SCORING OF i-IFTA: POTENTIAL RULES & ROLE IN CHRONIC TCMR

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I HAVE NO CONFLICTS OR FINANCIAL DISCLOSURES RELEVANT TO THIS TALK

DEFINITION OF IFTA

- IFTA = Interstitial fibrosis + Tubular atrophy
- i-IFTA= inflammation in areas with IFTA
- i+IFTA= inflammation in ?non-atrophic

- IF & TA often occur concurrently but do not always keep pace with each other
  - ct>>ci: BKVN, chr pyelo, RA stenosis
  - ci>> ct: compensatory H, nephron loss
- ci+ct used by some to capture both changes

Tubular Atrophy

- TBM thickening

OR

- Tubular basement membrane redundancy

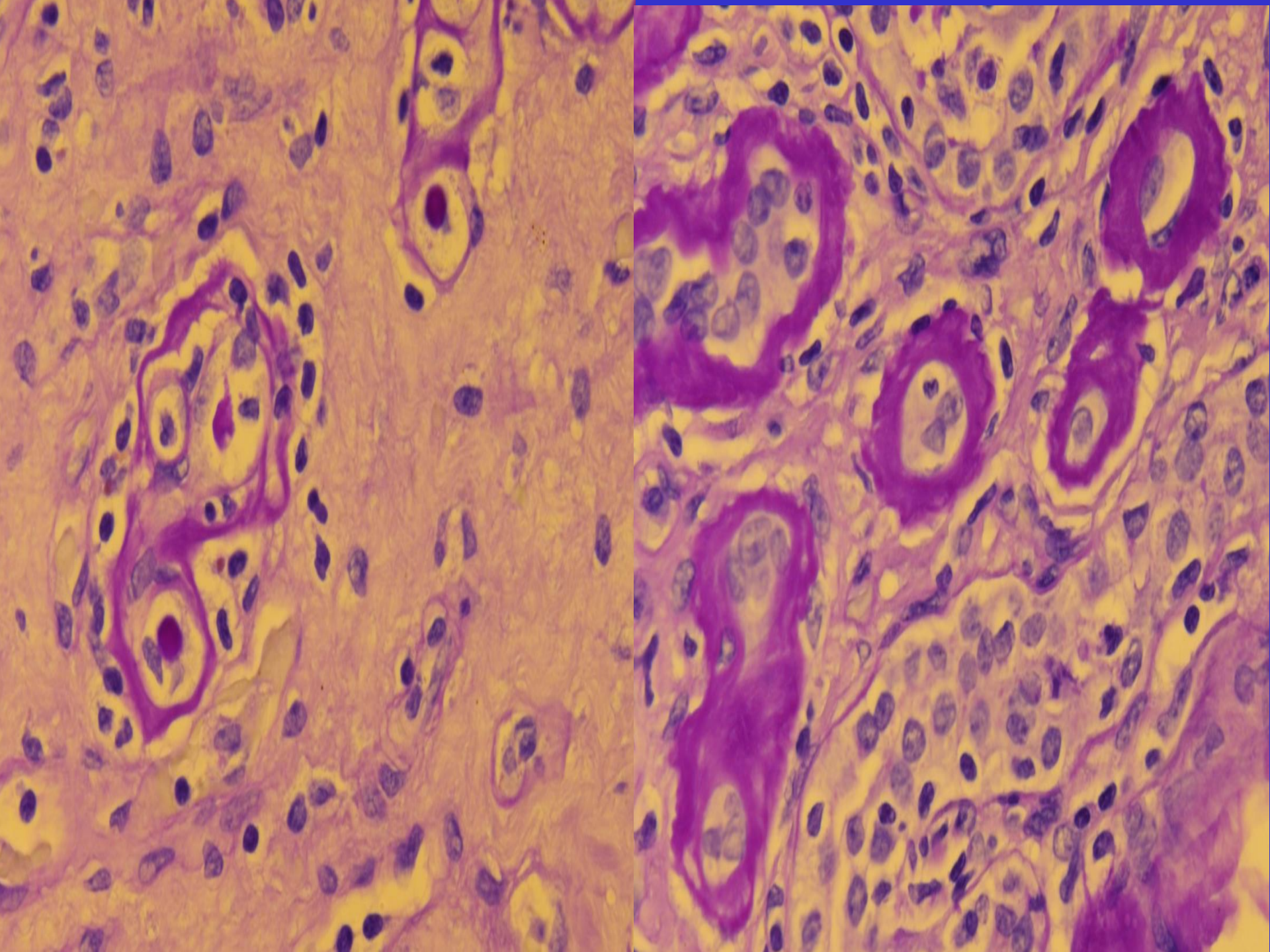
OR

- Reduction in tubular diameter >50%----compared to non-atrophic tubules in the cortex

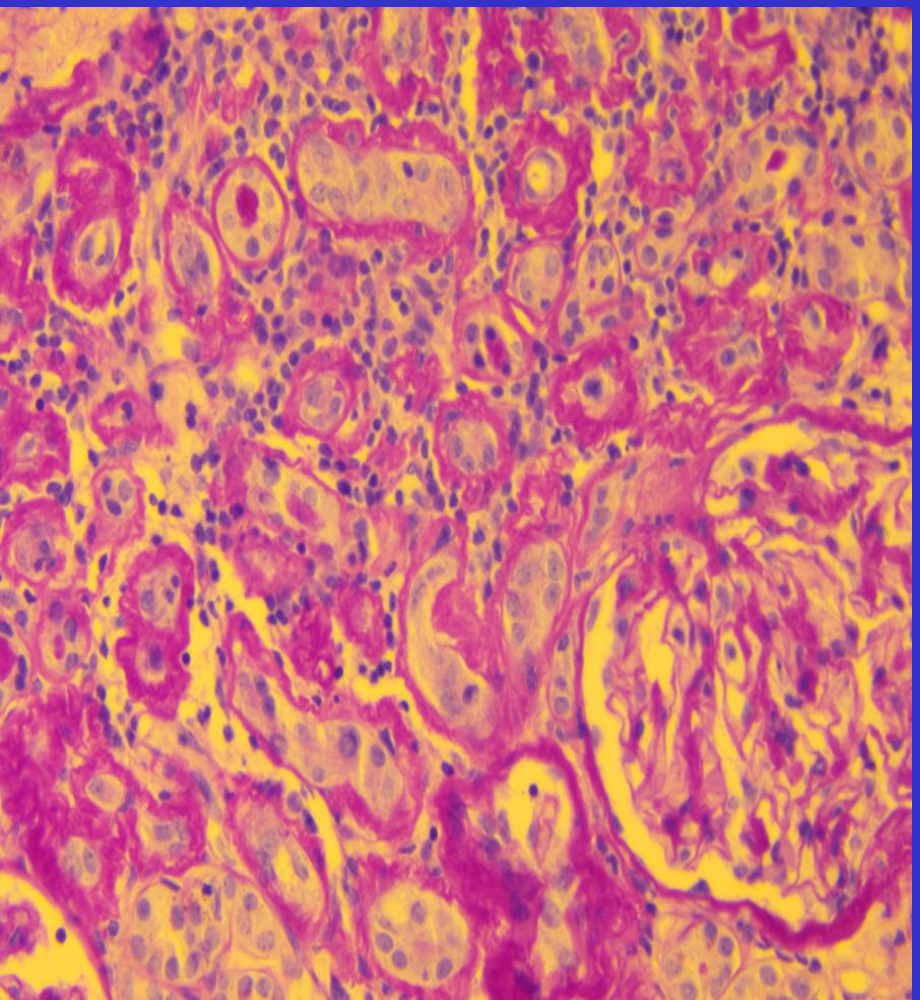
(Banff 1995 Schema)

