at what time points should implants placed in augmented sites be assessed?

The time of completion of the implant-supported prosthesis should be used as a baseline for assessment. Similar to implants placed in pristine sites, implants placed in augmented sites should have time-points for subsequent assessments determined by the individual risk profile of the patient.

#### 3.3.2 | Do patients with implants in augmented sites require specific supportive care?

Patients with implants in augmented and pristine sites should both be enrolled in regular supportive care. Special consideration should be given to periodontally susceptible patients with implants placed in augmented sites.

### 3.4 | Recommendations for future research

- The influence of factors including defect morphology, augmentation technique, and augmentation materials (bone substitutes and barrier membranes) on the occurrence of biologic complications should be investigated in observational and randomized controlled trials.
- The impact of implant placement in augmented versus pristine sites on the development of biological complications and implant failure.
(loss) needs to be investigated in randomized controlled clinical trials.

- The impact of compliance with supportive care in patients with implants placed in augmented sites on the development of long-term biological complications and implant failure (loss) needs to be investigated in well-designed observational studies and randomized controlled clinical trials.

4 | OUTCOMES OF PERI-IMPLANTITIS TREATMENT FOLLOWED BY SUPPORTIVE CARE

4.1 | Preamble

There is a need to establish effective treatment protocols for the management of peri-implantitis to achieve stable long-term outcomes. The 5th ITI Consensus found successful 12-month outcomes following peri-implantitis treatment could be achieved in a limited number of studies (Heitz-Mayfield, Needleman, Salvi & Pjetursson, 2014). In these studies, although favorable short-term peri-implantitis treatment outcomes were reported in the majority of patients and implants, nonresolution of peri-implantitis, disease recurrence, progression of bone loss and implant loss were also reported. The majority of studies reported treatment outcomes inconsistently. Few studies reported medium to long-term outcomes. Furthermore, the effect of supportive care (supportive peri-implant periodontal therapy, SPT) on treatment outcomes was not addressed.

Therefore, the aim of this systematic review was to evaluate the clinical outcomes for patients with implants treated for peri-implantitis who subsequently received supportive care for at least 3 years.

The primary outcome was survival (both at implant and patient level), defined as the presence of the implant, regardless of the health of the surrounding tissues. Secondary outcomes were implant success and peri-implantitis recurrence, if defined by the authors.

The results of this systematic review are based on 18 studies, of which 13 could be used for quantitative assessments. On average, 26 patients (median, IQR 21–32) with 36 implants (median, IQR 26–45) were included in those 13 studies. Sufficient data were available to perform meta-analyses of the primary outcome.

4.2 | Consensus statements

4.2.1 | Consensus statement 1

In patients successfully treated for peri-implantitis, an individualized supportive care program, including professional and self-performed biofilm removal at implants and teeth, is associated with positive medium- to long-term outcomes.

This statement is based on the results of 18 studies.

4.2.2 | Consensus statement 2

Under current peri-implantitis treatment protocols, which include supportive care, about three-quarters of implants treated for peri-implantitis may still be present after 5 years. These outcomes might be affected by patient, implant-, prosthesis-, and treatment-related factors.

This statement is based on 13 studies, presenting an estimated cumulative implant survival of 76%–100% across 4 studies at 5 years and of 70%–99% across 2 studies at 7 years.

4.2.3 | Consensus statement 3

Although limited, there is evidence that implant surface can affect the medium- to long-term stability of peri-implantitis treatment outcomes.

This statement is based on the findings of two studies. One study found reduced success outcomes of implants with TPS (titanium plasma sprayed) compared with SLA (sandblasted large-grit acid-etched) surfaces over 7 years. One study found reduced outcomes of moderately rough compared with turned/minimally rough implant surfaces over 3 years.

4.2.4 | Consensus statement 4

Despite receiving regular supportive care, certain patients may require retreatment, adjunctive therapies, and/or implant removal due to disease progression or recurrence.

This statement is based on 2 studies that reported peri-implantitis recurrence and 5 studies that reported on treatment success.

4.3 | Clinical recommendations

4.3.1 | What definition of peri-implantitis treatment success is practical in clinical practice?

Peri-implantitis treatment success is defined as stable peri-implant bone levels, absence of probing depths >5 mm, and no bleeding or suppuration on probing.

Success in clinical practice, however, may be defined as the absence of progression of the disease, regardless of whether clinical parameters adhere to the above strict success criteria.

In addition, patients may also require that their implant reconstructions are aesthetic, comfortable, and easy to clean in order to consider the treatment a success.

4.3.2 | What clinical signs indicate that there is recurrence of peri-implantitis?

After having achieved resolution of peri-implantitis, the presence of bleeding and/or suppuration on probing together with an increase in probing depth may indicate recurrence of disease. A radiograph may be indicated if a diagnosis remains unclear.
4.3.3 What peri-implantitis treatment protocols could be considered appropriate to use in daily clinical practice?

