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FDA PUBLIC WORKSHOP
ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

April 12, 2017

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, MD 20903

Reported by: Michael Farkas
Capital Reporting Company

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| 22 | | 22 | (University of Michigan) |

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| 1 | C O N T E N T S | 1 | A third goal, to discuss the natural course of |
| 2 | (Continued) | 2 | acute and chronic AMR as a continuum and its temporal |
| 3 | PAGE | 3 | association with cellular rejections and changes in |
| 4 | Calcineurin Inhibitor (CNI) and 348 | 4 | GFR. |
| 5 | Corticosteroid Minimization/Avoidance | 5 | And, finally, to discuss the unmet medical |
| 6 | Protocols and HLA Antibodies | 6 | needs and potential clinical trial design challenges |
| 7 | Speaker: Arthur Matas, MD (University | 7 | for the prevention and treatment of AMR. |
| 8 | of Minnesota) | 8 | Again, in your agenda, you see that over the |
| 9 | | 9 | next 2 days, we'll cover topics in five sessions. |
| 10 | Nonadherence -- Definitions, Monitoring, 359 | 10 | Session 1 will be an overview, new |
| 11 | Prevention/Management | 11 | developments, patient perspectives and diagnostic |
| 12 | Speaker: Rita Alloway, PharmD (University of | 12 | challenges in AMR. |
| 13 | Cincinnati) | 13 | The second will be factors contributing to |
| 14 | | 14 | antibodies in the pretransplant period in treatment |
| 15 | The Role of Acute Cellular Rejection 377 | 15 | options. |
| 16 | Episodes in the Development of HLA Antibodies | 16 | Third, factors contributing to antibodies in |
| 17 | Speaker: Robert S. Gaston, MD (University | 17 | the posttransplant period. |
| 18 | of Alabama) | 18 | Tomorrow, the morning will start with a |
| 19 | | 19 | session posttransplant monitoring, diagnosis, and |
| 20 | Public Comment and Discussion 393 | 20 | treatment of AMR. And the final session will be |
| 21 | | 21 | clinical trial design challenges for developing new |
| 22 | Wrap Up -- Day 1 425 | 22 | treatments as well as topics on animal models of AMR. |
| Page 19 | | Page 21 | |
| 1 | P R O C E E D I N G S | 1 | So as in previous workshops, this is only a |
| 2 | Welcome, Topics and Goals | 2 | day-and-a-half meeting, and therefore the scope of the |
| 3 | DR. ALBRECHT: Good morning, everyone. My | 3 | meeting needs to be focused. So we will be hearing the |
| 4 | name is Renata Albrecht. I'm the Division Director of | 4 | latest scientific information on AMR, such as |
| 5 | the Division of Transplant and Ophthalmology Products. | 5 | diagnosis, treatment, prevention, desensitization, |
| 6 | And on behalf of our division as well as our Office of | 6 | clinical trial considerations, and, as I mentioned, |
| 7 | Antimicrobial Products, headed by Dr. Edward Cox, who | 7 | animal models. The discussion of biomarkers will focus |
| 8 | is present with us this morning, it is my great | 8 | primarily on donor-specific antibodies, mainly anti-HLA |
| 9 | pleasure to welcome all of you to the Antibody-Mediated | 9 | DSAs. |
| 10 | Rejection and Kidney Transplantation FDA Public | 10 | The way each session is organized, there will |
| 11 | Workshop over the next day and a half. | 11 | be a series of formal presentations, and during that |
| 12 | You received at the registration desk an | 12 | series, we'll ask you to hold your questions until all |
| 13 | agenda, and in that agenda, you see that we have four | 13 | the formal presentations are concluded. Each of the |
| 14 | goals that we aim to achieve today. | 14 | sessions, after the formal presentations, will be |
| 15 | One is to examine and emphasize the importance | 15 | followed by a public comment and discussion section, |
| 16 | of immunosuppressive medication nonadherence in the | 16 | which will last about 45 to 60 minutes. |
| 17 | development of DSAs as well as subsequent AMR. | 17 | During that session, the moderators will first |
| 18 | The second is to discuss new developments in | 18 | ask the audience if they have any clarifying questions |
| 19 | transplantation, their impact on patient management, | 19 | about the presentations, and, subsequently, there will |
| 20 | such as pretransplant sensitization not manifested by | 20 | be a discussion of the FDA and Planning Committee- |