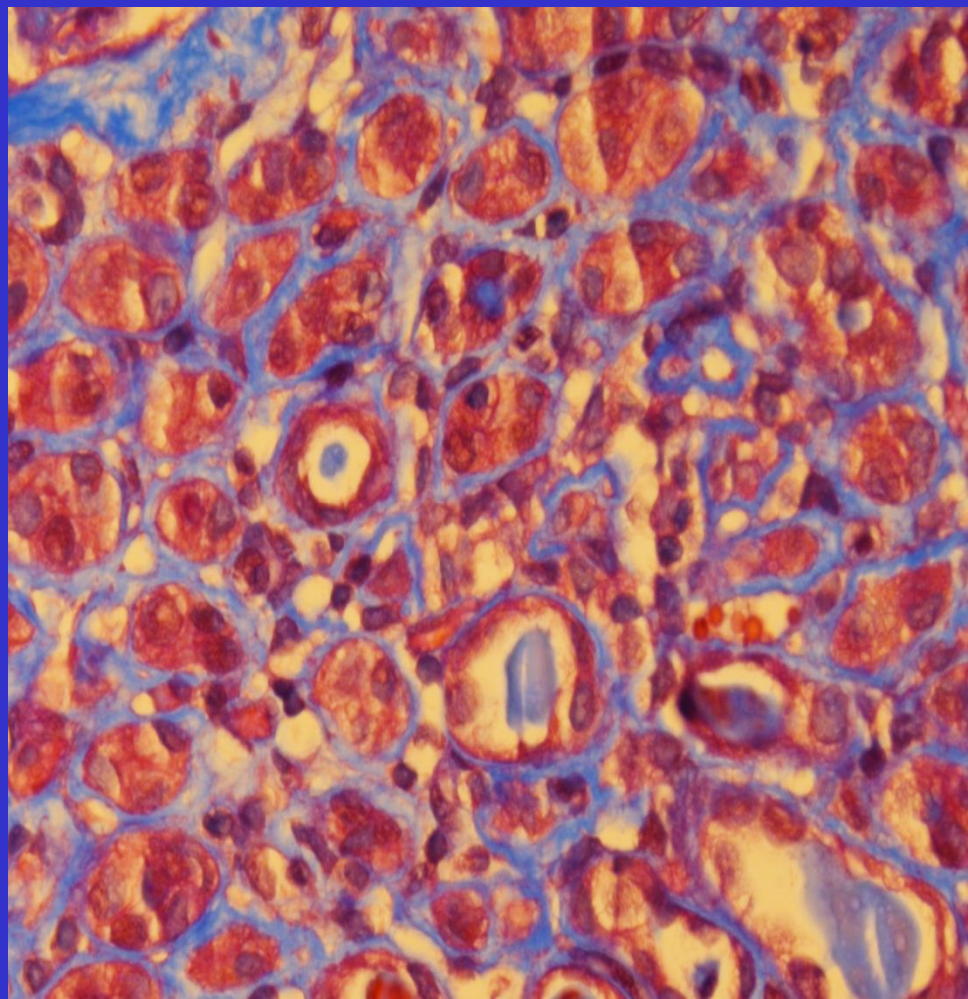
BIOCHEMICAL PERSPECTIVE

- Increased EC matrix separating the tubules.
- Matrix composed of mature fibrillar collagens which are a growing family (Types I, II, III, V, XI, 24, 27)
- Demonstrated by stains such as trichrome & sirius red or IHC for COL3
- Precursor collagen molecules soluble & resemble mucopolysaccharides in ischemia-reperfusion injury (sometimes called scleredema)

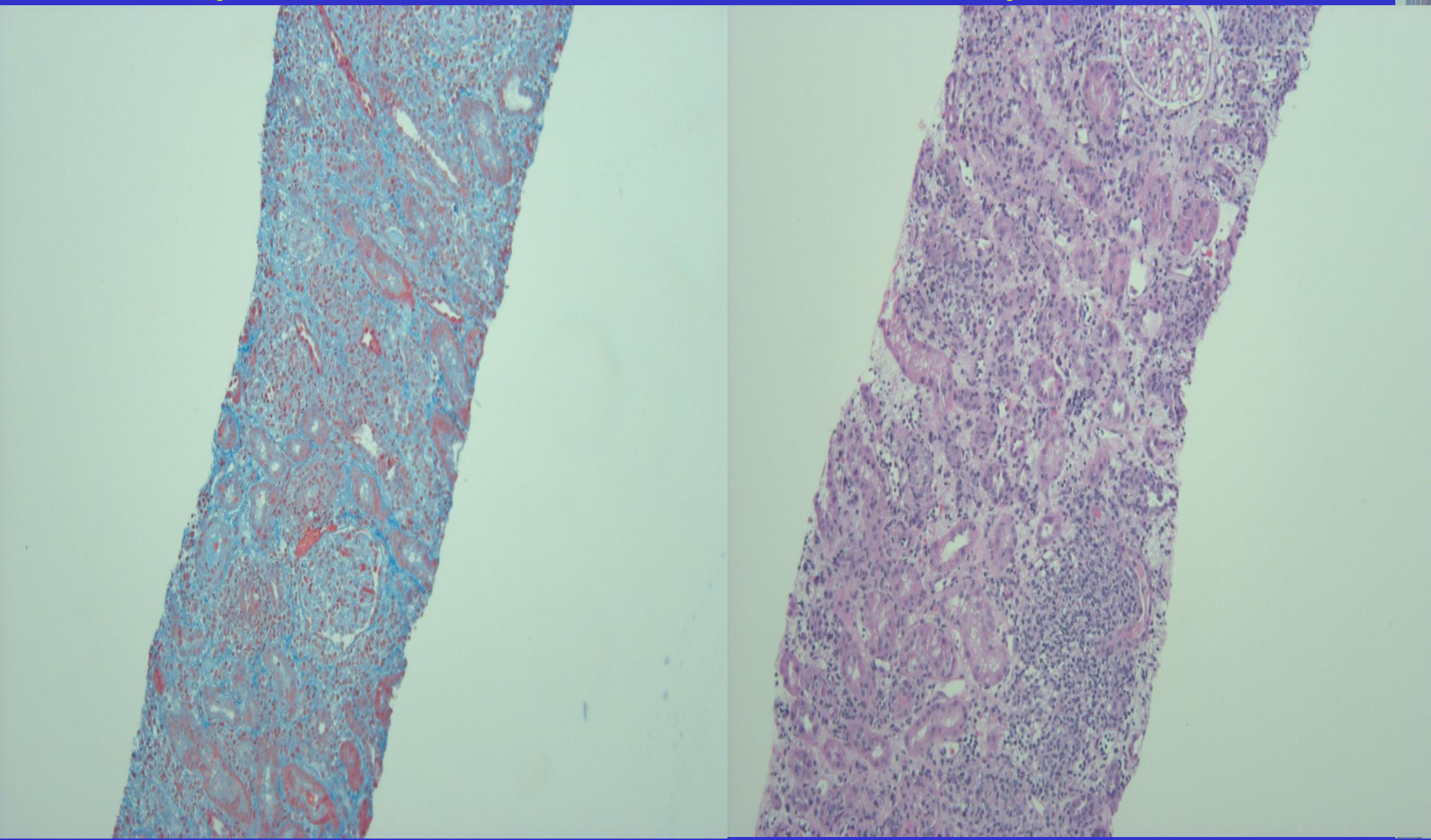


Atrophy Disproportionate to Fibrosis
(Mild/Trivial Inflammation)





