12º ENDO SUL

SBEM SC

Cushing Subclínico

Julia Appel
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Declaração de conflito de interesse

- Resolução RDC 96/2008 da ANVISA
  - Declaro não haver conflito de interesse na apresentação desta palestra

Cushing Subclínico- SC

Clinical Study | J Shen and others | Guidelines for subclinical Cushing's syndrome | 171:4 | 421–431

Nonconformity in the clinical practice guidelines for subclinical Cushing's syndrome: which guidelines are trustworthy?

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Annales d'Endocrinologie xxx (2017) xxx–xxx

Annales d'Endocrinologie Annals of Endocrinology

Klotz communications 2018: Cortisol and all its disorders

Do the diagnostic criteria for subclinical hypercortisolism exist?

Les critères diagnostiques de l'hypercortisolisme infraclinique existent-ils ?

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Endocrine
DOI 10.1007/s12020-016-1017-3

VIEWPOINT

Six controversial issues on subclinical Cushing's syndrome

Iacopo Chiodini[1] · Adriana Albani[2] · Alberto Giacinto Ambrogio[3,4] · Michela Campo[5] · Maria Cristina De Martino[6] · Giorgia Marcelli[7] · Valentina Morelli[1,4] · Benedetta Zampetti[8] · Annamaria Colao[6] · Rosario Pivonello[6] on behalf of the ABC Group

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Endogenous subclinical hypercortisolism: Diagnostic uncertainties and clinical implications

Authors Authors and affiliations

S. Tsagarakis, D. Vassiliadi, N. Thalassinos

Cushing Subclínico- SC

Agenda

1. Definição
2. Relevância
3. Diagnóstico
4. Manejo
5. Conclusões/ Resumo

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1. Definição
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Cushing SC - Definição

Cushing Subclínico (SC) " é um estado de hipercortisolismo leve na ausência de sinais específicos relacionáveis ao excesso de cortisol em um paciente com incidentaloma adrenal"

Definição:

- ❑ **Achado bioquímico de hipersecreção de cortisol**
- ❑ **Ausência de fenótipo de Cushing**

(pletóra facial, moon face, estrias violáceas,miopatia proximal)

- ❑ **Incidentaloma adrenal**

Terzolo, Clinical Endocrinology (2012) 76 12-18

Cushing SC - Definição

Cushing Subclínico (SC) " é um estado de hipercortisolismo leve na ausência de sinais específicos relacionáveis ao excesso de cortisol em um paciente com incidentaloma adrenal"

Definição:

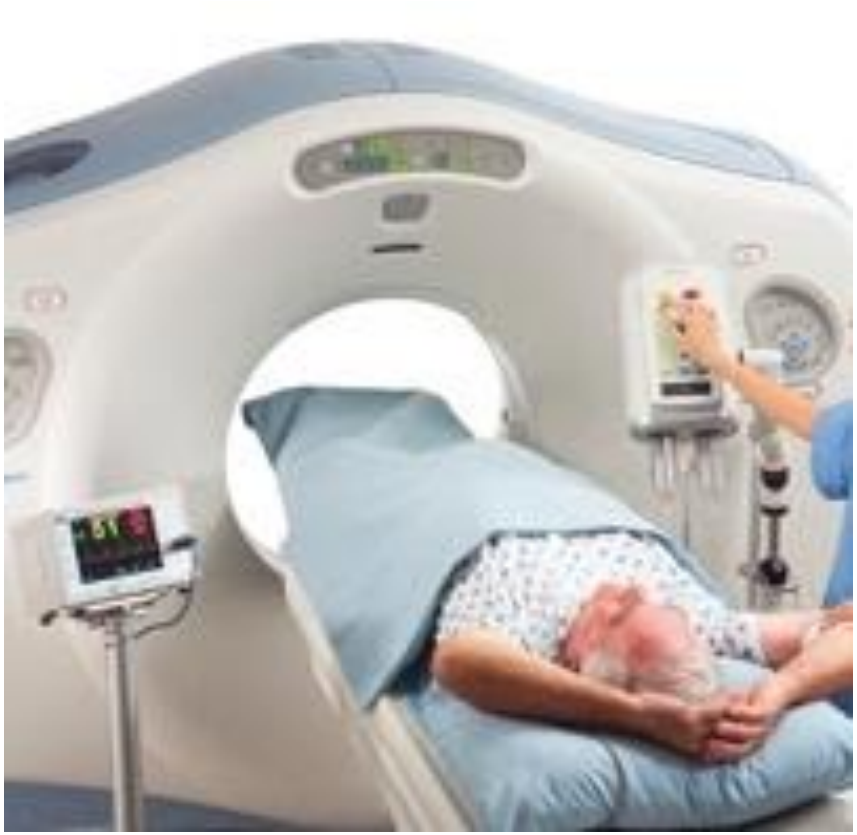
- ❑ **Achado bioquímico de hipersecreção de cortisol**
  - Mesmos cut-off de overt Cushing,mesmo sendo sutil**?**
- ❑ **Ausência de fenótipo de Cushing**

(pletóra facial, moon face, estrias violáceas,miopatia proximal)

  - obesidade, diabetes, osteoporose,HAS – causa X consequência **?**
- ❑ **Incidentaloma adrenal**
  - incidentaloma hipofisário?/ Screening DM2 e osteoporose**?**

Terzolo, Clinical Endocrinology (2012) 76 12-18

Relevância

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52D CBC - HEMATOCRIT
52G CBC - MCHC
52F CBC - MEAN CELL VOLUME
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LAB INSTITUTIONAL RE

Relevância

- Incidentaloma Adrenal (IA) presente 4-7% adulto
- Cushing Subclínico presente em cerca de 5-30% dos IA
- Logo, podemos estimar Cushing SC em 0.2-2% desta população
- Embora a Hist. natural seja pouco conhecida e raramente existir progressão para Cushing Clínico (0-11%), o hipercortisolismo ainda que leve parece ter consequências no longo prazo – DM, HAS, Obesidade, osteoporose.

JCEM, 96:1123-1236,2011

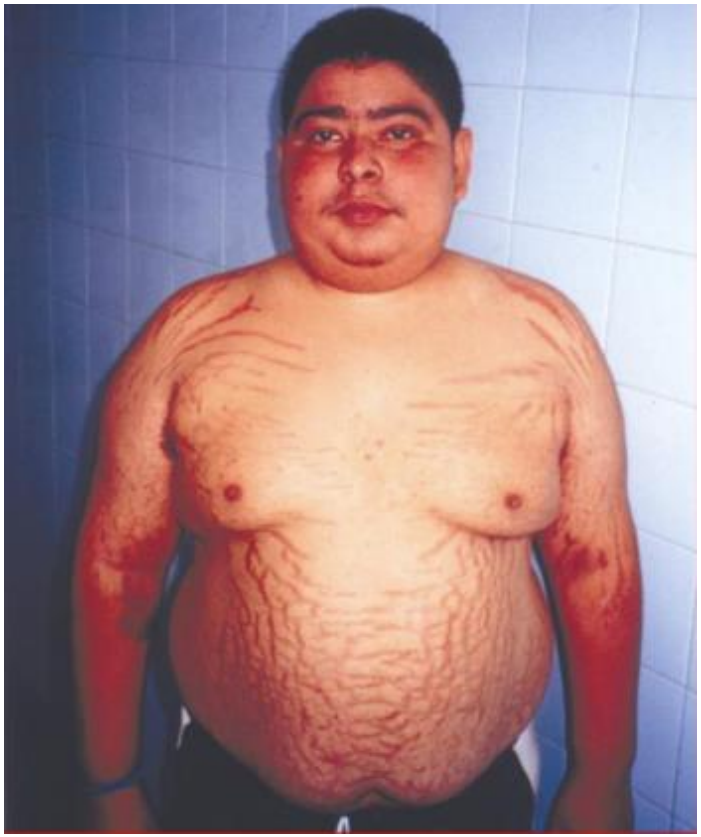
Lancet Diabetes Endocrinol 2014

Diagnóstico

- Como fazer o diagnóstico de Cushing Subclínico?

Diagnóstico

- Porque é tão difícil?