Certain steps should be followed during the active treatment of peri-implantitis as outlined in the 5th ITI Consensus Statements (Heitz-Mayfield et al., 2014). These steps include:

1. Thorough assessment and diagnosis.
2. Control of modifiable local and systemic risk factors for peri-implantitis.
3. Nonsurgical debridement.
4. Early reassessment of peri-implant health, generally within 1-2 months.
5. Surgical access if resolution has not been achieved, including:
   - Open flap debridement
   - Thorough surface decontamination of the implant and associated prosthetic components.
   - Option of regenerative/reconstructive or resective approaches
   - Appropriate postoperative anti-infective therapy
6. Supportive care tailored to the patient risk profile, most likely 3–6 monthly.

4.3.4 What supportive care protocols can be considered appropriate to use in daily clinical practice?

Various supportive care protocols have been proposed. It is recommended to provide individualized supportive care according to the patient’s needs and risk profile.

Supportive care should include oral hygiene measures, biofilm removal, monitoring oral health, and reduction in modifiable risks related to peri-implantitis. Every effort should be made to motivate the patient and facilitate their ability to maintain plaque control both at implants and teeth, aiming for a low full mouth plaque score (FMPS <20%).

4.3.5 Are there any implant variables that could influence long-term outcomes of an implant successfully treated for peri-implantitis?

Clinicians should be aware that implant surface characteristics may have an impact on treatment success. Other implant and prosthetic variables may also impact on treatment success, requiring modification of the supportive care program.

4.4 Recommendations for future research

- Studies to evaluate the influence of patient-, implant-, and prosthesis-related factors on supportive care protocol choice, following peri-implantitis treatment, are required.
- Studies to evaluate the influence of patient-, implant-, and prosthesis-related factors on the long-term outcomes of patients in supportive care following peri-implantitis treatment are required.
- Health economic and cost–utility analyses for supportive care programs following peri-implantitis treatment are required.
- Patient-reported outcomes (e.g., oral health-related quality of life, patient preference, and aesthetics) for peri-implantitis treatment protocols that include supportive care should be evaluated.

5 EFFECT OF ADVANCED AGE, AND/OR SYSTEMIC MEDICAL CONDITIONS ON DENTAL IMPLANT SURVIVAL

5.1 Preamble

Today’s aged generation presents new challenges in the field of implant dentistry. Implant patients of advanced age often present with functional dependency, systemic medical conditions (comorbidities), and frailty. In addition, the aging of the immune system, termed immunosenescence, may result in a compromised host defense to a bacterial challenge at dental implants which adversely affects peri-implant health.

Furthermore, the presence of systemic conditions and treatment of these conditions may present a risk for implant placement, maintenance of peri-implant health, and ultimately implant survival. The most common systemic conditions in geriatric patients, as reported by the World Health Organization (WHO) in 2015, are cardiovascular disease (CVD), cancer, respiratory diseases, diabetes mellitus, liver cirrhosis, osteoarthritis, and conditions that involve neurocognitive impairment.

This systematic review addressed the focused questions: “In patients undergoing dental implant therapy, what is the effect of advanced age (≥75 years) and/or common systemic medical conditions on implant survival and biologic complication rates?”

The systematic review included evidence from 60 studies, of which 7 provided sufficient information to perform meta-analyses based on the primary outcome - implant survival in geriatric patients (≥75 years). One-year implant survival was based on 7 prospective studies with a mean of 35 implants, and 5-year implant survival was based on 3 prospective studies with a mean of 25 implants.

The remaining 53 studies reported on implant survival in patients with the most common systemic medical conditions and their respective treatments (CVD, radiation therapy, antiresorptive therapy (ART), hyposalivation/dry mouth, diabetes mellitus, and neurocognitive impairment), irrespective of the patients’ age.

Annual mean peri-implant marginal bone loss (PI-MBL) was reported in seven studies.
5.2 | Consensus statements

5.2.1 | Consensus statement 1
Advanced age alone (≥75 years) is not a contraindication for implant therapy.
This statement is based on 7 prospective studies.

5.2.2 | Consensus statement 2
Peri-implant marginal bone loss (PI-MBL) in geriatric patients is low and similar to other age groups after one to 5-year follow-up.
This statement is based on 7 prospective studies, where PI-MBL was calculated to be between 0.1 mm and 0.2 mm annually over a recall period of up to 5 years and 0.51 mm for the first-year after loading.

5.2.3 | Consensus statement 3
Few studies in implantology focus on geriatric patients (≥75 years) and systemic medical conditions (comorbidities) common in old age.