| 21 | DSA donor/recipient HLA epitope matching, routine | 21 | developed questions, which, again, are included in your |
| 22 | posttransplant DSA monitoring. | 22 | agenda. |

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| <p>1 During this session, we will invite the</p> <p>2 audience, along with the panel members, to interact and</p> <p>3 provide comments and perspectives on the questions that</p> <p>4 we're going to be discussing.</p> <p>5 Now let me cover a few housekeeping issues.</p> <p>6 Dining is available downstairs. If you exit the</p> <p>7 conference room in the back and go to the right, the</p> <p>8 dining room is downstairs. Breakfast, lunch, and</p> <p>9 dinner are served. And also out of consideration for</p> <p>10 our workshop, they will have coffee available and</p> <p>11 snacks available throughout the day.</p> <p>12 A note, credit card and debt card payments</p> <p>13 only. They do not accept cash.</p> <p>14 There is Internet access. There is a little</p> <p>15 card with the username and password for the network</p> <p>16 that you can have available.</p> <p>17 Okay, taxis. For those that are traveling</p> <p>18 either today or tomorrow, the request has been made</p> <p>19 that you ask at the information desk about getting</p> <p>20 taxis to take you to either other hotels or the</p> <p>21 airport.</p> <p>22 And after I conclude my opening remarks, we're</p> | <p>1 epidemiologist with CTI.</p> <p>2 DR. CAVAILLÉ-COLL: Marc Cavaille-Coll,</p> <p>3 Medical Officer, FDA.</p> <p>4 DR. KNOLL: Greg Knoll. I'm a nephrologist at</p> <p>5 the University of Ottawa.</p> <p>6 DR. WOODLE: Steve Woodle, surgeon, University</p> <p>7 of Cincinnati.</p> <p>8 DR. ALLOWAY: Rita Alloway, transplant</p> <p>9 pharmacist, University of Cincinnati.</p> <p>10 DR. COLVIN: Bob Colvin, pathologist, Mass</p> <p>11 General Hospital and Harvard Medical School.</p> <p>12 DR. HAAS: I'm Mark Haas. I'm a renal</p> <p>13 pathologist at Cedars-Sinai Medical Center in Los</p> <p>14 Angeles.</p> <p>15 DR. VELIDEDEOGLU: Ergun Velidedeoglu, medical</p> <p>16 officer, FDA.</p> <p>17 DR. GASTON: Bob Gaston, nephrologist,</p> <p>18 University of Alabama at Birmingham.</p> <p>19 DR. COX: Good morning. Ed Cox, Director of</p> <p>20 the Office of Antimicrobial Products at FDA.</p> <p>21 DR. NICKERSON: Peter Nickerson, transplant</p> <p>22 nephrologist, University of Manitoba.</p> |
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| <p>1 actually going to go around the table and ask people to</p> <p>2 introduce themselves. And what I wanted to mention is</p> <p>3 that, consistent with the FDA's Patient-Focused Drug</p> <p>4 Development Program that was authorized under PDUFA V,</p> <p>5 the Prescription Drug User Fee Act Reauthorization</p> <p>6 Number V, and, most recently, the inclusion of Patient-</p> <p>7 Focused Drug Development as a component of the 21st</p> <p>8 century act, we are very fortunate to have three</p> <p>9 patient representatives present with us today.</p> <p>10 What I wanted to mention is we actually, the</p> <p>11 Office of Strategic Planning, reached out to and</p> <p>12 invited five patients to participate. Unfortunately,</p> <p>13 two have not been able to join us for medical reasons,</p> <p>14 which I think emphasizes the challenges that our</p> <p>15 transplant patients face.</p> <p>16 So with that, what I would like to do is ask</p> <p>17 the panel members to introduce themselves and provide</p> <p>18 their affiliation. And I would like to start on the</p> <p>19 left with Dr. Bala.</p> <p>20 DR. BALA: I'm Shubal Bala, FDA, CDER.</p> <p>21 DR. WANG: Yan Wang, statistical team at FDA.</p> <p>22 DR. IRISH: Bill Irish, statistician and</p> | <p>1 DR. MANNON: Roslyn Mannon, transplant</p> <p>2 nephrologist, University of Alabama at Birmingham.</p> <p>3 DR. GEBEL: Howie Gebel, HLA Director, Emory</p> <p>4 University, Atlanta.</p> <p>5 DR. WIEBE: Chris Wiebe, transplant</p> <p>6 nephrologist, University of Manitoba.</p> <p>7 DR. DJAMALI: Arjang Djamali, transplant</p> <p>8 nephrologist, University of Wisconsin, Madison.</p> <p>9 DR. TAMBUR: Anat Tambur, HLA Lab,</p> <p>10 Northwestern, Chicago.</p> <p>11 DR. BELEN: Ozlem Belen, Division of</p> <p>12 Transplant Ophthalmology Products, FDA.</p> <p>13 DR. STEGALL: Mark Stegall. I'm a transplant</p> <p>14 surgeon at Mayo Clinic.</p> <p>15 DR. EDWARDS: Dawn Edwards, patient</p> <p>16 representative.</p> <p>17 DR. MITTELMAN: Michael Mittelman, patient</p> <p>18 representative.</p> <p>19 DR. LENNON: Jack Lennon, patient</p> <p>20 representative.</p> <p>21 DR. CHALASANI: Meghana Chalasani, FDA, CDER.</p> <p>22 DR. ALBRECHT: A couple more comments. When</p> |