ATROPHY DISPROPORTIONATE TO FIBROSIS
(Severe Inflammation & Tubulitis)



SCORING INFLAMMATION IN FIBROSIS

(i-IFTA)

BANFF 1997 SCHEMA

Inflammation can not be meaningfully graded:

1. In fibrous scars
2. In subcapsular cortex
3. In adventitia around large vessels

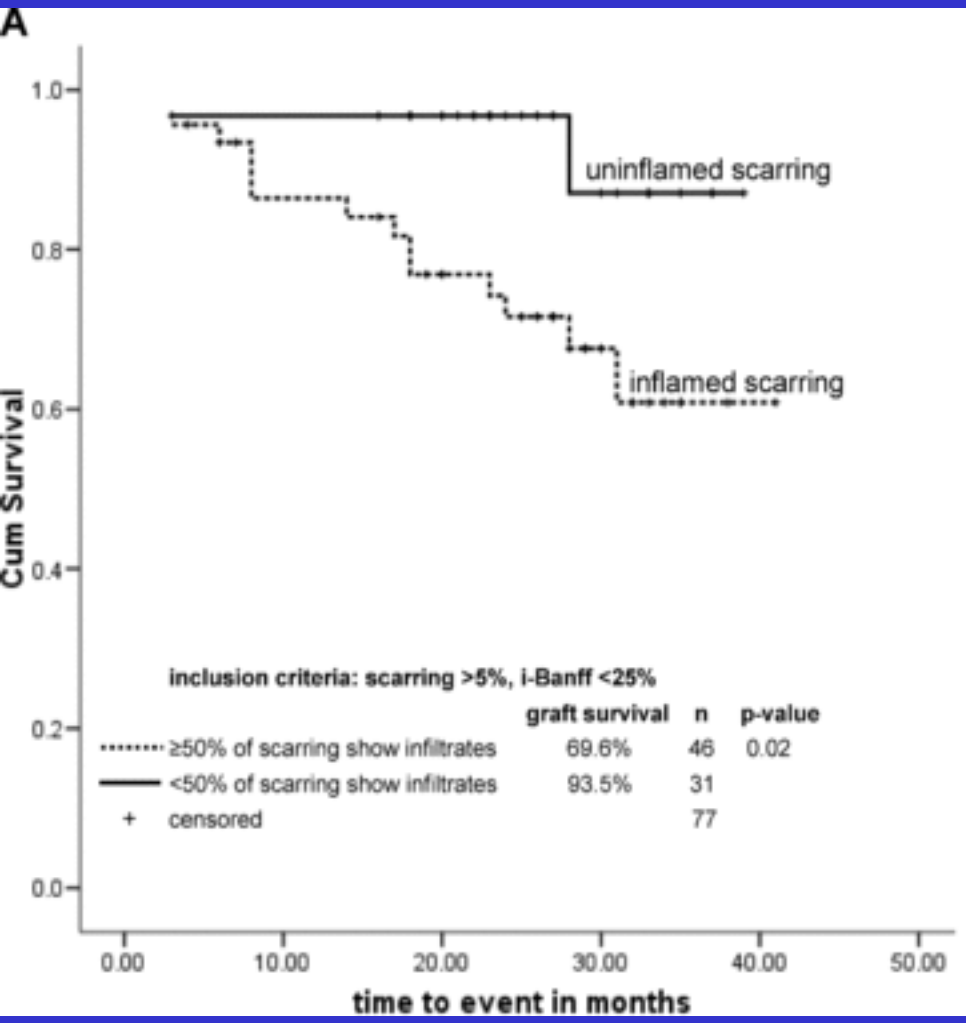
Degree of scarring allowed is not explicitly specified, but is usually understood to be mild

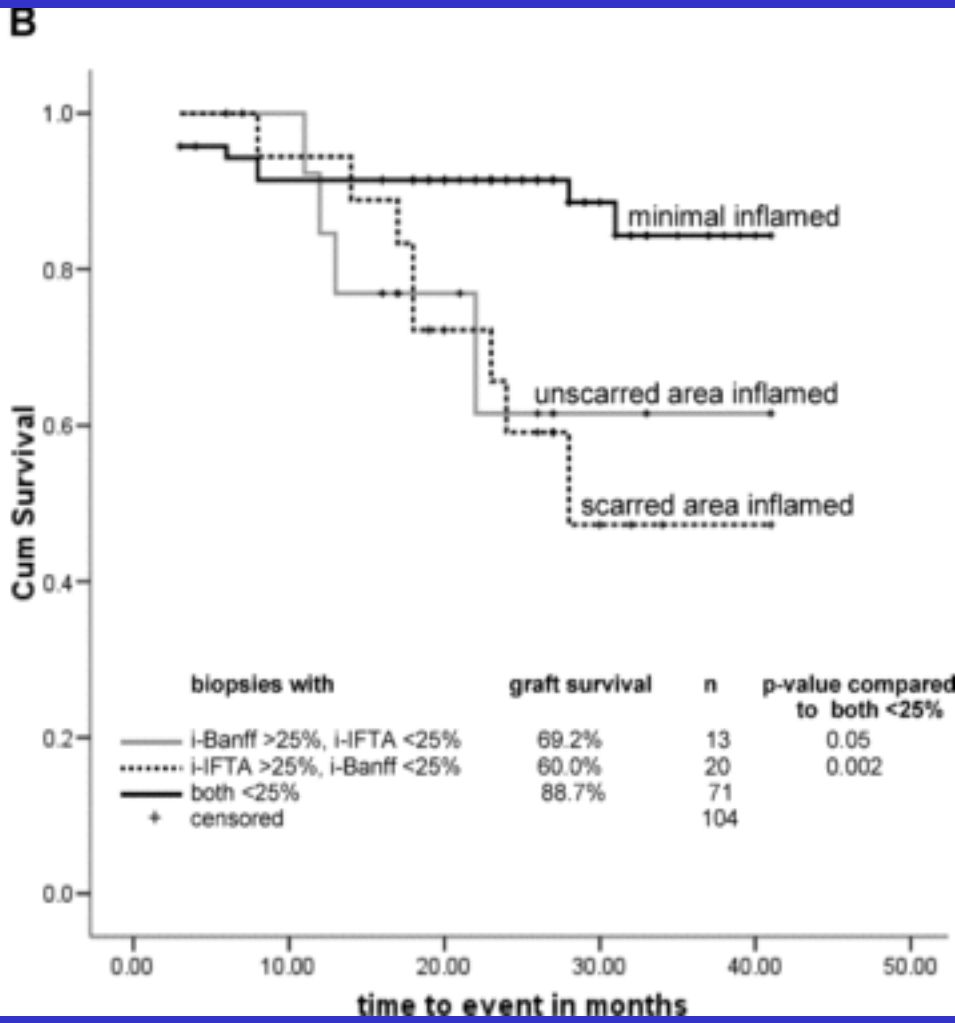
Basis for recommendation: heckling of Kim Solez by 2 opinionated pathologists after ist Banff conference