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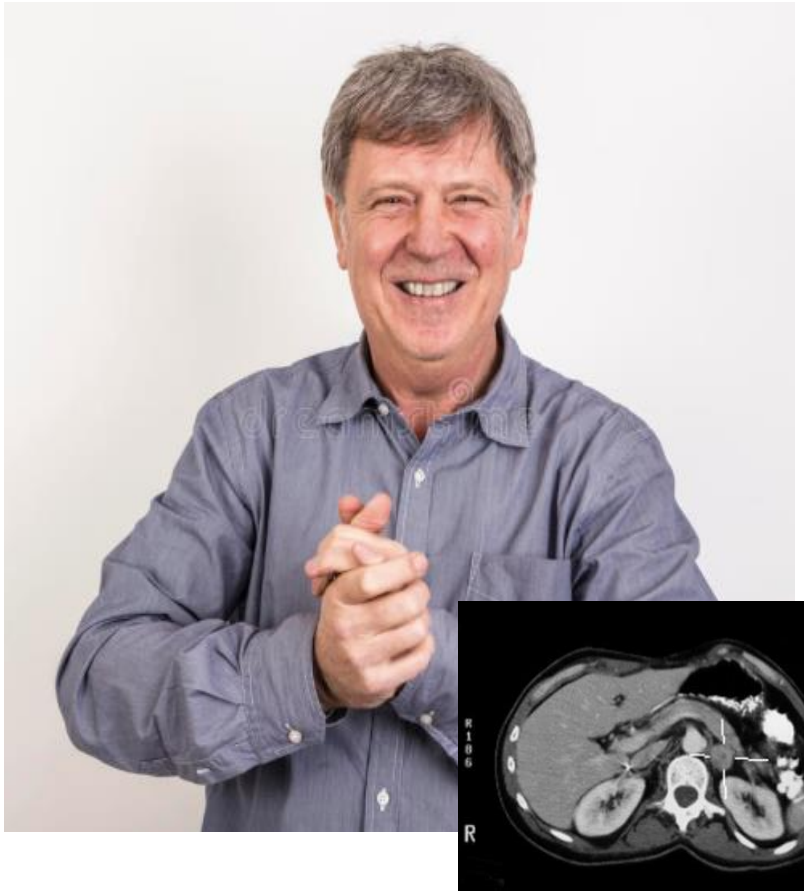

Diagnóstico

Table 3 Recommendations in the five clinical practice guidelines for SCS.

Recommendation	NIH	ES	AACE/AAES	FSE	IACE
Diagnosis					
The first screening test					
1-mg overnight DST	Recommended	Recommended	Recommended	Recommended	Recommended
Cutoff point	≥5.0 μg/dl	>1.8 μg/dl	>5.0 μg/dl	>1.8 μg/dl	<1.8 μg/dl: exclude >5.0 μg/dl: consider 1.8–5.0 μg/dl: indeterminate
Late-night salivary cortisol	NM	Recommended	NR	NR	NR
Cutoff point		>145 ng/dl			
The second screening test					
24-h urine free cortisol	NM	NR	NR	Recommended	Recommended
Late-night serum cortisol	NM	NR	NM	Recommended	Recommended
Late-night salivary cortisol	NM	NR	NR	Recommended	NR
High-dose DST	NM	NM	NM	NM	NR
The confirmatory test					
Low-dose 2-day DST	NM	NR	Recommended	NM	NR
Cutoff point			NR		
Evaluation of autonomous cortisol secretion from an adrenal adenoma					
ACTH	NM	Recommended	Recommended	Recommended	Recommended
Cutoff point		Suppressed	Low or suppressed	NM	Low or suppressed
DHEAS	NM	Recommended	Recommended	NR	NR
Cutoff point		Suppressed	Low		
Adrenal scintigraphy	NR	NM	NM	Recommended	NR

European Journal of Endocrinology (2014) 171, 421-431

Diagnóstico

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High-dose DS					
The confirmat					
Low-dose 2-d					
Cutoff point					
Evaluation of					
cortisol secre					
an adrenal a					
ACTH					
Cutoff point					
DHEAS					
Cutoff point					
Adrenal scint					

Bem estabelecido!

- Screening – DST 1mg

O Que difere?

- Cut off 1,8 X 3 X 5mcg/dl?
- Segundo teste?

European Journal of Endocrinology (2014) 171, 421-431

Diagnóstico

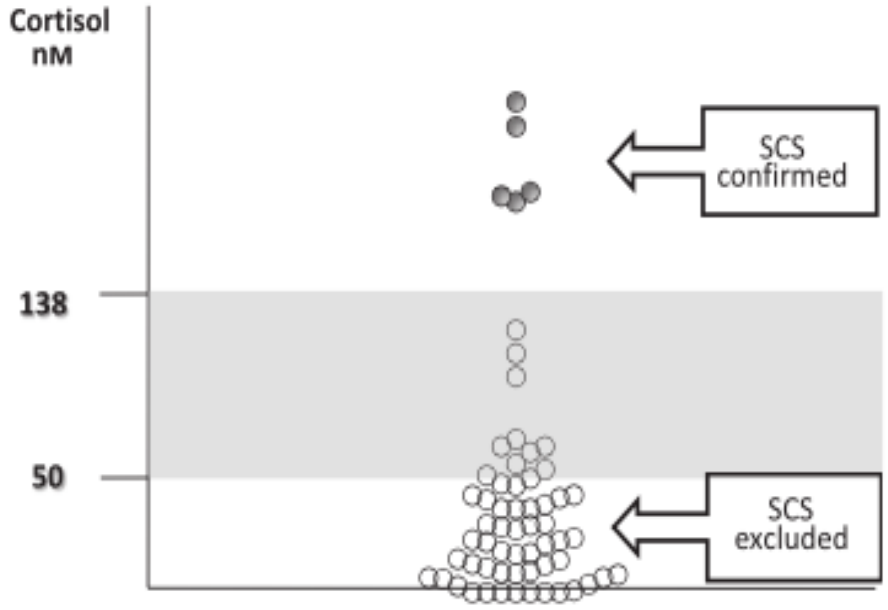
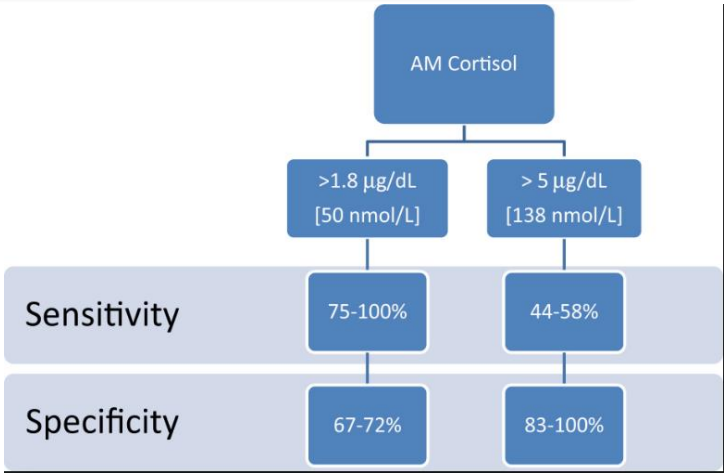
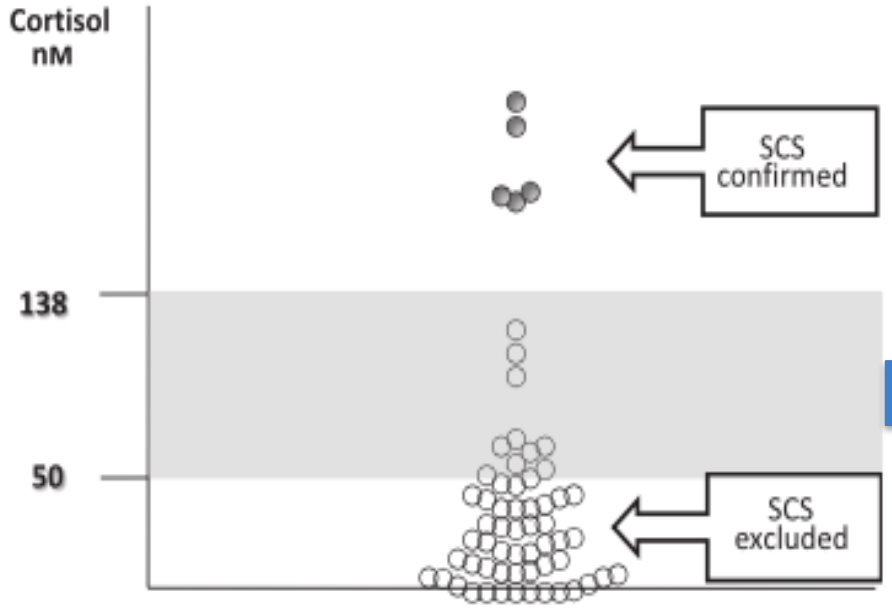
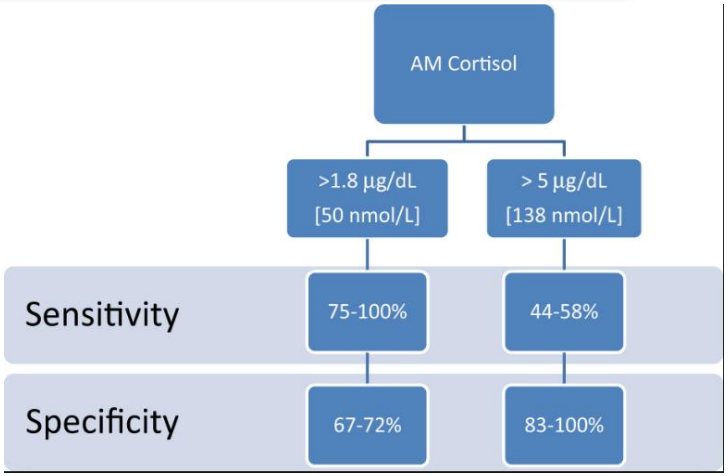


Fig. 1 Proposed definition of subclinical Cushing's syndrome by using different cut-off levels of cortisol after 1-mg overnight dexamethasone suppression test. Cortisol levels <50 nM exclude the condition, while levels ≥138 nM are confirmatory. Cortisol levels in between are indeterminate and should be interpreted with clinical data (see text for further details). Data from a personal series of 100 consecutive patients with an adrenal adenoma discovered serendipitously.