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| <p style="text-align: right;">Page 26</p> <p>1 you're not speaking, if you would be so kind to turn 2 off your mic by pressing the red button. 3 And, finally, on the slide, you see the link 4 to the workshop. The information there is publicly 5 available, and it provides all the presentations and 6 other information. 7 With that, what I would like to do is turn 8 this over to Dr. Ergun Velidedeoglu and Dr. Robert 9 Gaston to start moderating the first session. Thank 10 you. 11 Session 1: Overview, New Developments, 12 Patients' Perspectives, and Diagnostic Challenges in 13 Antibody-Mediated Rejection 14 Part I 15 DR. VELIDEDEOGLU: Hi. Good morning, 16 everybody. As you might have noticed in the agenda, 17 Session 1 is the longest session in our workshop. It 18 consists of two parts, Part 1 and Part 2. And there 19 will be a discussion session at the end of each part. 20 And we will also have a short break in between the two 21 sessions. 22 So the purpose of this session, as</p> | <p style="text-align: right;">Page 28</p> <p>1 DR. MANNON: Thank you. These are my 2 disclosures. 3 I can't get the slides to advance. Could you 4 give me the -- oh, perfect, like magic. 5 I was asked to provide an overview in the next 6 15, 20 minutes of all of these topics in the hopes of 7 introducing the entire session. So my apologies to my 8 colleagues that I didn't include. It doesn't mean I 9 didn't want to, but I really did cut a lot of my 50 10 slides down before submitting it. And also for those 11 colleagues that I do highlight their work, it's really 12 a 37,000-foot overview. It's not to provide any kind 13 of opportunity with them to not highlight their work. 14 I think it's important for the group to 15 recognize the work that FDA has put into kidney 16 transplantation over the last 5 years. Shown here is a 17 summary of the public workshops that we have been 18 participating in, including the 2012 meeting with the 19 Generics Division, with the societies, both AST and 20 ASTS. 21 And importantly, as has been referred to 22 already this morning, the recent, this past fall, the</p> |
| <p style="text-align: right;">Page 27</p> <p>1 Dr. Albrecht mentioned, is to discuss the new 2 developments in the field since our last FDA AMR 3 workshop back in 2010, and also discuss somewhat 4 controversial areas, and new developments in the field. 5 So one thing unique about this session is, 6 again, as Dr. Albrecht mentioned, we have a voice of 7 the patient session, which is the first time that we 8 incorporated into our workshop, and we have three 9 patient representatives. Originally, we had five 10 patient representatives, but unfortunately two patient 11 representatives had urgent medical conditions which 12 precluded them from attending today. So we have three 13 patient representatives today. 14 So the first talk will be given by Roslyn 15 Mannon, from the University of Alabama. The title is 16 "New Developments in Kidney Transplantation Since the 17 2010 FDA AMR Workshop, Including Nonadherence, HLA 18 Mismatch, Banff Updates, and the New Kidney Allocation 19 System." 20 New Developments in Kidney Transplantation 21 Since the 2010 FDA AMR Workshop -- Nonadherence, HLA 22 Mismatch, Banff Updates, Kidney Allocation</p> | <p style="text-align: right;">Page 29</p> <p>1 Patient-Focused Drug Development meeting where we were 2 actually able to hear the patient voices, learn more 3 about patient-reported outcomes, and understand the 4 concerns that patients have in terms of drug 5 development. 6 Not on this slide have been the multiple 7 meetings that have occurred both offline and online 8 between the societies -- ASN, AST, ASTS -- in the hopes 9 of developing a private-public partnership focused on 10 transplantation. 11 I think one of the success stories over the 12 last year that many of you may not be aware about is 13 the Therapeutic Area Data Standards User Guide for 14 Kidney Transplant, abbreviated TAUG or TAUG-KT 15 Version 1 for short. An example of this is shown in 16 the panel on the right. This was a compilation of 17 terms and processes focused on therapeutic 18 interventions to prevent rejection in transplanted 19 kidney patients. 20 This was an accomplishment, and it's available 21 online to the public, between funding from FDA, CFAST, 22 CDISC, and C-Path, as well as the American Society of</p> |

