Infection Risk-Adjusted Antibiotic Prophylaxis Strategies in Arthroplasty: Low-Dose Single vs. High-Dose Dual Antibiotic-Loaded Bone Cement

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Contents

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62.1 Introduction

Periprosthetic joint infection (PJI) is a rare, but devastating complication following joint replacement. The overall PJI incidence is in the range of 1–3% in primary arthroplasty, but it is higher in some high-risk situations such as revision procedures (Zimmerli et al. 2004; Ong et al. 2009; Kasch et al. 2017; Bosco et al. 2015). PJI treatment is complex and often requires multiple surgeries resulting in a high burden for the patient and in high costs for the health care system (Kasch et al. 2016). The number of PJI cases is expected to further increase as a consequence of the growing numbers of primary and revision arthroplasty procedures worldwide. Despite higher awareness of this complication, infection rates have not changed much over the last two decades. This observation may be explained by the trend to operate more on older patients with many comorbidities together with the spread of more resistant pathogens (Fernandez-Fairen et al. 2013).

Many surgeons in Europe use local antibiotics in cemented arthroplasty procedures in the form of antibiotic-loaded bone cement (ALBC) as a complementary strategy to perioperative antibiotic prophylaxis (PAP). The rationale behind this strategy is the formation of an additional antimicrobial "frontline" in the joint cavity itself (Kühn et al. 2014).

> One of the major advantages of this strategy is that high-peak concentrations of bactericidal antibiotics are achieved where contaminations may have occurred without exposing the patient to a major risk of side effects.

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In fact, several clinical studies and arthroplasty registry results have provided evidence for lower revision rates when systemic and local antibiotic prophylaxis are combined (Engesaeter et al. 2003; Jämsen et al. 2009; Jiranek et al. 2006; Wu et al. 2016). In line with these registry observations, a meta-analysis of the available clinical data has concluded that the systematic use of ALBC may reduce PJI incidence by up to 50% in primary procedures and up to 40% in revision operations (Parvizi et al. 2008).

We have recently reported on our own experiences made since the implementation of routine use of the ALBC PALACOS R+G for all cemented primary hip and knee procedures in our institution leading to a reduction of PJI cases by 60–70% compared to the period when non-ALBC was used (Sanz-Ruiz et al. 2017). The introduction of ALBC was further found to be highly cost-efficient with cost savings of 2672 € per patient in hip arthroplasty as a consequence of considerably lower PJI treatment costs (Sanz-Ruiz et al. 2017).

62.2 Risk Factors for Infection and the Idea of a Risk-Tailored Antibiotic Prophylaxis

It is now widely accepted that arthroplasty patients may have a different PJI risk profile, which can be quantified using validated risk calculators (Tan et al. 2018). A recent prospective observational cohort study analyzing 623,253 primary hip procedures performed between 2003 and 2013 in England and Wales has determined to which extent each of these factors may contribute to a higher infection risk (Lenguerrand et al. 2018). BMI $\geq$40 kg/m^2, malnutrition, wound dehiscence, surgical-site infections, and previous surgeries were found to be associated with a much higher PJI incidence than "normal" (3- to 9-fold higher PJI rate). However, it should be noted that the exact hazard ratio of each potential risk factor is still a matter of debate.

> Given the fact that the majority of arthroplasty patients suffer from several risk factors, the practical conclusions for surgeries from such risk factor tables are also not yet clear and must be further discussed.

However, assuming that the prior identification of individuals at higher PJI risk (in particular if several risk factors are combined) may, indeed, help to further optimize prophylactic strategies during surgery, the extra effort may appear justified. So far, the implementation of a risk-adjusted antibiotic prophylactic regimen is still rather an idea than an evidence-proven concept. If taken further, two possible complementary modifications to standard protocols exist:

- Modification of the routine perioperative antibiotic prophylaxis scheme by either extending the postoperative duration (e.g., beyond 24 hours [Inabathula et al. 2018]) and/or by adding a second antibiotic to the standard regimen (e.g., vancomycin or teicoplanin to a cephalosporin [Tornero et al. 2015]).
- Use of high-dose ALBC with antibiotic combinations for implant fixation in the joint cavity.