Diagnóstico





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Combinação
de parâmetros

Diagnóstico

- Combinação de parâmetros:

Endocrine Journal, 2013

Clinical Endocrinology, 2010

Clinical Endocrinology, 2017

*Todos os estudos em Incidentalomas Adrenais

Diagnóstico

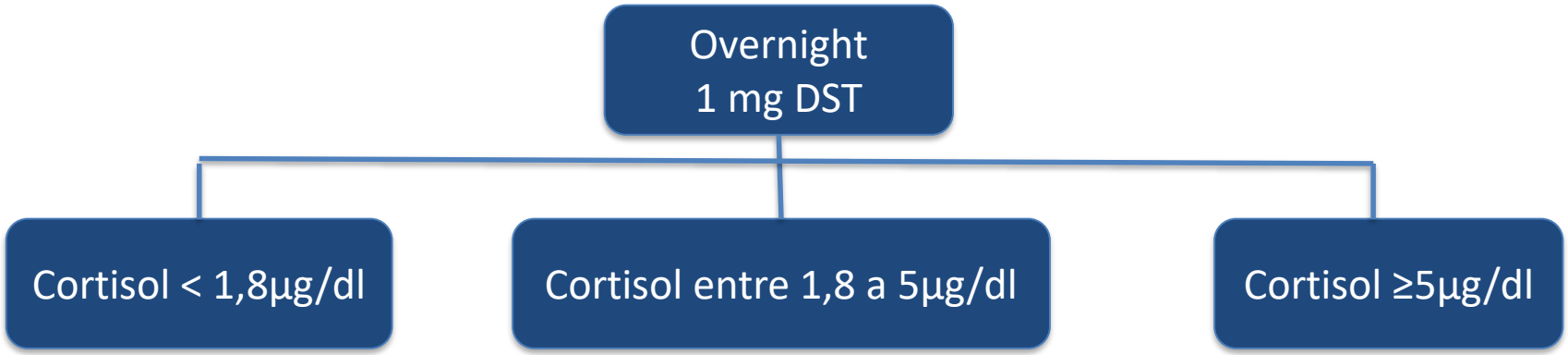
- Para Cushing Subclínico hipofisário:

Table 1 Criteria for the diagnosis of subclinical Cushing's disease according to the Ministry of Health, Labour, and Welfare, Japan (2010).

1. Suspicion of SCD
(1) Suspicion or presence of pituitary lesion on MRI.
(2) Normal–high plasma ACTH with normal morning cortisol level.
(3) Absence of typical Cushingoid appearance (moon face, central obesity or dorsocervical fat pad (buffalo hump): purple striae, thin skin and easy bruising, proximal myopathy. In children, decrease in weight gain rate with obesity).
Perform screening tests when (1), (2) and (3) are positive.
2. Screening tests
(1) Incomplete suppression of plasma cortisol level (>3 μg/dL) in low-dose (0.5 mg) overnight dexamethasone suppression test (DST).
(2) High plasma cortisol level (>5 μg/dL) during nocturnal sleep.
(3) Response of plasma ACTH level to desmopressin (DDAVP) test (>50% increase in plasma ACTH level after test).
(4) High salivary cortisol level (>1.5, compared with mean level for the hospital) during nocturnal sleep.

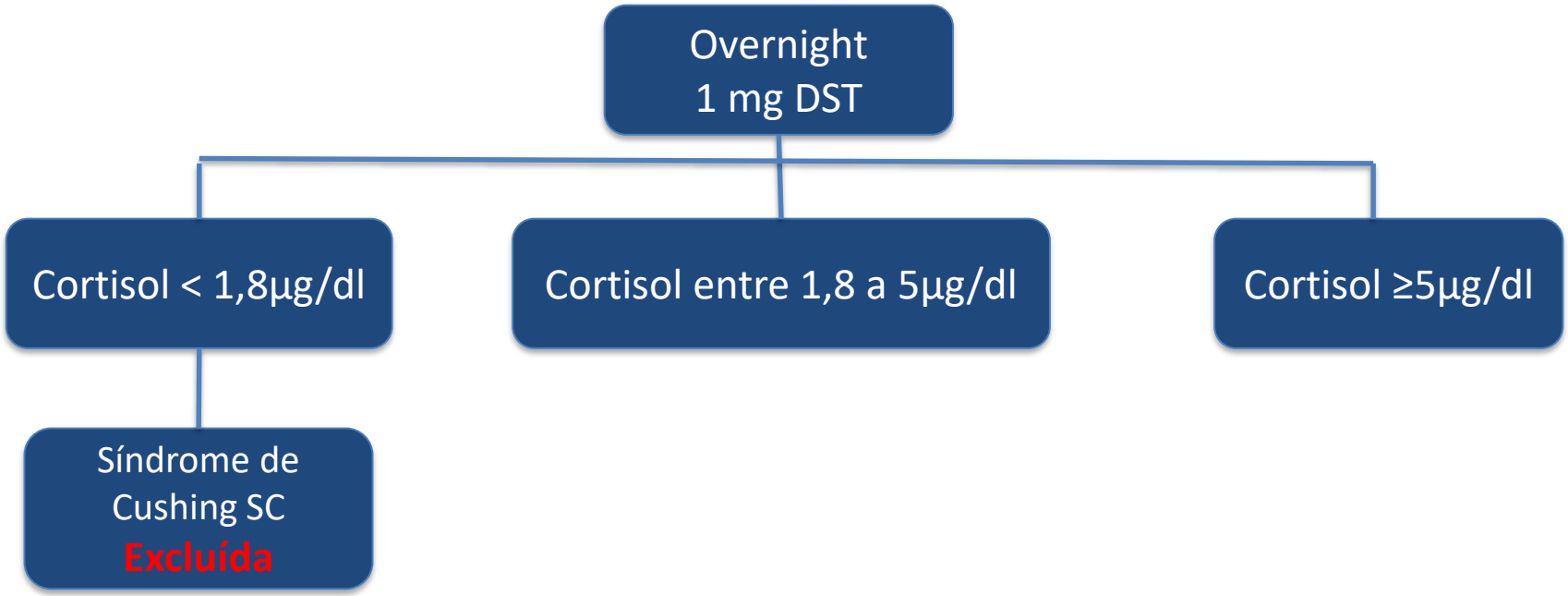
Tamada, Endocrine Journal 2016, 63(1),47-52