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| <p style="text-align: right;">Page 30</p> <p>1 Nephrology's Kidney Health Initiative, and the American 2 Society of Transplantation, and many volunteer hours. 3 The goal of the standard development was to 4 accelerate clinical research and medical product 5 development, creating and maintaining data standards, 6 tools, and methods for conducting research in 7 transplantation. And the very thoughtful detail here 8 is not only available for industry, but I think quite a 9 useful tool for many of the investigator-initiated 10 studies performed by a number of people in this room. 11 Switching gears slightly, I would like to talk 12 a little bit about some of the changes in Banff, and 13 we'll hear more about this later this morning, but also 14 the mental-cultural changes in transplantation and the 15 sense that when we see allograft injury and rejection, 16 that there are now multiple phenotypes. I recall that 17 Banff now has acute cellular rejection consisted of 18 T-cell-mediated rejection and acute antibody-mediated 19 rejection. "Chronic rejection" is no longer a global 20 term, but really separated into chronic antibody- 21 mediated and chronic T-cell-mediated rejection, the 22 latter of which is somewhat now undergoing some</p> | <p style="text-align: right;">Page 32</p> <p>1 very, very long time. I'll allude to this in another 2 slide shortly. But the ENDATs were described by Banu 3 Sis and colleagues with Phil Halloran a number of years 4 ago. 5 Shown here is a panel from that paper. And 6 while I think most of us are not currently 7 incorporating this in our labs, and certainly not at 8 our center, which is fairly high volume, the 2017 Banff 9 meeting did call into question what the transcriptional 10 features are antibody-mediated rejection and have 11 debated whether the ENDATs really are the true 12 signature. And I'll leave it to those individuals 13 doing that work to comment further. 14 There have also been changes in the 15 morphologic criteria for chronic AMR. Again, in Banff 16 2013, highlighted in red, is that the critical feature 17 is the threshold for transplant glomerulopathy, the so- 18 called CG lesion, and also the incorporation or the 19 opportunity to use electron microscopy to document 20 peritubular capillary laminations. 21 Why does this matter? Because in studies now, 22 and most recently, when look at the 2017 criteria</p> |
| <p style="text-align: right;">Page 31</p> <p>1 thorough review by the Banff working groups to define 2 what that actually is. Many of us have seen mixed 3 cellular and antibody-mediated rejection, particularly 4 late posttransplant. And then the idea that there 5 could be acute and chronic features in a rejection 6 episode would be the antibody or cellular. 7 Significantly since this last meeting in 2010, 8 there have been revised criteria for the pathology of 9 antibody-mediated rejection, and I summarize them here. 10 You may not be able to see them well, but you still are 11 required to have three critical features for the 12 diagnosis, which includes histologic evidence of tissue 13 injury, evidence of antibody interaction with the 14 vascular endothelium, and serologic evidence of donor- 15 specific antibody. 16 Importantly, and what the arrow tries to 17 highlight, is linear C4d staining is no longer a 18 specific requirement. You may have, alternatively, 19 evidence of microvascular injury, and, alternatively, 20 you can have increased expression of gene transcripts. 21 The idea that we would use transcriptional or gene 22 expression data was one that has been debated for a</p> | <p style="text-align: right;">Page 33</p> <p>1 compared to the 2013 criteria I highlight in red on 2 this slide, you can see that using the 2013 criteria, 3 more of the subjects being studied in these biopsy 4 studies fit into antibody-mediated rejection. In the 5 De Serres study, the lack of C4d actually increased and 6 allowed the diagnosis of AMR in their biopsy study, and 7 ABMR was associated with worse graft outcomes. 