-He used Total i-score to interpret bxs before that

-Pgh always done so & continues to for clinical care

Mengel 2008: i-IFTA has Prognostic Relevance





Mengel et al. Am J Tx 9: 169: 2008

Observation Confirmed by Multiple Studies

1. Mengel/Halloran: Am J Transplant 2009: 9: 1859
2. Mannon/Rush: Am J Transplant 2010: 10:2066
3. Cosio/Stegall: J Am Soc Nephrol 2010:21:1987
4. Cosio/Stagall: Am J Tx 2012: 12: 1199
5. Naesens: Am J Transplant 2013: 13; 86 & Kid Int 2011: 80: 1364
6. Batal/Chandrakar: J Am Soc Nephrol 2015: 26; 3102

No controversy that i-IFTA = PROGNOSTIC parameter

Possible Utility i-IFTA in the Diagnosis of Chronic TCMR

Banff criteria for chronic active TCMR

- Chronic allograft arteriopathy
  - arterial intimal fibrosis, mononuclear inflammation in fibrosis, formation of neointima
  - can represent chronic active ABMR as well as TCMR
- 2015: Chr. active TCMR may also manifest in the tubulo-interstitial compartment (TIC)
- i-IFTA discussed as candidate lesion in 2015, but felt to be non-specific, & not accepted

Loupy et a. Am J Tx 2017: 17: 28

Historic Objections to Accepting i-IFTA as a Criterion for chronic -TCMR

1. Seen in native biopsies with ci-ct
2. Hence not a specific response to alloantigens
3. Accepting it as a criterion & treating it as such may not result in therapeutic responses
4. Put the patient at risk for complications of over-immunosuppression

Most Biopsies with i-IFTA Share GE Profiles with Indicative of Immunologic Injury

Shown in 3 independent studies from respected labss

- Halloran Lab. Am J Tx 2012: 12: 191 (TCMR score)
- Salomon Lab. AJT, 2016:16:1982 (GE-AR, ≠C4d/DSA)
- Sarwal Lab. Kid Int 2011:80: 1364 (acquired/innate genes: T/B-cell proliferation & NK/Mac activation

Proposal: i-IFTA be accepted as an exclusion based criterion for chr rej,--- be called ALLOIMMUNE-i-IFTA, & further subclassfied into TCMR/ABMR when possible

Alloimmune i-IFTA Should be a Diagnosis of Exclusion

- Chronic BKVN
- Chronic pyelonephritis/obstruction
- Recurrent disease, Donor disease
- Chronic calcineurin inhibitor toxicity
- Uncontrolled hypertension

i-IFTA should refer to a pattern of injury --- analogous to MPGN or FSGS---- the d/d of which requires clinicopathologic correlation

Subclassfication of Alloimmune-IFTA

- Chronic ABMR or Chronic TCMR if relevant criteria satisfied
- Probable Chr ABMR/TCMR: pathology ≠ diagnostic; prior episodes ABMR/TCMR documented
- Retain the term i-IFTA NOS for biopsies where sufficient information not available to support ABMR/TCMR

Formal Listing of Suggested Criteria to Diagnose Chronic TCMR in i-IFTA

- Any ci score > 0 but donor disease should be excluded
- Inflammation >i0 should be present in non-scarred areas
- Allow for Ti & i to have the same ordinal scale, 1, 2 or 3
- No evid Ab-E interactions/C4d, No DSA, concurrent/past
- Chr active & chronic inactive forms TCMR (only active form listed in Banff 2015 table)------criteria for activity any tubulitis/TBM disruption, and possibly tubular damage, edema, RBC & eosinophils as noted in CCTT

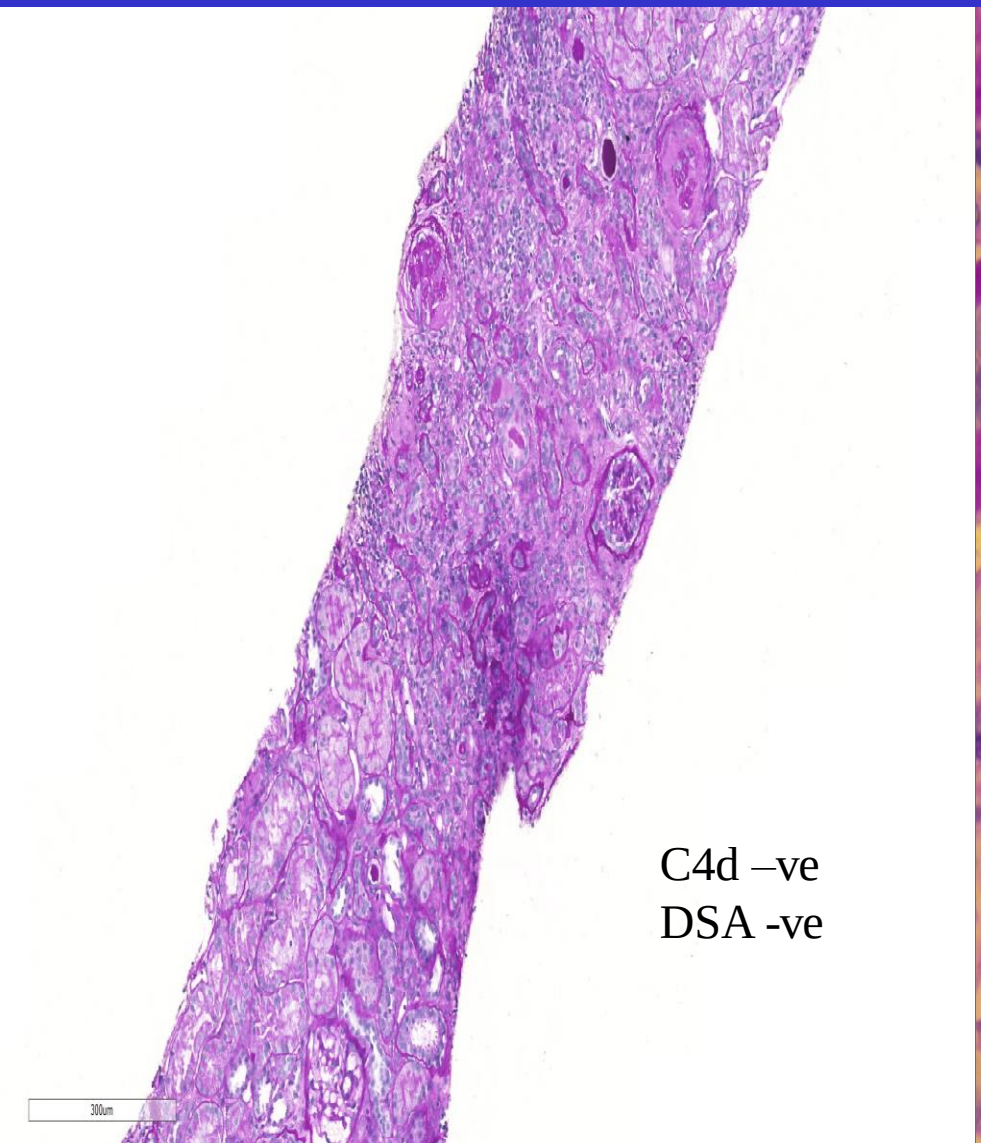
Pittsburgh:
Diagnosis of ACUTE TCMR in i-IFTA