Diagnóstico - Fluxograma



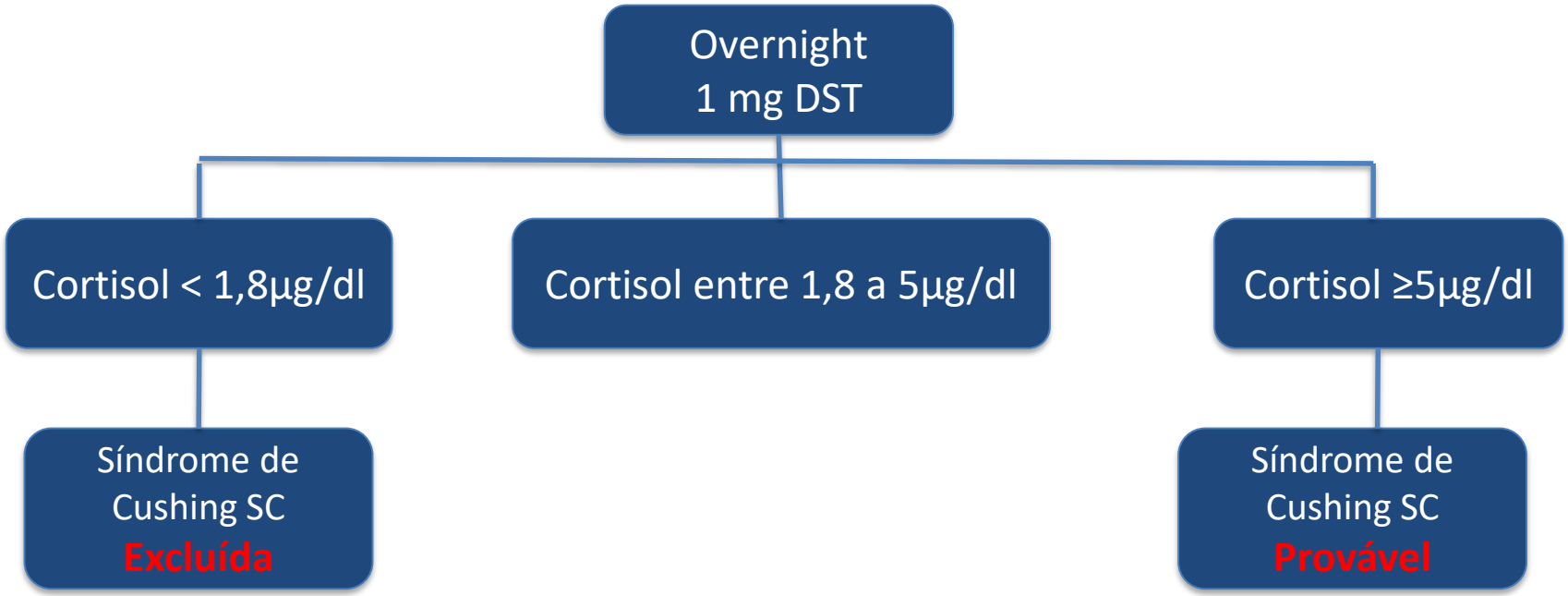
Chiodioni, Endocrine, 2016

Diagnóstico - Fluxograma



Chiodioni, Endocrine, 2016

Diagnóstico - Fluxograma



Chiodioni, Endocrine, 2016

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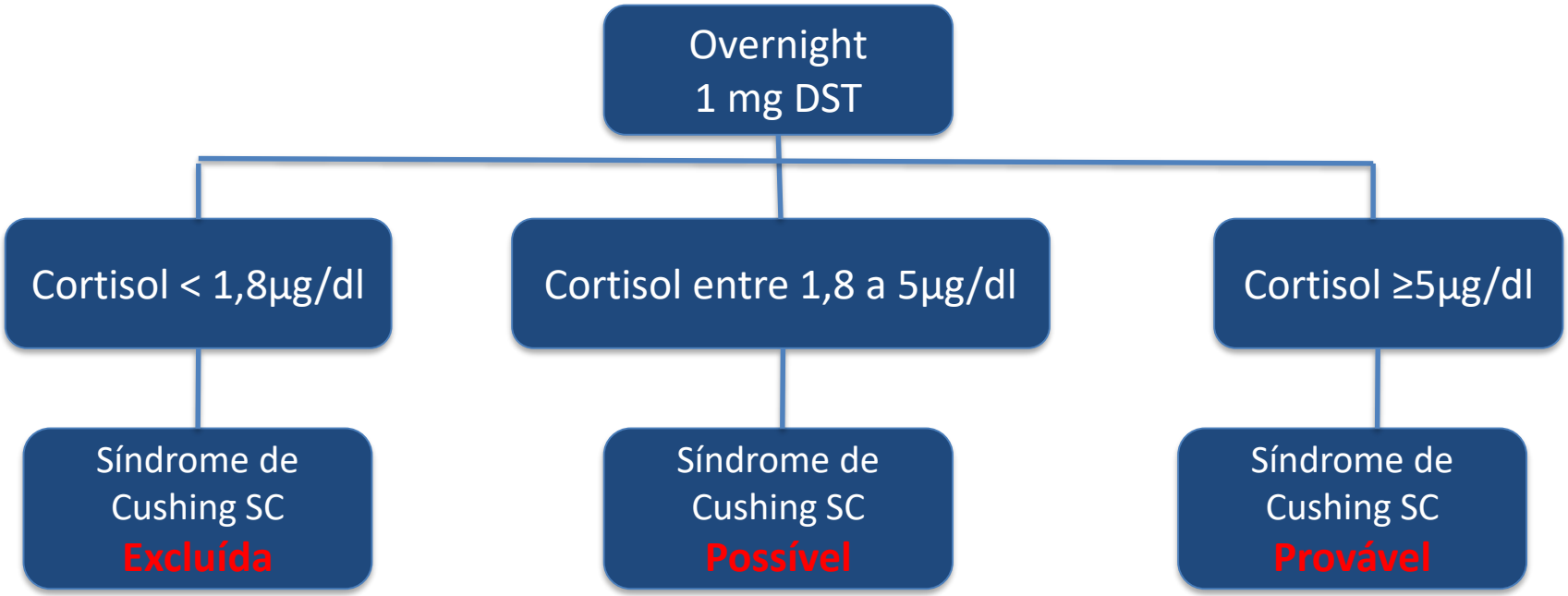
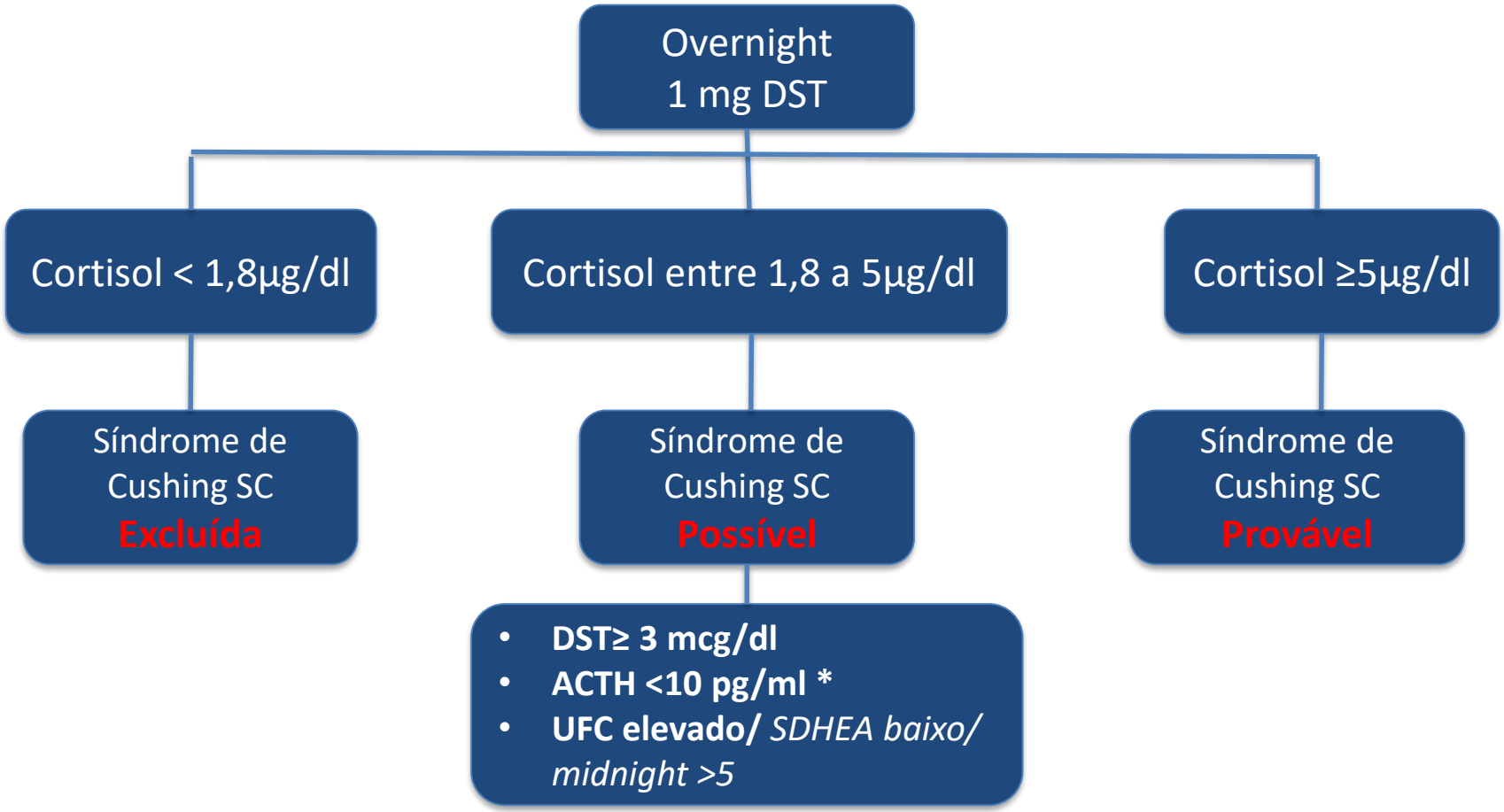