8 In the Gimeno study, the main difference in 9 inclusion of these patients, which was substantial, was 10 the inclusion of microvascular inflammation, the 11 g+ptc>2. Again, these were biopsy studies done 12 typically for cause looking at the impact of ABMR on 13 graft outcomes. 14 As we discussed in the previous meeting, and 15 as the literature has accumulated, the development of 16 de novo donor-specific antibody, meaning individuals 17 that don't have antibody against their donor but 18 develop it over time, has been a poor prognostic 19 feature. There has been the creation -- and we'll be 20 discussing this again in a little bit -- the 21 sensitization in transplantation, assessment of risk, 22 thankfully abbreviated as "STAR." The North American</p> |

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| Page 34 | <p>1 2017 Working Groups, led by Anat Tambur and Peter 2 Nickerson, combine volunteer effort between the 3 American Society of Transplantation and ASHI to look at 4 specific aspects of both naive patients, so-called 5 naive and so-called previously transplanted patients in 6 all solid organs, to come up with some common 7 recommendations in terms of monitoring and follow-up. 8 This slide, which you cannot really read very well, 9 indicates -- I'm sorry, I meant to go -- if you could 10 just slide me back, not that far back.</p> <p>11 This just is a compilation of the 25 studies 12 on de novo DSA -- and there have been two more 13 published since we put this together in February -- 14 highlighting the complexity of the studies. 15 Importantly, I think what I would like to really give 16 you as a take-home point is that the frequency of de 17 novo DSA really varies from study to study -- and I 18 highlight some of the key ones here -- ranging anywhere 19 between 2 percent in the first year up to 27 percent. 20 This is at Colorado. This is the Manitoba group. 21 Again, highlighting, though, that the patient 22 population that's being studied, the measuring</p> | Page 36 | <p>1 and Orandi.</p> <p>2 But de novo DSA, when we think of the risk 3 factors -- typically rejection episodes, delayed graft 4 function, for example -- I think we're going to be 5 talking about it here, and so I want to remind 6 everybody of the other adherence, and that is our goals 7 for therapy conversion and minimization. We have 8 created these protocols in order to make patients feel 9 better, to mitigate the comorbidities associated with 10 immunosuppression, and summarized here are a series of 11 studies where there has either been minimization or 12 conversion with an associated increase in risk in the 13 development of de novo DSA. Some of this de novo DSA 14 appeared independently of rejection, but a vast number 15 of these studies were associated with higher rates of 16 rejection during conversion and minimization with 17 associated de novo DSA.</p> <p>18 Other considerations about DSA is that not all 19 DSA are the same. This is work by Loupy's group in 20 Paris identifying that those DSA that bind C1q are 21 associated with worse graft outcome, although one might 22 really allude that this is really because of a very</p> |
| Page 35 | <p>1 technique that's being used, the frequency of 2 measurements, and the baseline immunosuppression, and 3 the complexity of the patient type really determine the 4 frequency of de novo DSA. And so having a working 5 group to define specific follow-up patterns is 6 critical, I think, if we're going to eventually evolve 7 into therapeutic initiatives.</p> <p>8 The impact of de novo DSA, as I've already 9 alluded to, has been quite negative. This is work from 10 Wiebe, et al., again, highlighting the half-life of a 11 graft after the detection of de novo DSA with graft 12 dysfunction shown in this bottom red line of about 3.3 13 years, significantly better than if you don't have 14 graft dysfunction of proteinuria.