Typically in patient with acute rise creatinine late post-tx

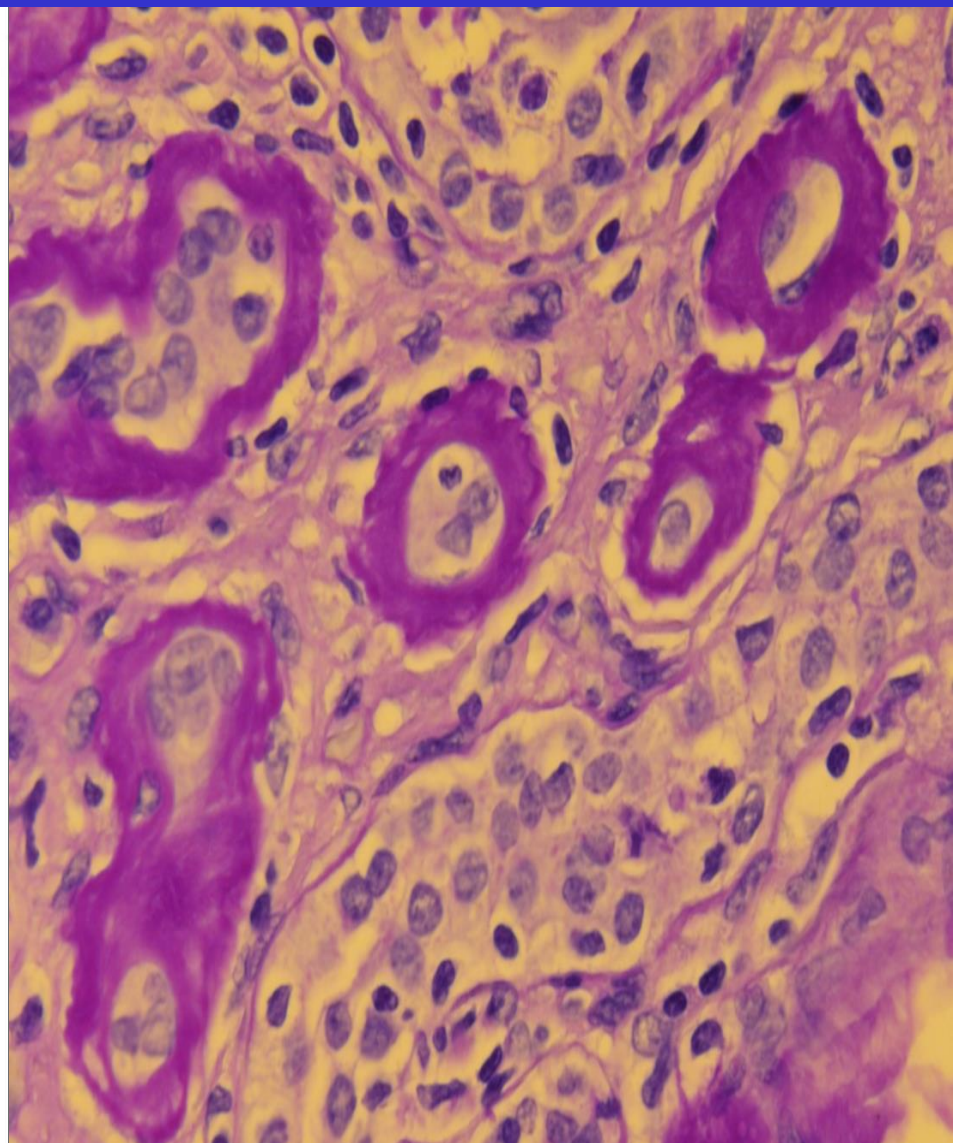
- Conventional i & t scores often close to zero
- Ti score can convey extent of inflammation
- Grade non-atrophic tubules in IFTA as index of severity of acute injury (usually found admixed with atrophic tubules)

- 1A= Ti>1 t>1; 1B requires t3; 2A requires v>0

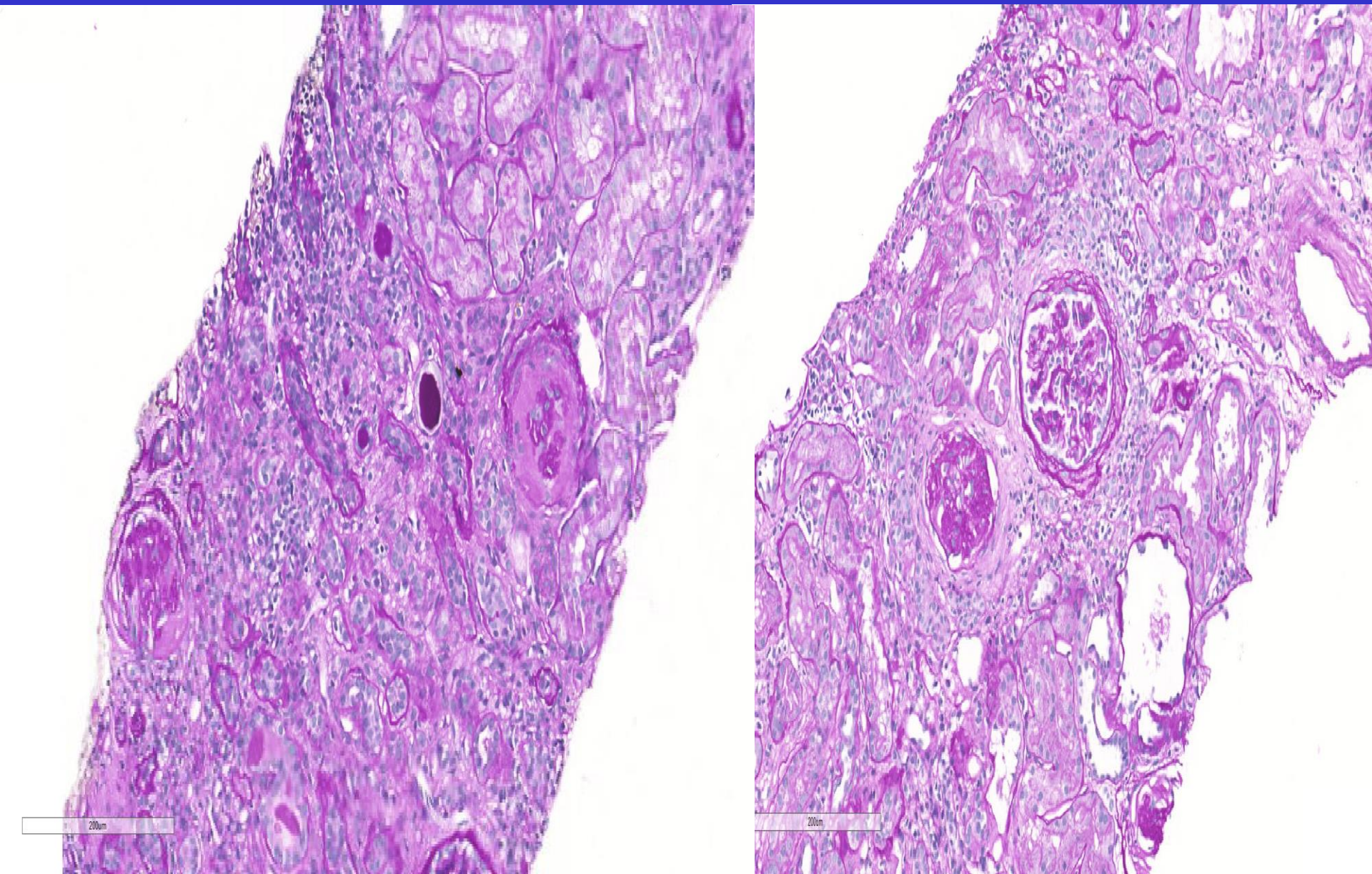
Dx of Grade 1A TCMR in setting of IFTA



C4d –ve
DSA -ve



Post-Treatment Biopsy



PRACTICAL ASPECTS OF SCORING LESIONS OF CHRONIC ACTIVE TCMR

BANFF 2015: Total Inflammation (ti score)