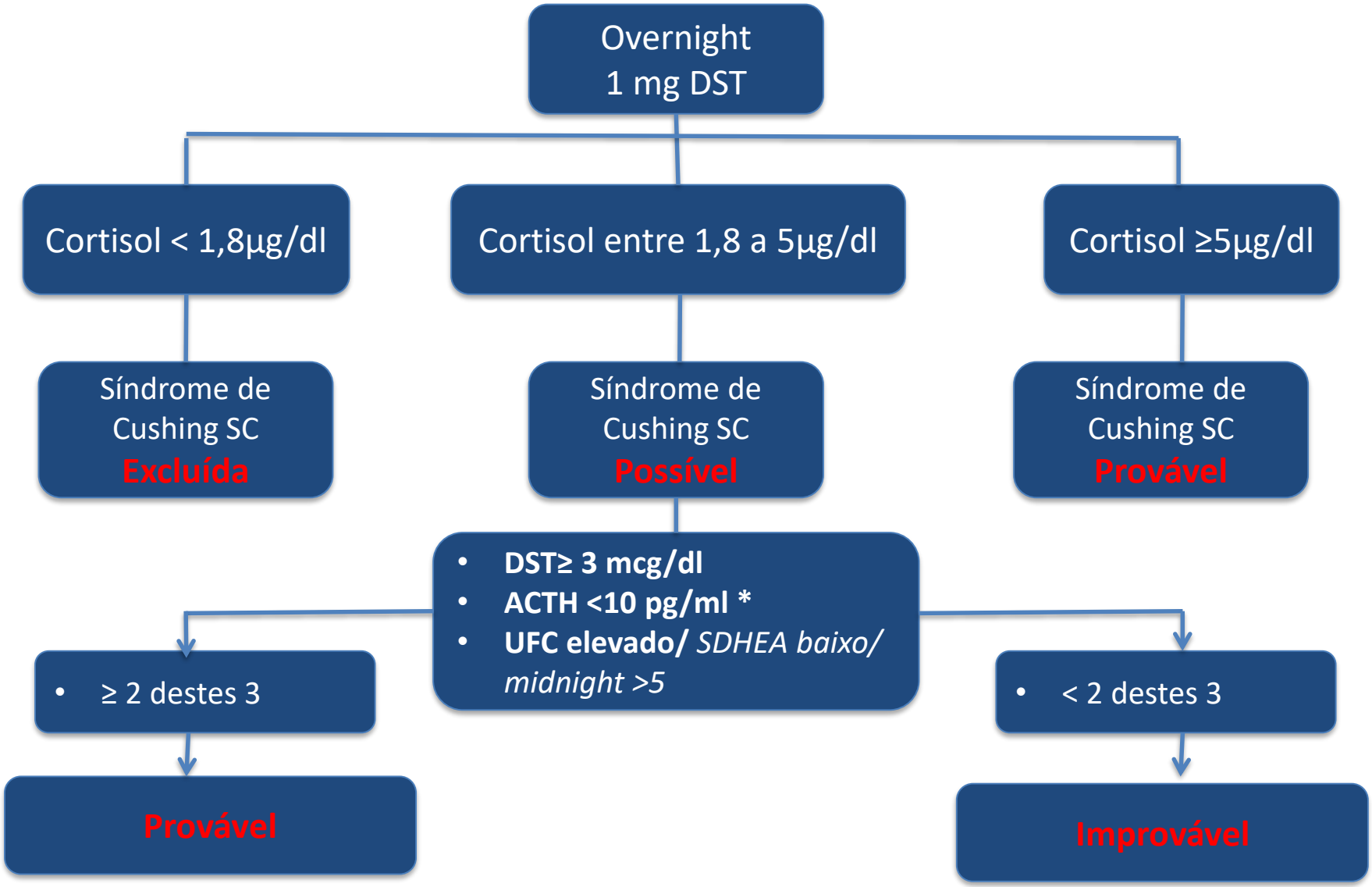
Chiodioni, Endocrine, 2016

Diagnóstico - Fluxograma



Chiodioni, Endocrine, 2016

Diagnóstico - Fluxograma



Manejo

Clínico **X** Cirúrgico

Manejo

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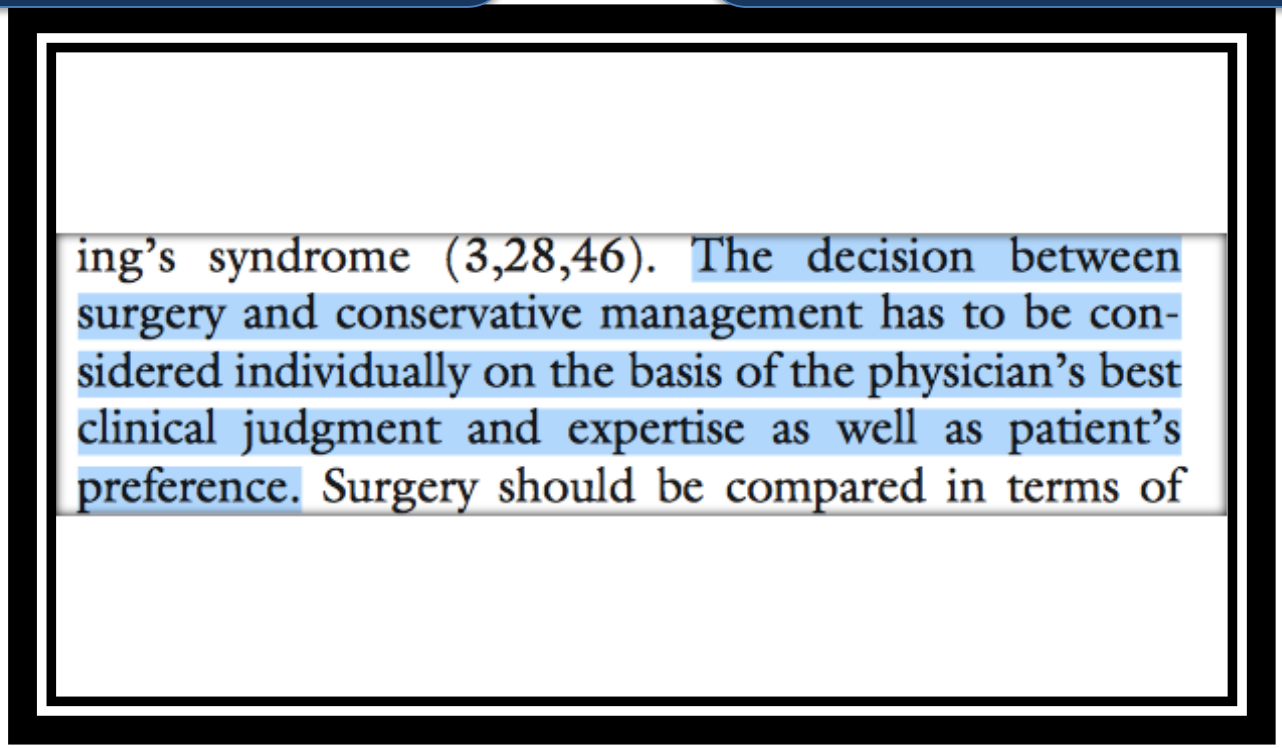

ing's syndrome (3,28,46). The decision between surgery and conservative management has to be considered individually on the basis of the physician's best clinical judgment and expertise as well as patient's preference. Surgery should be compared in terms of

Manejo

TABLE 4. Studies investigating the effect of the recovery from SH on blood pressure, body weight, fasting glucose, and bone

First author, year (Ref.)	Design	SH+ Surg (n)	SH+ Cons (n)	SH− Surg (n)	SH− Cons (n)	FU (months)	SH criteria	BP	BW	FG	Bone
Rossi, 2000, (18)	Prosp.	5	7	13	25	18–300	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of F rhythm, blunted ACTH after CRH	↑[a]	–	↑[a]	–
Midorikawa, 2001 (46)	Prosp.	4	–	8	–	1	Cortisol >3.0 μg/dl after 1-mg DST and low ACTH	↕[a]	↓	↑[a]	–
Emral, 2003 (54)	Prosp.	3	1	3	57	n.a.	Cortisol >3.0 μg/dl and UFC reduction < 50% after 3-mg DST	↑	↑	↑	–
Bernini, 2003 (93)	Prosp.	6	–	9	–	12	Cortisol >5.0 μg/dl after 1-mg DST	↑[a]	↓	↑[a]	–
Erbil, 2006 (94)	Retrosp.	11	–	–	83	12	Cortisol >3.0 μg/dl after 1-mg DST and 8-mg DST	↕	↕	↕	–
Mitchell, 2007 (95)	Retrosp.	9	–	–	–	1–30	Cortisol >1.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, low DHEAS, lateralization with AVS, clinical signs	↑	↑	↑	–
Tsuiki, 2008 (96)	Retrosp.	10	12	–	–	7–19	Cortisol >3.0 μg/dl after 1-mg DST and ≥1.0 μg/dl after 8-mg DST plus 1 out of: low ACTH, loss of CCR, low DHEAS, AS uptake	↑	↓	↕	–
Toniato, 2009 (57)	Prosp. Rand.	23	22	–	–	24–204	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of CCR rhythm, blunted ACTH after CRH	↑	–	↕	↓
Sereg, 2009 (97)	Retrosp.	5	8	42	70	109 ± 37	Cortisol >3.6 μg/dl after 1-mg DST and/or MSeC >5 μg/dl	↓	↓	↓	–
Chiodini, 2010 (61)	Retrosp.	25	16	30	37	18–54	2 out of: cortisol >3.0 μg/dl after 1-mg DST, low ACTH, high UFC	↑[a]	↑	↑	–