</p> <p>15 Those individuals, so-called subclinical DSA, 16 there is a population of those individuals in follow- 17 up. They behave very frequently worse than stable 18 patients, but again very similar to those with 19 allograft dysfunction from other etiologies. Again, so 20 the notion that there is clinical dysfunction with DSA 21 detection having worse outcomes in subclinical have 22 also been highlighted by recent publications by Loupy</p> | Page 37 | <p>1 high titer antibody that binds C1q, but again bringing 2 into question, the quantity and the quality of the 3 donor antibody.</p> <p>4 Another contribution to the literature this 5 past year has been by Carmen Lefaucheur, again looking 6 at the IgG subtypes, that not all DSA is the same. 7 IgG3 does the worst. And I think we'll hear more later 8 this morning about specific epitopes and also the 9 identification and titering of antibodies, so 10 understanding interventions and the implications of 11 interventions.</p> <p>12 So summarized here to the talk at this point 13 -- and this is from one of the Wiebe papers -- again, 14 that there is some event that occurs and that there is 15 a period of time before clinical manifestations occur. 16 And so I think a lot of what we'll be talking about 17 today are to help us identify the subclinical injury in 18 order to avert further damage, whether these can be 19 used potentially as endpoints before getting to the 20 critical or negative outcomes that we see here.</p> <p>21 Switching gears to the Banff's scoring system, 22 I want to highlight the inflammation aspects because</p> |

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| <p style="text-align: right;">Page 38</p> <p>1 there has been such a significant amount of effort 2 focused on antibody-mediated injury. And I think this 3 past Banff meeting in Barcelona in 2017 really 4 highlighted the hand-in-hand association between 5 inflammation and antibody-mediated injury. 6 So you may recall that a total i score was 7 developed and incorporated into the Banff report in 8 2007. This means that not only do you have 9 inflammation in non-scarred area, but a total score 10 that includes inflammation in scarred and unscarred 11 areas. And there is some discussion now currently 12 underway of whether this ti score should be included 13 with the i score as part of a new category for chronic 14 T-cell-mediated rejection or not, and that's under 15 debate. 16 Why does it matter? Well, we know from work 17 from the DeKAF cohort that the so-called "iatr," which 18 now has been called by Banff to be "i-IFTA," so I have 19 to keep changing my slides around, but the presence of 20 inflammation in scarred areas is a singularly and 21 independently associated risk factor for patient grafts 22 failure, independent of other features, including serum</p> | <p style="text-align: right;">Page 40</p> <p>1 identified looking at about 550 protocol biopsies. 2 Those biopsies identified at 6 weeks with i+IFTA, 3 meaning inflammation in non-scarred areas plus scarring 4 was an independent risk factor for the development of 5 de novo DSA. In this patient population that was 6 relatively low risk and treated with non-depletional 7 induction therapy and carefully monitored was about 9 8 percent per year. 9 I think the field is also struggling in 10 looking -- I don't want to say struggling, I think we 11 have a lot of competing interests right now in terms of 12 molecular classifiers. I'm not going to be talking so 13 much about biopsy classifiers because I'll leave that 14 to the pathologists' presentations. But as many of you 15 in the room know, we've been looking at markers both in 16 peripheral blood, markers in the urine, and recently 17 the cell-free DNA measurements. Again, the idea here 18 is maybe to prevent us getting to the clinical 19 demonstration of de novo DSA or the clinical 20 demonstration of allograft injury to be able to detect 21 and utilize these as potential biomarkers. 22 Moving on to therapeutic changes since the</p> |