Necessary to convey relative amounts of inflammation in scarred & non-scarred areas

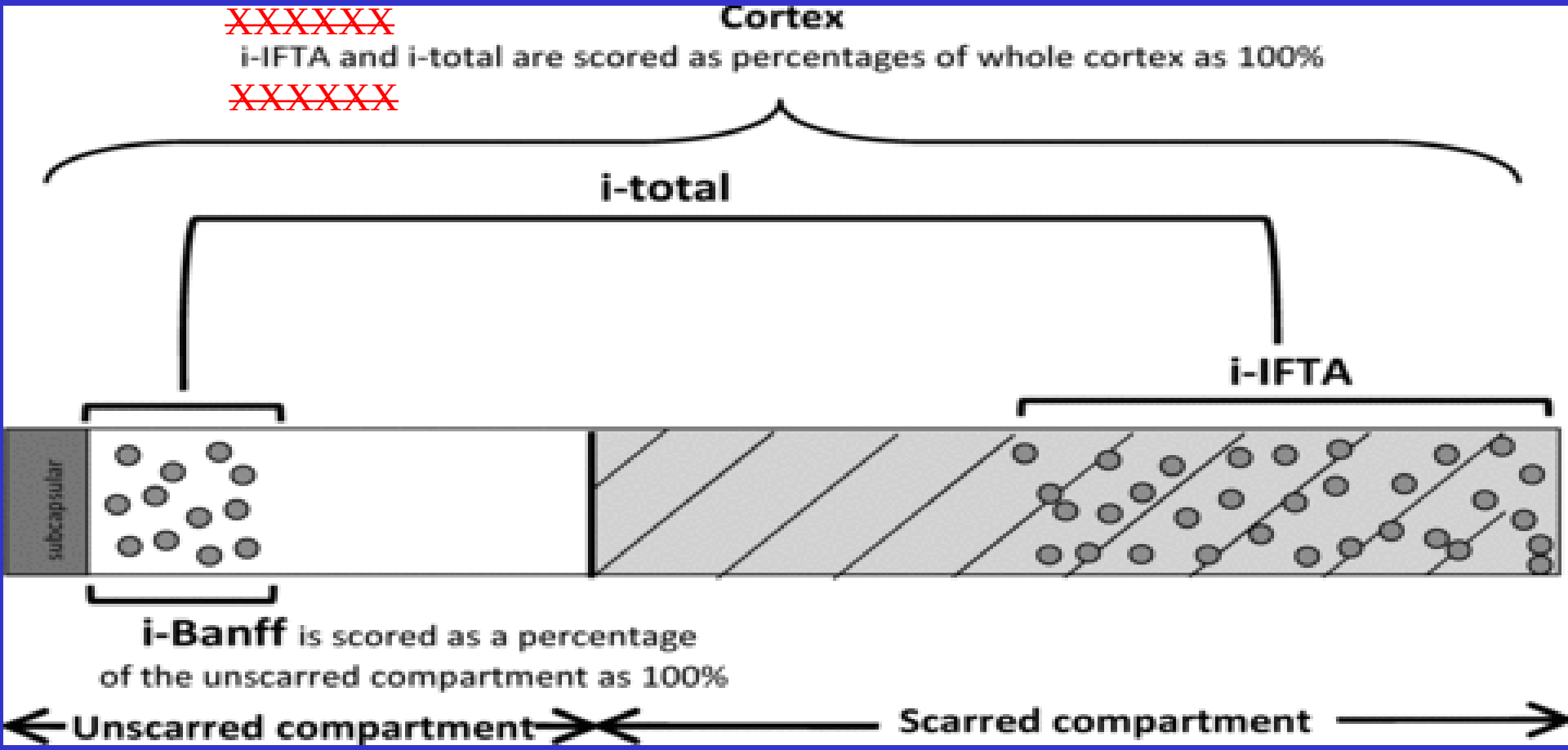
- ti0: No or trivial inflammation (<10% of cortex)
- ti1: 10-25% of total cortex inflamed
- ti2: 26-50% of total cortex inflamed
- ti3: >50% of total cortex inflamed

Loupy et a. Am J Tx 2017: 17: 28

BANFF 2015: SCORING OF i-IFTA

- i-IFTA0: No or trivial inflammation (<10%)
- i-IFTA1: inflammation in 10-25% of scarred cortical parenchyma, not the total cortex
- i-IFTA2: inflam 26-50%
- i-IFTA3: inflam>50%

Typographical Error in Seminal Publication



Sellares/Mengel/Halloran Am J Tx 11: 489: 2011

Comparison of i-IFTA Scores Derived from Total Cortex vs Total Scar as Denominator

- Total cortex:
  -low value in biopsies with little fibrosis
  -also low if lot of fibrosis but little inflamm
  - reference to ci, i and Ti scores helps
- Total scar:
  - can have high value even if scar is small but most of it is inflamed (check ci, i, Ti)

Which System Should We Use?

- Both have been shown correlate graft failure when large data sets examined

- No head to head comparison which one better

- Suggest sticking with what is already published in 2015, and adding an explanation about the potential pitfalls of evaluating very small scars

What Changes Can We Propose in Banff 2015 BL & TCMR Categories

Mark Haas

- Replace i score by Ti score in BL & Ac TCMR
- Remove requirement that t be scored in only mildly atrophic tubules (still ignore severe?)
- Add the term smoldering/chronic active to the chronic TCMR section: referring to bxs where i & t is (primarily) in areas of IFTA
- Base dx on grade of i-IFTA & tubulitis

Replacement of i-score by Total-I score & Simplifying Tubulitis Scoring

- Eliminate a non-evidence based rule that leads to discrepancies with molecular studies
- Allow more complete capture of inflammatory activity in the biopsy
- Permit easier scoring without subtraction of areas with edema & fibrosis which can be multifocal & spread across multiple fragments
- Simplicity should lead to better reproducibility