Proof of concept that the latter strategy may have a positive impact on the incidence of surgical-site and deep-implant infections has been recently demonstrated in a quasi-randomized clinical trial on 848 patients with an intracapsular neck-of-femur fracture (NOF) treated with cemented hemiarthroplasty in the Northumbria Hospital Trust in the UK (Sprowson et al. 2016). Treatment in the clinical study was performed either with a low-dose single antibiotic cement (PALACOS® R+G; G = gentamicin) in the group representing the current standard of care or with a high-dose dual antibiotic cement (COPAL® G+C;

gentamicin + clindamycin) in the intervention group. It was found that the rate of deep infections was significantly reduced from 3.5% (PALACOS® group) to 1.1% (COPAL® group). The rate of complications was similar in both groups.

62.3 Results

62.3.1 PJI Risk Classification at the University Hospital Gregorio Maranon, Madrid

Based on our own experiences as a large tertiary hospital and taking into account the practicality and clinical relevance of some literature-supported risk factors, in 2012 some surgeons in our hospital developed their own risk algorithm, which they then followed. Its calculation is based on the following general health-specific and orthopedic/trauma-specific risk factors (Table 62.1).

In the case of TKA, a patient at high risk for PJI was defined if he/she has at least two or more of these comorbidities or risk factors, and in the case of THA, at least three or more (Fig. 62.1). In addition, some isolated risk factors were identified, which justify a direct classification as a high-risk patient:

High Risk!
- Severe kidney or cardiac disease
- Immunodeficiency
- Previous infection or colonization (hips)
- Previous surgery at the same joint
- Revision surgery

Table 62.1 Differentiation of general and specific risk factors that to our experience in combination justify the classification of patients as PJI risk patients

General risk factors	Specific risk factors
Age >80 years	Previous infection/steroid injection <6 months
Nutritional status and weight (BMI >30 >19)	Pernicious anemia
Diabetes mellitus	Inflammatory disease
Tobacco consumption	Organic disease: kidney, cardiac
Rectal or urinary tract bacterial colonization	Revision surgery
Immunodeficiency	Hip fracture surgery
Previous hospital stay or institutionalized patient	Previous orthopedic or trauma surgery with implantation of hardware

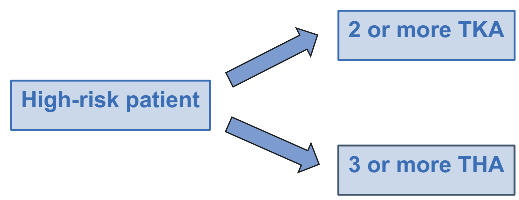

Fig. 62.1 Classification of risk patients based on the risk factors described in Table 62.1

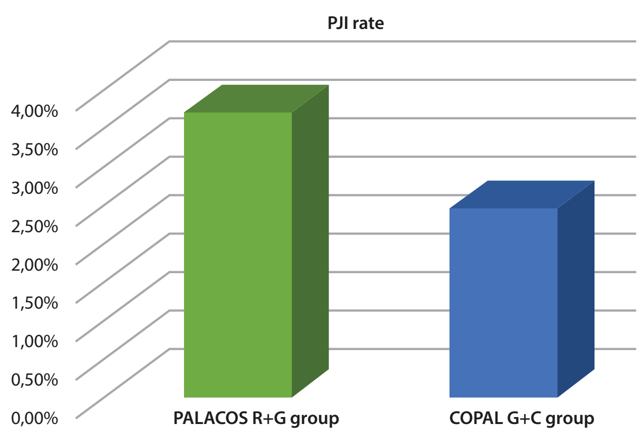

Fig. 62.2 PJI rate within 1 year between 2015 and 2018 in the group “PALACOS® R+G” with mixed PJI risk profiles (92.8%) and in the group “COPAL® G+C” (7.2%) with exclusive high-risk profile according to our recent risk stratification algorithm

62.3.2 Outcome Analysis with High-Dose Antibiotic Cement in High-Risk Patients to Reduce PJI

Based on this risk algorithm, all our cemented primary arthroplasty operations performed in the time period 2015–2018 on a total of 2551 patients (primary arthroplasties included TKA, THA, and hemiarthroplasties) were grouped into those who received single antibiotic-loaded low-dose cement PALACOS® R+G (92.8% = 2368 patients with a mixed low and high-risk profile) vs. a high-risk patient group receiving double antibiotic-loaded high dose cement COPAL® G+C (183 patients = 7.2%). The post-analysis of PJI cases that occurred in this time period was 3.7% for all patients, but only 2.45% in the more homogeneous high-risk patient COPAL® cohort (p = 0.65) (Fig. 62.2). This trend toward a reduction of PJI cases in the COPAL® group, albeit not statistically significant because of the heterogeneous patient profile in the comparator group, was contradictory to what we expected in this high-risk patient group (Sanz-Ruiz and Berberich 2020).

