

# LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATIONS IN HSCT AND CELLULAR THERAPY

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In this issue of the Journal of Bone Marrow Transplantation and Cellular Therapy, we present results of the 2020 update of the 2017 Bone Marrow Transplantation Consensus of the Brazilian Society of Bone Marrow Transplantation (Sociedade Brasileira de Transplante de Medula Óssea, SBTMO) for bone marrow transplantation indications.

Like earlier editions, we used the 2009 Levels of Evidence from the Oxford Centre for Evidence-Based Medicine for evidence and strength of recommendation grading<sup>1</sup>.

The process of these reviews involves the classification of the evidence (Levels of Evidence) and grading the strength of recommendation (Grades of Recommendation).

In brief, levels of evidence are classified 1 to 5, in which class 1 represents the highest level of evidence (usually randomized controlled trials) and class 5 represents the lowest one (expert opinion or based on physiology). Each 1 to 3 level of evidence is subdivided in 'a', 'b' and 'c' or 'a' and 'b', in lower case letters.

The analysis of the Levels of Evidence leads to a Grade of Recommendation, which are graded in A to D, in capital letters, in which grade A is the highest grade of recommendation, and D the lowest one.

Please note that the word 'levels' is reserved for evidence, while 'grades' is for recommendation. Also, do not mistake lower case letters of levels of evidence by capital letters of grades of recommendation.

Here, we present a summary of the 2009 Oxford Levels of Evidence.

## LEVELS OF EVIDENCE (TABLE 1)

### LEVEL 1 – MAINLY RANDOMIZED CONTROLLED TRIALS

Systematic reviews with meta-analysis of randomized controlled trials (RCT) are classified as 1a, as

long as there is homogeneity, or the heterogeneity is not worrisome. Worrisome heterogeneity should be classified as Level 1a- (1a minus). Level 1b is for individual RCT with narrow confidence interval (just like in meta-analysis, wide confidence interval should be marked with a 'minus' sign). Low quality RCT should be classified as Level 2, not 1. All or none case series should be graded as Level 1c. All or none studies is met when all patients died before the treatment became available, but some survive on it, or when some patients died before, and all survived on it.

### LEVEL 2 – MAINLY COHORT STUDIES

Level 2a is reserved for systematic review with meta-analysis of cohort studies (again, worrisome heterogeneity should be marked with a 'minus' sign). Individual cohort studies (except poor quality cohort studies, which should be labelled Level 4) and low quality RCT should be classified as Level 2b. Outcomes research and ecological studies (which are seldom available in the hematopoietic cell transplantation field) should be classified as Level 2c.

### LEVEL 3 – CASE-CONTROL STUDIES

Systematic reviews with meta-analysis of case-control studies without worrisome heterogeneity should be labelled as Level 3a; worrisome heterogeneity should be marked with a 'minus' sign. Individual case-control studies should be labelled as Level 3b.

### LEVEL 4

Level 4 is reserved for case-series and poor-quality cohort and case-control studies. According to the Oxford Levels of Evidence, "poor quality cohort study means one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of pa-

tients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders”.

**LEVEL 5**

Level 5 is evidence based on expert opinion or physiology.

**GRADES OF RECOMMENDATION**

The next step involves the classification of the Grade

of Recommendation. Usually, evidence level 1 leads to Grade of Recommendation A, evidence level 2-3 to Grade of Recommendation B, 4 to C and 5 to D. Note that inconsistent results or extrapolations may downgrade the Grade of Recommendation (table 2).

**REFERENCES**

1. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009) — Centre for Evidence-Based Medicine (CEBM), University of Oxford. <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>.

**TABLE 1 - Levels of Evidence**

Level	Therapy / Prevention, Aetiology / Harm
1a	Systematic review (with homogeneity) of Randomized Controlled Trials (RCT)
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	“Outcomes” Research or Ecological studies (seldom available in hematopoietic cell transplantation)
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”
Adapted from 1	

**TABLE 2 - Grades of Recommendation**

Grade of Recommendation	Level of Evidence
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level
Extracted from 1	