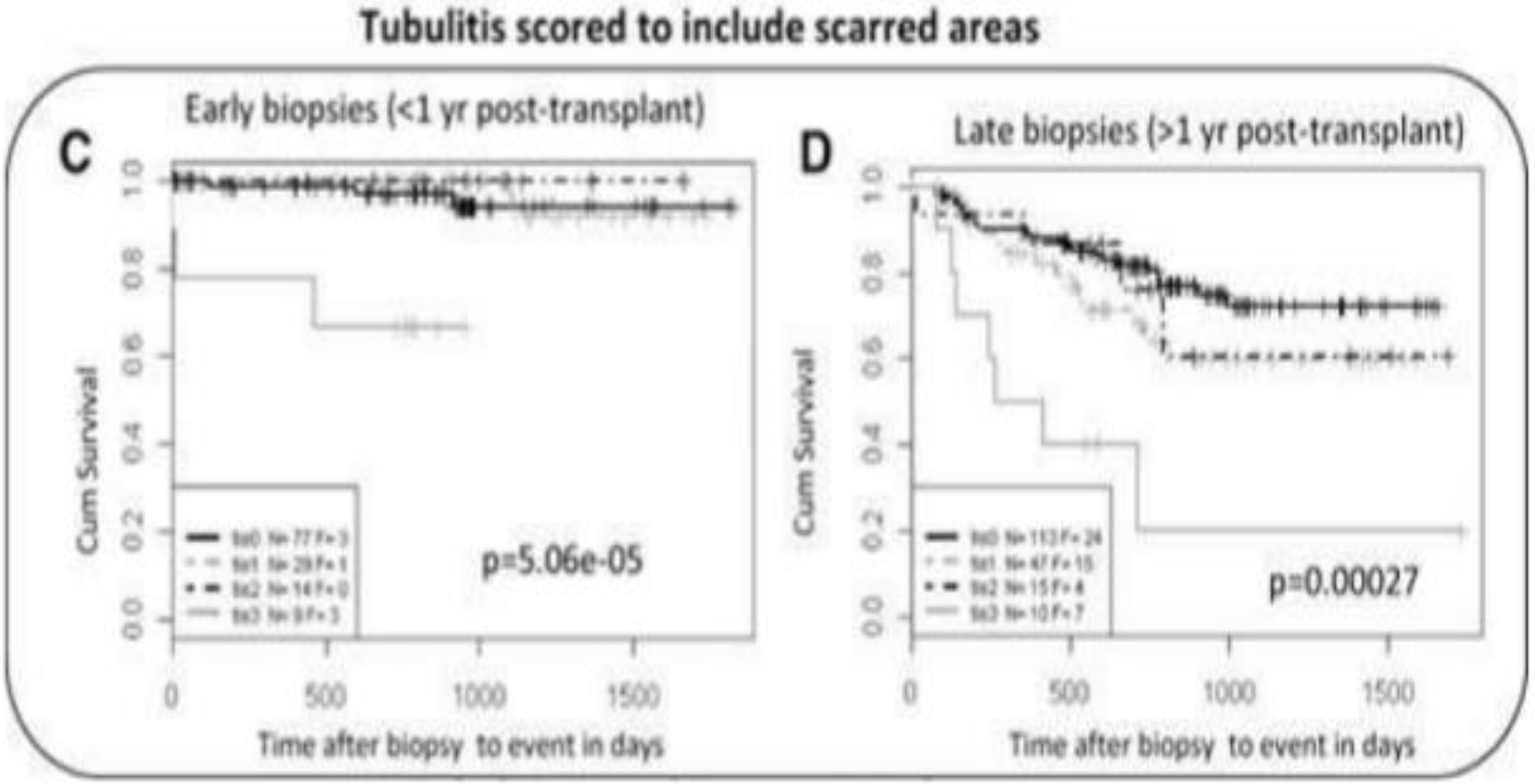
Using i-IFTA & t Grades for Diagnosis

- No new definition of i-IFTA is needed to decide if inflammation ‘significant’ or not.
- Use ci score >0 (>5%) unless donor disease is a consideration
- Use i>0 ALREADY accepted as an infiltrate worth reporting in bxs that fit BL category
- IHC for markers like CD3?

Grading of Tubulitis in i-IFTA

- No new formulation would be needed
- Use existing t-scoring rules: t0, t1, t2, t3
- Could insist on only grading mildly or moderately atrophic tubules (usually present admixed with more severely atrophic tubules)

Scoring of Tubulitis in IFTA Has Been Validated



Sellares et al. Am J Tx 2011: 11: 489

Suggestions for More Studies & No Action at This Time

- Compare prognostic value of i-IFTA & Ti separately in biopsies with ci1, ci2, and ci3.

  -Ti & i-IFTA already shown important, point of grading is only to convey a better sense of pathology

- Evaluate Rx response different grades ci/IFTA

  - Tall order for c-TCMR, not yet done for c-ABMR

  - Lack of effective response with current regimens will not prove c-TCMR does not exist

More Studies -

- Explore DEKAF data for correlations between tubulitis in scarred vs non-scarred
  - Lack of correlation will not explain why tubulitis exists in ~20% IFTA bxs with no good reason
  - accepting these as c-TCMR is no different from accepting Acute TCMR in a bx with no scarring & lack of evidence for infectious/drug/paraprotein ISN
- Wait for current studies by WG before accepting i-IFTA as a criterion for cTCMR
  - i-IFTA is not the focus of any of our current studies

MY RECOMMENDATIONS

- Accept i-IFTA as A qualifying but per se not sufficient criterion for chronic-TCMR.
- Diagnosis c-TCMR clinical correlation and reasonable exclusion of other etiologies
- Activity c-TCMR Should be graded by Total i score and severity of tubulitis
- Severity should be graded by a combination of Banff 2015 i-IFTA score & associated ci score to avoid misinterpretations

