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Brazilian guidelines for the diagnosis and treatment of cystic fibrosis

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Chart 1A. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[a]

Question	Step 1 (Level 1[b])	Step 2 (Level 2[b])	Step 3 (Level 3[b])	Step 4 (Level 4[b])	Step 5 (Level 5[b])
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances[c]	Local non-random sample[c]	Case-series	N/A
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies or studies without consistently applied reference standards	Case-control studies, or "poor or non-independent reference standard	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial[b]	Case-series or case-control studies, or poor quality prognostic cohort study[c]	N/A
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/ follow-up study[c]	Case-series, case-control studies, or historically controlled studies[c]	Mechanism-based reasoning
What are the common harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n- of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/ follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient)[c]	Case-series or historically controlled studies[c]	Mechanism-based reasoning
What are the rare harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/ follow-up study[c]	Case-series, case-control studies, or historically controlled studies[c]	Mechanism-based reasoning

[a]Adapted from Oxford Centre for Evidence-Based Medicine [homepage on the Internet]. Oxford: Oxford Centre for Evidence-Based Medicine [cited 2017]. The Oxford 2011 Levels of Evidence; 2011 [Adobe Acrobat document, 1p.]. Available from: http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf. [b]Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small. Level may be graded up if there is a large or very large effect size. [c]As always, a systematic review is generally better than an individual study.

Chart 2A. Phases of sweat test.

Phase	Description
Sweat stimulation	- by means of pilocarpine iontophoresis method (pilocarpine nitrate solution, 2-5 g/L, or Pilogel® disks) - maximum electrical current: 4 mA - stimulation time: 5 min
Sweat collections	- on sterile filter paper/gauze (absence of chloride) or microtubes (Macroduct® plastic device) - maximum time for collection: 30 min - minimum sample amount: 75 mg or 15 µL - sample storage: Eppendorf tubes can be used up to 72 h - do not mix two samples
Sweat analysis	- chloride quantification (gold standard) - electrical conductivity
Result report	- identification of the patient and referring physician - day and time of sweat collection/result - weight/volume of sweat sample - method of analysis - chloride level or conductivity result (mmol/L or mEq/L) - reference values[a]

[a]See Table 1 in the main text.

Chart 3A. Conflict of interest.

Author	Statement
Rodrigo Abensur Athanazio	Financial support for events and conferences from Novartis, Roche, Vertex, TEVA, AstraZeneca, and Boeringher-Ingelheim; member of advisory boards: Roche, Novartis, TEVA, and Bayer; financial support for projects: Novartis, Roche, and Vertex; civil servant: *Hospital das Clínicas*, University of São Paulo, and Hospital Emílio Ribas, São Paulo, Brazil.
Luiz Vicente Ribeiro Ferreira da Silva	Financial support from AbbVie, Roche, Novartis, and Vertex for scientific events; lecturer and member of advisory boards
Alberto Andrade Vergara	Financial support from Roche and Vertex for scientific events
Antonio Fernando Ribeiro	Financial support from Roche, Vertex, Danone, and Abbot for scientific events
Carlos Antonio Riedi	Financial support from Roche, Vertex, and Actelion for scientific events; financial support from AstraZeneca for a lecture; lecturer at Vertex
Elenara da Fonseca Andrade Procianoy	No conflicts of interest
Fabíola Villac Adde	No conflicts of interest
Francisco José Caldeira Reis	Financial support from Zambon for participating in the European Cystic Fibrosis Conference
José Dirceu Ribeiro	No conflicts of interest
Lidia Alice Torres	Financial support from Roche for scientific events and for a medical conference in the State of Goiás, Brazil
Marcelo Bicalho de Fuccio	No conflicts of interest
Matias Epifanio	Financial support from Mead Johnson, Biolab, Danone, and Abbott for lectures and academic publishing
Mônica de Cássia Firmida	Financial support from Roche for scientific events; member of Vertex advisory board
Neiva Damaceno	No conflicts of interest
Norberto Ludwig Neto	No conflicts of interest
Paulo José Cauduro Maróstica	Advisor for Vertex Pharmaceuticals in 2016; financial support from Roche for giving lectures and participating in the European Cystic Fibrosis Conference, 2015
Samia Zahi Rached	Financial support from Roche for scientific events
Suzana Fonseca de Oliveira Melo	Financial support from Zambon, Roche, and Danone for scientific events

Table 1A. Vitamin D supplementation.

Age	Ergocalciferol, IU		
	Treatment onset	25(OH)D	
		10-20 ng/mL	20-30 ng/mL
< 12 months	400-500	2,000 IU	800-1,000 IU (max, 2,000)*
1-10 years	800-1,000	4,000 IU	1,600-3,000 IU (max, 4,000)*
> 10 years	800-2,000	10,000 IU	1,600-6,000 IU (max, 10,000)[a]

25(OH)D: 25-hydroxyvitamin D. [a]Second step: increase the dose in case 25(OH)D levels are 20-30 ng/mL, even with appropriate treatment. Observation: serum calcidiol <10 ng/mL: consider rickets.