| <p style="text-align: right;">Page 39</p> <p>1 creatinine at the time of the biopsy and proteinuria, 2 and that the greater strength, the more i-IFTA you 3 have, or iatr you have, the more severe the graft 4 outcome failure is. And so I think the community now 5 is really recognizing that inflammation in these areas 6 previously overlooked is important, and whether we call 7 it i-IFTA or ti remains to be seen. 8 Not only does scarring in scarred areas 9 matter, but i+IFTA -- it's very confusing, but I'm 10 going to learn it eventually. So i+IFTA is another 11 category. This is inflammation in non-scarred areas in 12 the presence of fibrosis and atrophy. 13 here are prior older studies that have 14 identified inflammation in sort of standard of care 15 biopsies associated with progression of fibrosis in 16 graft failure, more recently surveillance biopsies when 17 you see inflammation in non-scarred areas associated 18 with IFTA. A number of groups have identified shorter 19 graft survivals. 20 And, interestingly, linking this inflammatory 21 concept to donor antibody and outcome, a recent very 22 nicely done surveillance biopsy study by Garcia-Carro</p> | <p style="text-align: right;">Page 41</p> <p>1 2010 meeting, the last approved drug on the docket has 2 been belatacept in 2012. This medication unfortunately 3 has not grabbed hold in the transplant community 4 because of the higher risk of early graft rejection. 5 Shocking, and not surprisingly, but I think 6 shockingly, in the recent data, the persistent 7 improvement in glomerular filtration rate, shown by 8 these two upper lines, of patients on belatacept 9 remains statistically significantly improved compared 10 to patients which happen to be on a cyclosporine-based 11 regimen with mycophenolate and prednisone. 12 And the debates are, Why is this? Is this 13 because it's a CNI-free regimen? An important concept 14 here highlighted in the New England Journal paper is 15 belatacept-treated patients had lower frequency of the 16 development of de novo DSA. This is marked and 17 statistically significantly better than the 18 cyclosporine-treated group. Again, this is a patient 19 population that had a higher risk of rejection and, in 20 fact, did not actually develop de novo DSA, again, 21 unlinking two critical risk factors. 22 Why is this occurring? Whether it's a</p> |

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| Page 42 | <p>1 specific role of adherence because patients receive</p> <p>2 this as an infusional therapy every month and have less</p> <p>3 of an opportunity not to take the drug, or whether</p> <p>4 there is a specific interaction because it's a co-</p> <p>5 stimulatory blockade, there may be an interaction</p> <p>6 limiting T follicular helper cell activation of B cells</p> <p>7 when those cells become activated. And this is an area</p> <p>8 now under investigation by a number of labs.</p> <p>9 The other area of therapeutic focus that will</p> <p>10 be likely discussed in this room is the use of</p> <p>11 complement inhibition for therapies for antibody-</p> <p>12 mediated rejection. Many of us in this room have</p> <p>13 participated in trials using eculizumab, a downstream</p> <p>14 C5 inhibitor. There are now trials undergoing for C1</p> <p>15 esterase inhibition, a more proximal blockade.</p> <p>16 Some of the advantages touted by this therapy</p> <p>17 are the fact that many of the co-stimulatory effects of</p> <p>18 complement activation would be mitigated and limiting</p> <p>19 injury. Not only has this been used for HLA-</p> <p>20 incompatible living donor transplants, it's been used</p> <p>21 for treatment of antibody-mediated rejection, these</p> <p>22 agents, and these agents have been targeted in studies</p> | Page 44 | <p>1 Shown here is Chakker Harini's analysis of UNOS data</p> <p>2 identifying the multiple mismatches and the hazard</p> <p>3 ratios for graft failure, showing that even with the</p> <p>4 potency of immunosuppression and our ability to get</p> <p>5 patients through the first year, that graft failure</p> <p>6 rates are higher with more HLA mismatches.</p> <p>7 Now, I don't want to sound catty, like it's</p> <p>8 easy to match. We really do have an issue because one</p> <p>9 of the unmet needs is the lack of available</p> <p>10 transplants. And so I know that over the years we've</p> <p>11 kind of accepted the mismatch issue. But as time goes</p> <p>12 on, we are now realizing that this mismatch brings</p> <p>13 patients into a higher risk.</p> <p>14 And so as Peter will show you -- and I keep</p> <p>15 quoting his and Chris's data -- mismatches in DR and DQ</p> <p>16 are really critical, and when you combine that to</p> <p>17 nonadherence, shown in this orange line down here and</p> <p>18 in this bottom graph, there is a significant effect on</p> <p>19 rejection-free survival, a negative effect, and a</p> <p>20 significantly negative effect on death-censored graft</p> <p>21 survival as well. So the combination of the two</p> <p>22 effects is significant.</p> |