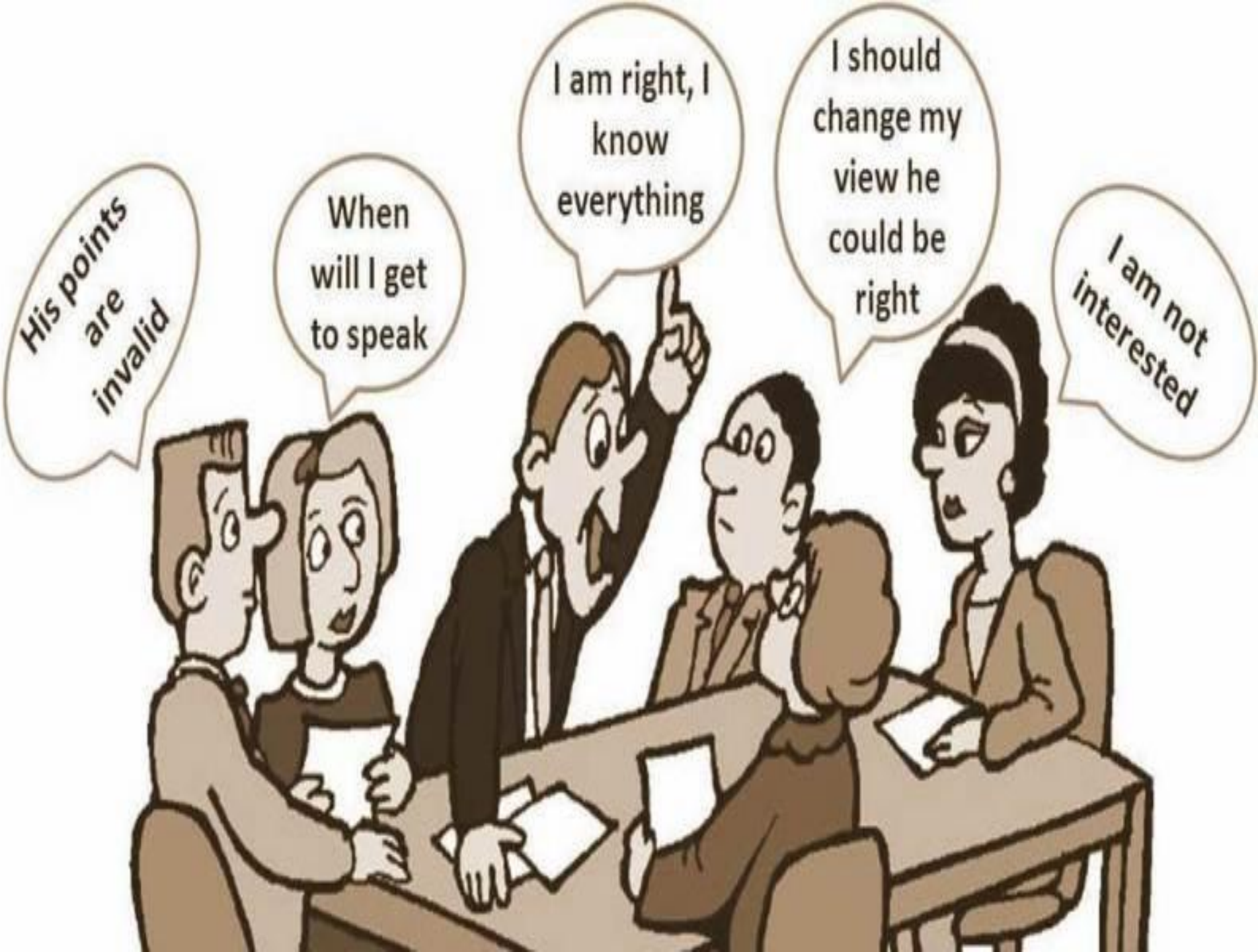
Potential Benefits of Proposed Changes

- Increase recognition of subtle & indolent T-cell injury as a factor in graft loss
- Identify patients who are under immunosuppressed
- Encourage adjustment of I.S. on case by case basis
- Facilitate dx/rx of late rej in setting of tissue scarring, non-compliance & infectious triggers (URIs)

THE NEED TO ACT IS NOW

- 68% E-67% NE agree i-IFTA can repres.c-TCMR
- Ti already being reported by 62% E & 48% NE
- 67% E & 70% NE agree on sep. i-IFTA score
- 71%E & 45% NE agree on need to comment on presence/absence of tubulitis in i-IFTA

- Tx community perceives need for change
- Need based changes in Banff have been made before (minimal C4d FFPE, g+ptc>2)


His points are invalid
When will I get to speak
I am right, I know everything
I should change my view he could be right
I am not interested

Expanded Definition of Chronic Active TCMR

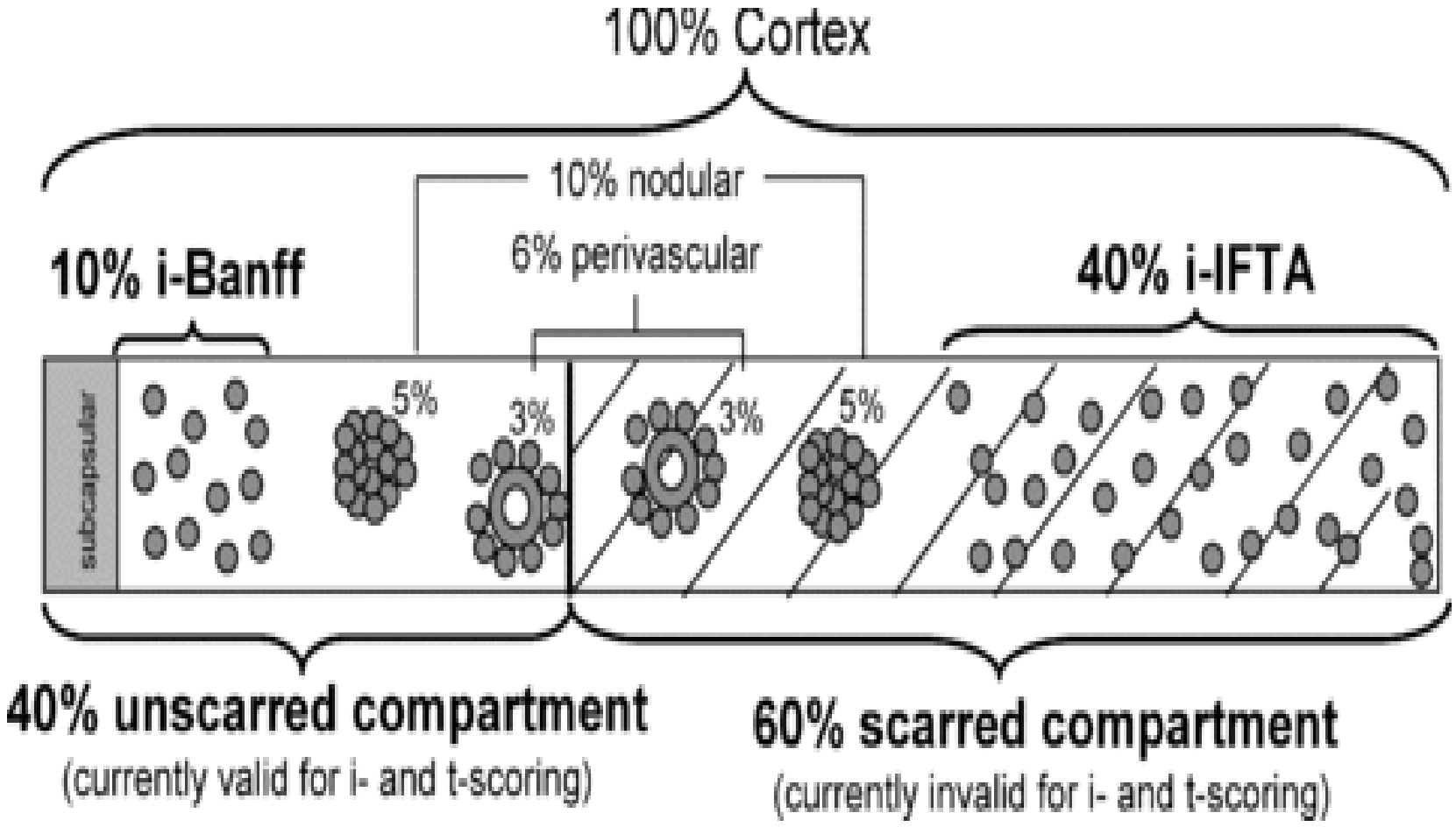
1. Chronic allograft arteriopathy (already recognized)
2. i-IFTA where other causes reasonably excluded

R/o antibody injury & non-immune injury for 1 & 2

- Further study biopsies with cg & no Ab-E/DSA on multiple occasions—may be as a LESS COMMON cause of cTCMR (meanwhile report C4d-DSA-CG)

- Keep an open mind: PTCML in biopsies with no Ab-E or DSA on multiple occasions (occurrence PTCi capillaritis in ac TCMR already accepted by Banff)

THE ORIGINAL DIAGRAM BY MICHAEL MENGEL



American Journal of Transplantation
Volume 9, Issue 1, pages 169-178, 31 OCT 2008 DOI: 10.1111/j.1600-6143.2008.02462.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2008.02462.x/full#f1

3 Different Inflammation Scores are Possible in Scarred Biopsies

	Numerator	Denominator
i-banff	Area inflamed in unscarred cortex	Total area in unscarred cortex
i-IFTA	Area inflamed in scarred cortex	Total area cortex
Total i-score	Area inflamed in whole cortex	Total area cortex

Tubular Disruption in IFTA