Table 62.2 Comparison of PJI rate in aseptic revision cases occurring 2015–2018 in patients receiving PALACOS® R+G vs. patients receiving COPAL® G+C[a]

Cases	PALACOS® R+G	COPAL® G+C	All
No. of aseptic revision cases	143	103	246
PJI cases	6	0	6
% PJI	**4.1%**	**0%**	**2.44%**

[a]Septic revisions, oncologic cases, or periprosthetic fractures excluded; comparable patient profile in both groups

In order to determine the "true effect" of the bone cement COPAL® G+C for fixation and infection prophylaxis, it was necessary to compare strictly homogeneous groups. Therefore, we focused our analysis on solely aseptic cemented revision knee arthroplasty cases, which were performed between 2015 and 2018.

Among the 246 retrospectively analyzed TKA revisions, 143 were cemented with PALACOS® R+G and 103 with COPAL® G+C. Patient-specific risk profiles in each group were comparable. An overall infection rate among all aseptic revision patients of 2.44% was determined in this time period. However, when comparing the infection rate between the individual cement groups, a statistically significant reduction (p = 0.035) of PJI cases was found in the COPAL® G+C group (no infection case in 103 patients = 0% infection rate) compared to the number of infections in the PALACOS® R+G group (6 infection cases in 143 patients = 4.1% infection rate – Table 62.2) (Sanz-Ruiz et al. 2020).

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> It should be noted that the surgical practice and the choice of perioperative antibiotic prophylaxis did not differ between both groups.

It was shown that the risk-adjusted use of COPAL® G+C in aseptic revision arthroplasty was highly cost-effective with a cost saving of 1261 € per patient treated with COPAL® G+C (Sanz-Ruiz et al. 2020).

Conclusion

Our data appear to confirm the hypothesis that a prior PJI risk classification of arthroplasty patients may be beneficial if combined with special risk-adjusted prophylactic measures. For the first time, we show here that the rationale of using either PALACOS® R+G as low-dose cement for relatively healthy patients in primary procedures or COPAL® G+C as high-dose double antibiotic-loaded cement for patients with multiple comorbidities and in revision situations leads to less PJI cases in the orthopedic ward and is highly cost-effective. These data extend the observations from a randomized clinical trial with neck-of-femur fracture patients in the UK that COPAL® G+C can, indeed, substantially lower the superficial and deep infection risk in patients at high infection risks. The principle of a more effective in situ protection appears to hold true also in a more general perspective and deserves further investigations.

Take-Home Messages

- The risk for PJI is significantly higher in patients with multiple comorbidities and in revision arthroplasties.
- Among the prophylactic measures taken to prevent PJI, use of ALBC can be an important tool. Its effect may be stronger in patients at higher infection risk.
- Prior risk classification can be helpful to determine whether an infection risk-adjusted prophylactic regimen should be considered.
- Several factors exposing a patient to an increased infection risk in joint replacement procedures have been defined, but the exact hazard ratios of each risk factor are still debated. A simple risk algorithm and scoring system as the one developed in our hospital may overcome this complexity.
- Our risk scoring model on the basis of two or three risk factors, respectively, has proven easy, practical, and effective to differentiate patients with lower and higher risk profiles for PJI. Some single risk factors were even weighted as sufficient in our clinical practice to classify a patient as a high-risk patient.
- Our retrospective analysis of patient groups treated with either the low-dose cement PALACOS® R+G or with the high-dose dual antibiotic-loaded cement COPAL® G+C has provided evidence that the latter can be even more useful in reducing the number of PJI cases in high-risk patients, especially after hip fracture and aseptic knee revision surgery.
- The prophylactic use of the dual ALBC COPAL® C+G in aseptic revision was found to be cost-effective.

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