JCEM 96:1223-1236,2011

Manejo

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JCEM 96:1223-1236,2011

Surgical Versus Conservative Management for Subclinical Cushing Syndrome in Adrenal Incidentalomas: A Prospective Randomized Study

Antonio Toniato, MD, Isabella Merante-Boschin, MD,* Giuseppe Opocher, MD,† Maria R. Pelizzo, MD,* Francesca Schiavi, MD,* and Enzo Ballotta, MD‡*

								PA	P	DM	Osso
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Annals Surgery, 249, march 2009

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TABLE 3. Long-Term Outcome in the Surgical Group

		After Surgery			
	Before Surgery	**Normalization**	**Improvement**	**No Changes**	***P* Value**
Low plasma ACTH, n (%)	7/23 (30.4)	7/7 (100)	—	—	—
Elevated UFC, n (%)	9/23 (39.1)	9/9 (100)	—	—	—
Post-DMX text, n (%)	23/23 (100)	23/23 (100)	—	—	—
DM, n (%)	8/23 (34.8)	2/8 (25)	3/8 (37.5)	3/8 (37.5)	.619
Hypertension, n (%)	18/23 (78.3)	5/18 (27.8)	7/18 (38.9)	6/18 (33.3)	.046
Hypercholesterolemia, n (%)	8/23 (34.8)	3/8 (37.5)	—	5/8 (62.5)	.619
BMI >30, n (%)	6/23 (26.1)	3/6 (50)	—	3/6 (50)	—
Osteoporosis, n (%)	5/23 (21.7)	—	—	5/5 (100)	—

Annals Surgery, 249, march 2009

Surgical Versus Conservative Management for Subclinical Cushing Syndrome in Adrenal Incidentalomas: A Prospective Randomized Study

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Toniato, 2009 (57)	Prosp. Rand.	23	22			–	↕ ↓

7,7 anos de follow up-
Nenhum paciente do grupo conservador evoluiu para
Overt Cushing

TABLE 3. Long-Term Outcome in

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Annals Surgery, 249, march 2009

Beneficial Metabolic Effects of Prompt Surgical Treatment in Patients with an Adrenal Incidentaloma Causing Biochemical Hypercortisolism

Iacopo Chiodini, Valentina Morelli, Antonio Stefano Salcuni, Cristina Eller-Vainicher, Massimo Torlontano, Francesca Coletti, Laura Iorio, Antonello Cuttitta, Angelo Ambrosio, Leonardo Vicentini, Fabio Pellegrini, Massimiliano Copetti, Paolo Beck-Peccoz, Maura Arosio, Bruno Ambrosi, Vincenzo Trischitta, and Alfredo Scillitani*

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JCEM 96:1223-1236,2011

Beneficial Metabolic Effects of Prompt Surgical Treatment in Patients with an Adrenal Incidentaloma Causing Biochemical Hypercortisolism

Iacopo Chiodini, Valentina Morelli, Antonio Stefano Salcuni, Cristina Eller-Vainicher, Massimo Torlontano, Francesca Coletti, Laura Iorio, Antonello Cuttitta, Angelo Ambrosio, Leonardo Vicentini, Fabio Pellegrini, Massimiliano Copetti, Paolo Beck-Peccoz, Maura Arosio, Bruno Ambrosi, Vincenzo Trischitta, and Alfredo Scillitani*

								PA	P	DM	Osso
Chiodini, 2010 (61)	Retrosp.	25	16	30	37	18–54	2 out of: cortisol >3.0 μg/dl after 1-mg DST, low ACTH, high UFC	↑[a]	↑	↑	–

Análise crítica:
- Jovens
- Tumores maiores
- Exames mais alterados (excluidos F+)

JCEM 96:1223-1236,2011

Manejo- Racional

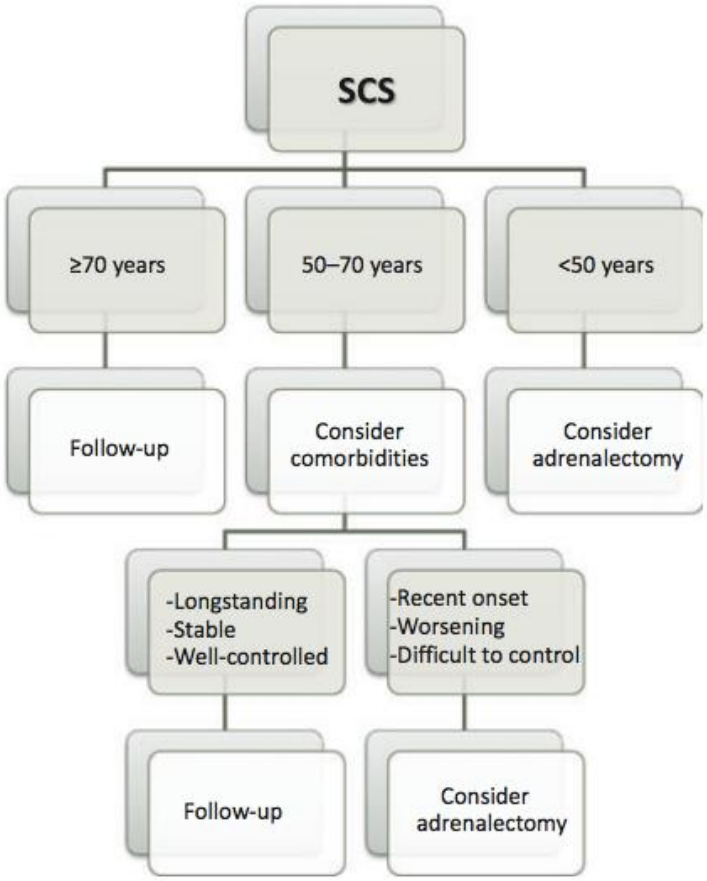
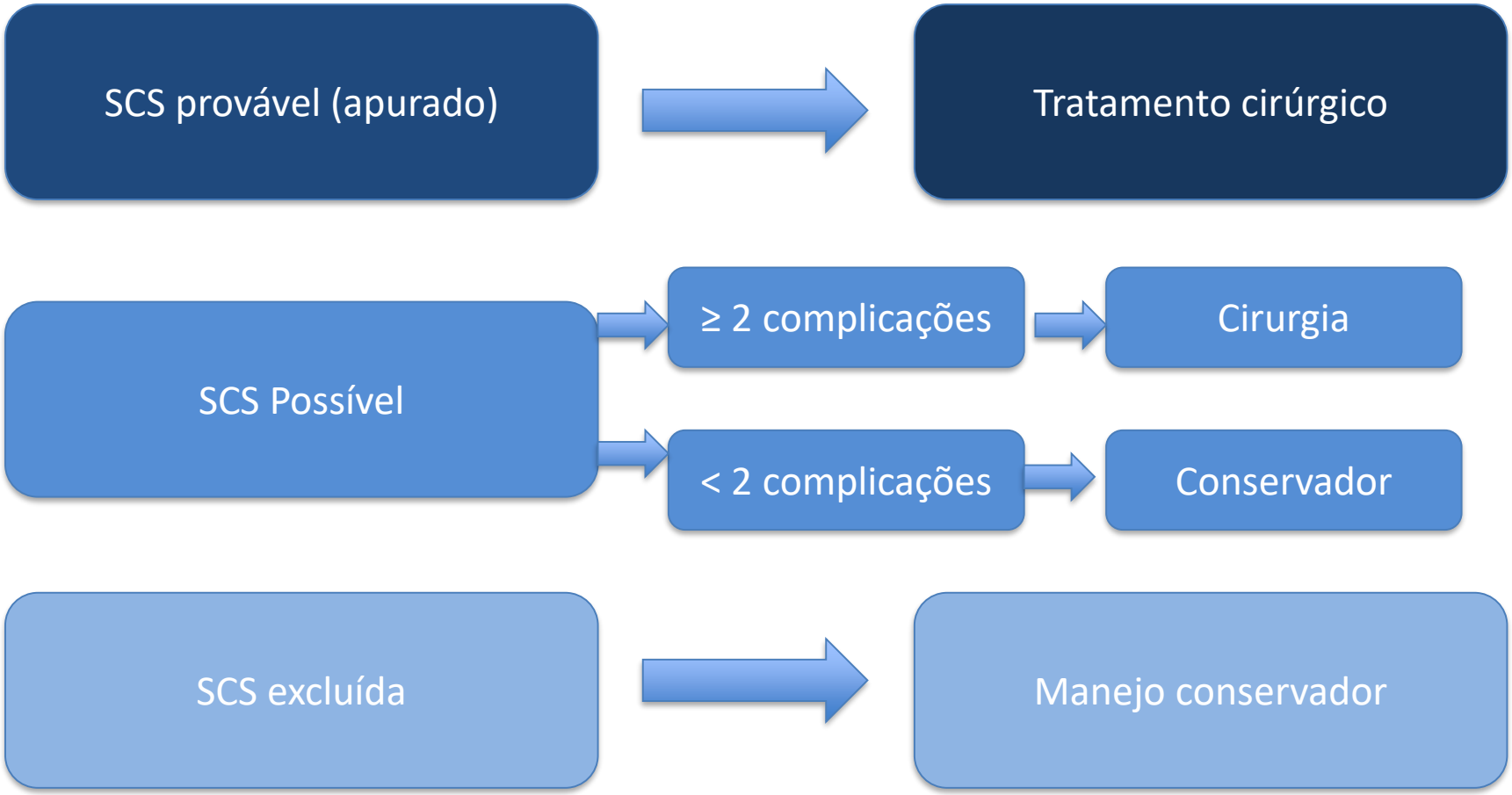


Fig. 2 Proposed management strategy of subclinical Cushing's syndrome.