5.2.4 | Consensus statement 4
Evidence suggests, that in patients with cardiovascular disease (CVD), including ischemic heart disease, stroke, and hypertensive heart disease, implant survival is similar to patients without CVD.
This statement is based on one cross-sectional and one cohort study. The calculated implant survival ranges from 98% to 100% in patients with CVD.

5.2.5 | Consensus statement 5
In patients with head and neck cancer, implant survival may be negatively affected by radiotherapy. Treatment protocols for implant placement in irradiated patients have been developed.
In oncology patients receiving high-dose antiresorptive therapy (ART), implant surgery carries a high risk for postoperative complications and is contraindicated. High-dose ART is described as any ART treatment administered in oncology patients with bone metastases. In oncology patients, the long-term effects of chemotherapy on oral tissues have not been investigated.
This statement is based on 16 studies on radiotherapy and on two studies on ART focussing on the development of medication-related osteonecrosis of the jaw (MRONJ). No studies reported on the effects of chemotherapy alone.

5.2.6 | Consensus statement 6
Treatment for cancer is commonly associated with hyposalivation. Hyposalivation is also commonly associated with polypharmacy and Sjögren’s syndrome. While implant survival in patients with Sjögren’s syndrome is reported to be very high, the effect of cancer treatment and polypharmacy has not been reported.
This statement is based on 5 studies.

5.2.7 | Consensus statement 7
In adult patients with diabetes mellitus type II, high implant survival rates may be achieved.
This statement is based on 7 studies for patients in the mean age range of 49.5–64 years.

5.2.8 | Consensus statement 8
Patients with conditions involving neurocognitive impairment (unipolar depression, Alzheimer’s disease and other dementias, and Parkinson’s disease) can experience high implant survival rates.
This statement is based on 7 studies, including 4 case reports. The mean age ranged from 44 to 83 years and an observation period of 3–72 months.

5.2.9 | Consensus statement 9
No evidence was identified related to other diseases that are common among the elderly (WHO, 2015) such as liver cirrhosis, respiratory diseases and osteoarthritis, in relation to implant therapy.

5.3 | Clinical recommendations

5.3.1 | Is there an upper age limit for implant therapy?
In geriatric patients, implant therapy may be considered irrespective of age. Implant and prosthesis maintenance must be assured by the patient and/or care provider.

5.3.2 | Which common comorbidities comprise contraindications for implant placement?
High-dose antiresorptive therapy (ART) poses a serious risk for postoperative complications and is a contraindication for implant surgery. If treated at all, these patients should be managed in a specialist setting.

5.3.3 | Which common comorbidities comprise risks for implant placement?
Comorbidities such as cancer, diabetes mellitus, and conditions involving neurocognitive impairment may carry risks for implant therapy. An individual risk assessment is necessary before considering implant surgery for these patients. Implant patients with comorbidities should be managed in close collaboration with a supervising physician with regular follow-up.
In patients with diabetes mellitus, oral hygiene should be closely monitored along with glycemic control and associated comorbidities of the disease.

5.3.4 | Which information must be taken into account when planning implant therapy for geriatric patients with common systemic diseases?

While there is no evidence to preclude geriatric patients (≥75 years) from implant therapy it is advisable to perform an individual risk assessment for patients with comorbidities. In geriatric patients, a holistic approach is required which should include assessment of functional dependency in addition to related limitations for the use of implant-supported prostheses and the ability to perform oral hygiene measures. The progression of existing systemic disease and dependency as well as the patient’s life expectancy should be considered in the context of availability of competent care.

5.3.5 | What are the risks and benefits associated with implant therapy in geriatric patients and patients suffering from the most common diseases in geriatric patients?

Implants may be considered in elderly and medically compromised patients when they can provide substantial functional and psychosocial benefits, which must outweigh the associated risks, cost, and burden of treatment.

5.3.6 | What public health issues are important to consider for successful implant therapy in geriatric patients?

When older patients lose independence, the availability of trained manpower in the caring professions is a potential limiting factor for implant therapy. Opportunities for education and additional training focused on oral health should be provided for those involved in caring for dependent persons.

5.4 | Recommendations for future research

- Future research is required to evaluate optimal implant–prosthesis design to facilitate oral hygiene measures for maintenance of peri-implant health in geriatric patients.
- Evaluation of access to quality oral health care for immobile and dependent persons is required to develop health policies for the provision of a minimum standard of oral care in aged care.

ORCID

Lisa J. Heitz-Mayfield  http://orcid.org/0000-0001-5755-8265
Danielle M. Layton  http://orcid.org/0000-0003-4886-2403
Andrea Mombelli  http://orcid.org/0000-0003-3386-8503
Giovanni E. Salvi  http://orcid.org/0000-0001-5523-3192
Martin Schimmel  http://orcid.org/0000-0001-9700-5534

REFERENCES