Clinical Endocrinology (2012) 76, 12-18

Manejo- Racional

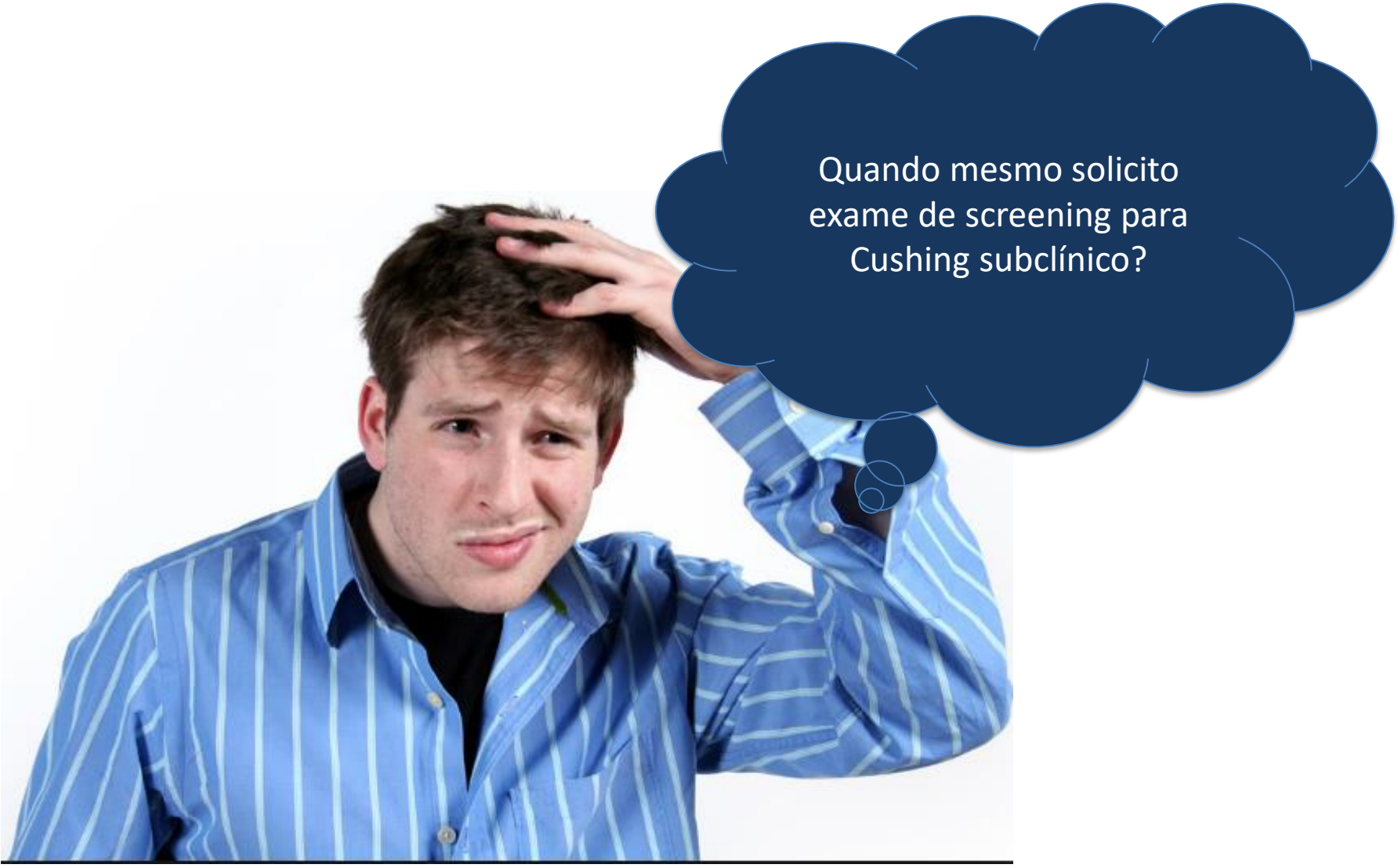


Chiodini, Endocrine 2016

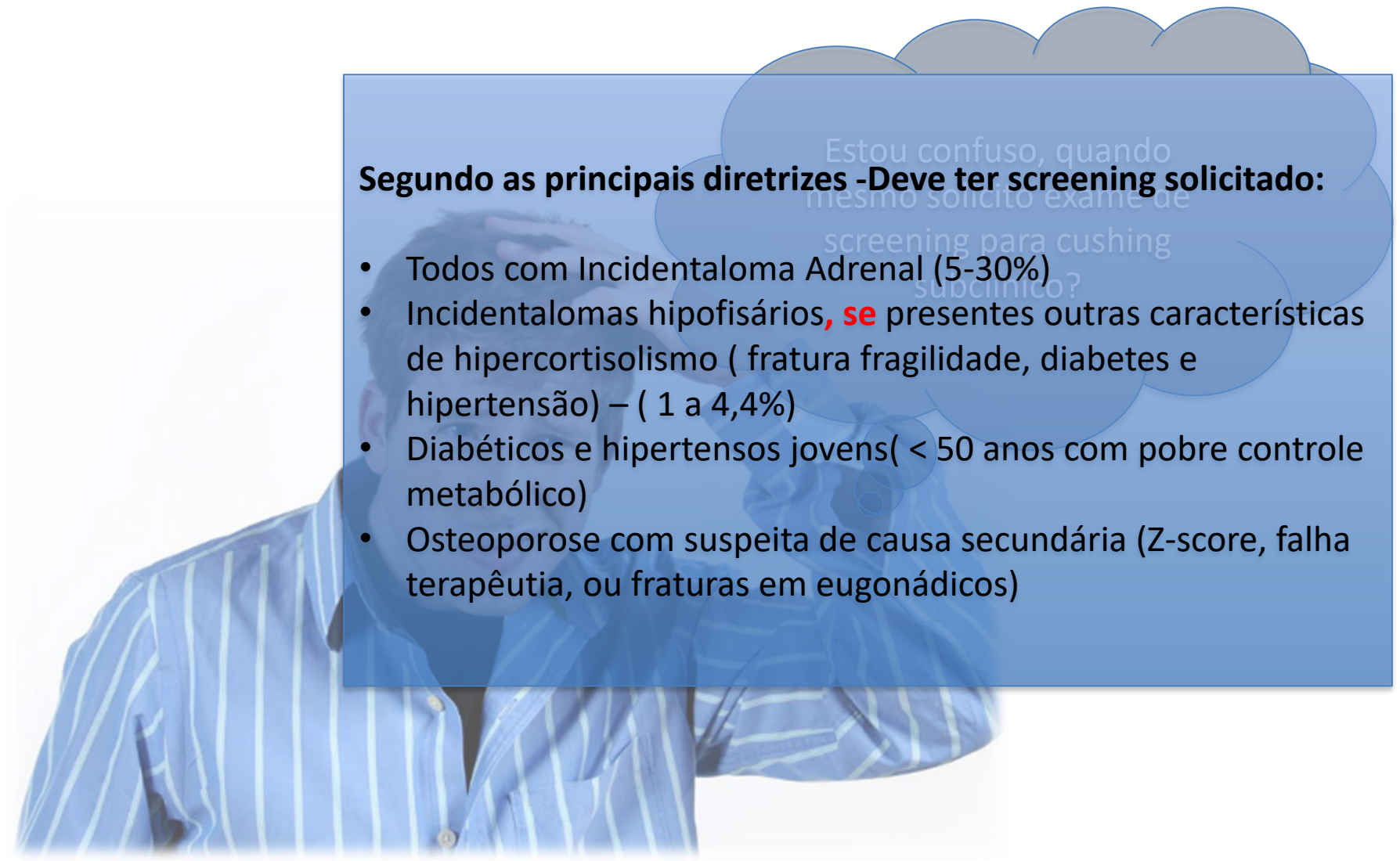
Conclusões

Julia, tua aula me deixou mais confusa, você pode resumir o que levar para casa??

Resumindo – Quando?



Resumindo



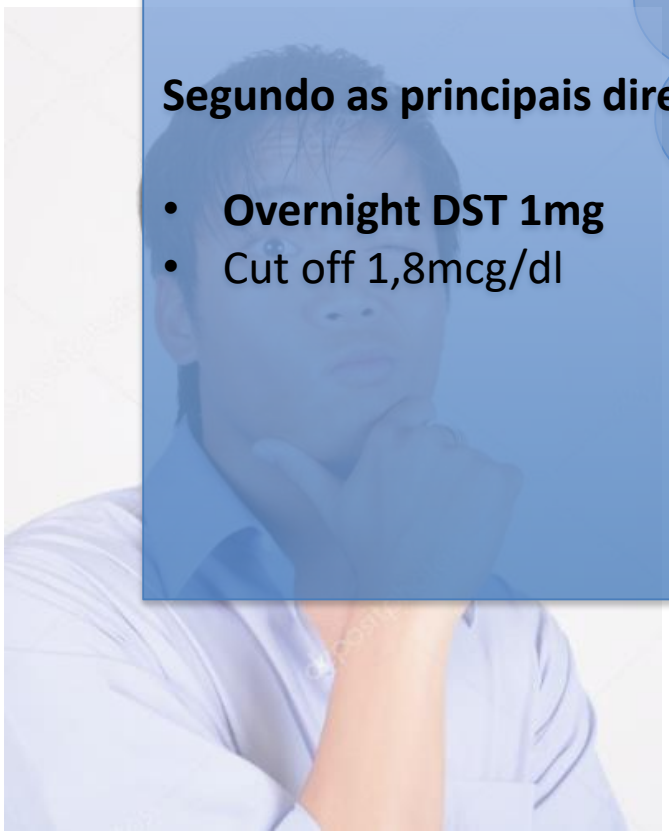
Segundo as principais diretrizes -Deve ter screening solicitado:

- Todos com Incidentaloma Adrenal (5-30%)
- Incidentalomas hipofisários**, se** presentes outras características de hipercortisolismo (fratura fragilidade, diabetes e hipertensão) – (1 a 4,4%)
- Diabéticos e hipertensos jovens(< 50 anos com pobre controle metabólico)
- Osteoporose com suspeita de causa secundária (Z-score, falha terapêutia, ou fraturas em eugonádicos)

Resumindo- Como?

Como pedir o exame de screening para Cushing SC?

Resumindo- Como?



Como pedir o exame de screening para Cushing SC?

Segundo as principais diretrizes –O exame de screening a ser solicitado:

- **Overnight DST 1mg**
- Cut off 1,8mcg/dl

Resumindo- Como?

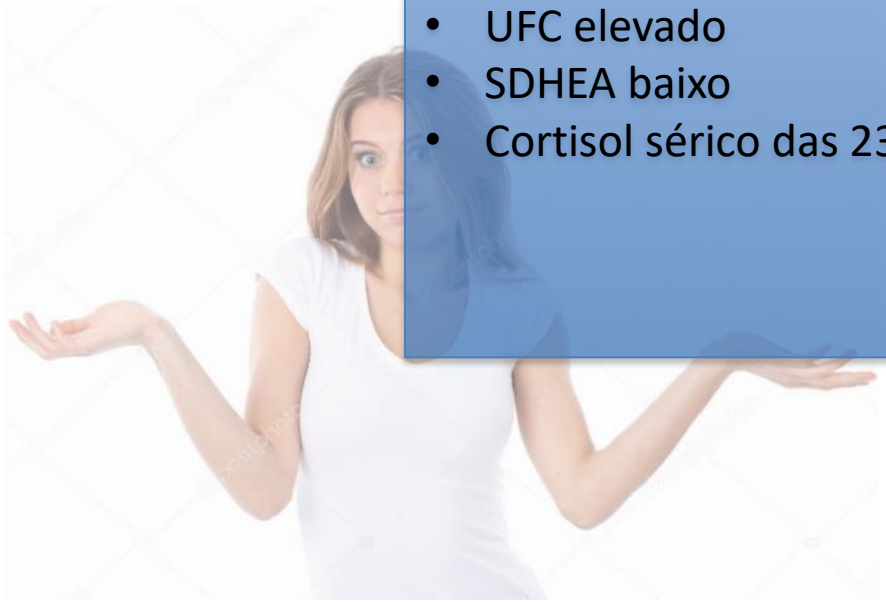
Eu pedi, mas o 1mg- DST veio na “trave” (entre 1,8 e 5mcg/dl) e agora?

Resumindo- Como?

Eu pedi, mas o DST veio na trave (entre 1,8 e 5) e agora?

Segundo as principais experts: Use combinação de parâmetros – idealmente ≥ 2 de 3 alterados :

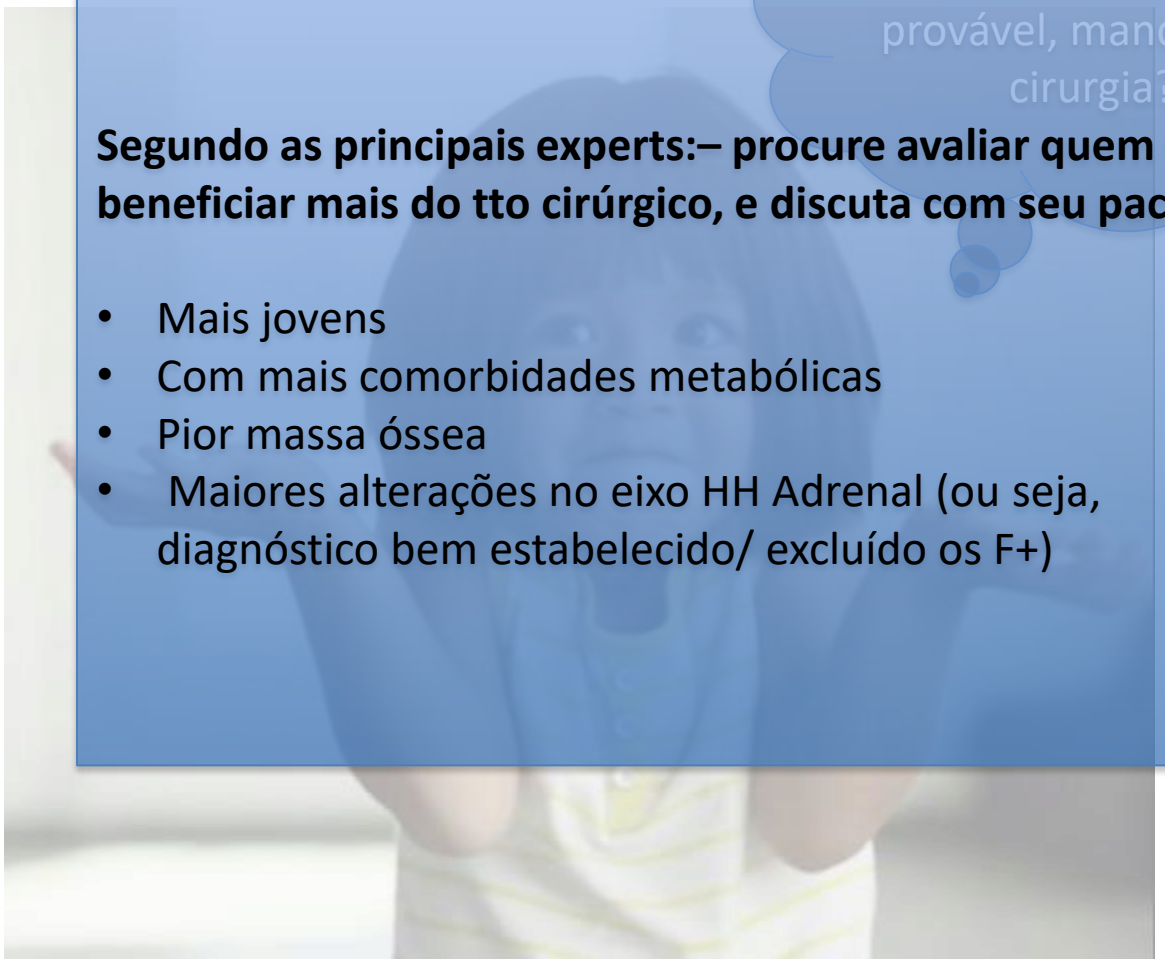
- DST≥ 3 mcg/dl
- ACTH <10 pg/ml *
- UFC elevado
- SDHEA baixo
- Cortisol sérico das 23h > 5 mcg/dl



Resumindo - Manejo

Resumindo - Manejo

O Diagnostico é mesmo de Cushing SC provável, mando para cirurgia?



Segundo as principais experts:– procure avaliar quem irá se beneficiar mais do tto cirúrgico, e discuta com seu paciente

- Mais jovens
- Com mais comorbidades metabólicas
- Pior massa óssea
- Maiores alterações no eixo HH Adrenal (ou seja, diagnóstico bem estabelecido/ excluído os F+)

Por fim...

Boa anamnese

Solicitação Criteriosa

Interpretação cuidadosa

Estudo/ Expertise

Dividir com paciente

***Evidência* for fraca/**
Julgamento Clínico

Obrigada pela atenção