| Page 43 | <p>1 for delayed graft function. I think the eculizumab</p> <p>2 trial is now undergoing analysis for the delayed graft</p> <p>3 function. So definitely therapeutic opportunities here</p> <p>4 in order to mitigate the injury associated with</p> <p>5 antibody-mediated rejection.</p> <p>6 We will be talking today quite a bit about</p> <p>7 nonadherence. And on the panel on the left, I</p> <p>8 highlight that the association of nonadherence was</p> <p>9 strongly associated with antibody-mediated rejection,</p> <p>10 chronic antibody-mediated rejection, and mixed cellular</p> <p>11 antibody-mediated rejection in a biopsy study published</p> <p>12 by Sellares back in 2012.</p> <p>13 And similarly, Wiebe and colleagues back in</p> <p>14 2012 also associated the presence of nonadherence, a</p> <p>15 strong marker for the development of de novo DSA and</p> <p>16 the monitoring of their patient population.</p> <p>17 So the presence of a nonadherence and trying</p> <p>18 to organize and focus our management strategies I think</p> <p>19 is going to be critically important.</p> <p>20 We're back to the future. Again now we have</p> <p>21 more data about HLA mismatch, and we'll be talking</p> <p>22 about this again in probably the next speaker actually.</p> | Page 45 | <p>1 And, finally, the Kidney Allocation System.</p> <p>2 As if it's not enough, we've had a massive change in</p> <p>3 the allocation system, and it happened to be when I was</p> <p>4 on call, and it was the worst 2 weeks of my life, and</p> <p>5 now we only round once a week at a time and a block</p> <p>6 time.</p> <p>7 But what happened is the notion of the</p> <p>8 algorithm that we had been using was waiting time. And</p> <p>9 so this was sort of a first come, first served basis of</p> <p>10 who got to see the transplant center first. And the</p> <p>11 goal was to have a more balanced, equitable</p> <p>12 distribution of deceased donor kidney transplants with</p> <p>13 maximal utility for those precious organs.</p> <p>14 So from the utility perspective, we now</p> <p>15 calculate kidney donor risk indices, which are based on</p> <p>16 a number of biological and some factors out of our</p> <p>17 control in terms of developing a kidney donor profile</p> <p>18 index. And this is the one where I tell patients</p> <p>19 getting 100 is not a good thing, it's the lower scores</p> <p>20 are the better scores and the better likelihood that</p> <p>21 the graft will do well.</p> <p>22 So now we take the 20 percent best kidneys</p> |

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| Page 46 | Page 48 |
| <p>1 that we expect to do the best after transplant and try 2 to match them to the patients, 20 percent of the 3 patients, with the best posttransplant survival, the 4 EPTS score, which is based on age, dialysis duration, 5 prior transplant, and diabetes. And so the idea is 6 that we're maximizing the utilization of these precious 7 organs, taking the best, and putting them into the, 8 quote/unquote, best.</p> <p>9 Equity has been addressed by increased 10 national and regional sharing, priority given to those 11 waiting for multi organs -- and that could be debated, 12 but not here -- the role of the panel-reactive 13 antibody. There are significant points provided to 14 individuals who have been previously transplanted or 15 highly sensitized. We afford zero mismatch kidneys 16 much more so. Pediatric candidates. And we strongly 17 give priority to individuals who were prior living 18 kidney donors.</p> <p>19 Most of all, the presence of listing after 20 dialysis, if you come to the transplant center late, 21 after you've already been initiated or you just are 22 uncomfortable about being transplanted, you no longer</p> | <p>1 So as I always say to my -- you know, when I'm 2 preparing my division chief annual report, I always 3 feel disappointed because I didn't get my project ran, 4 and my R1 may not have done well, and I sort of feel 5 like there has been no progress, but when you look at 6 the whole since 2010, there has been really remarkable 7 progress made in the field. Many of those individuals 8 are sitting here with me.</p> <p>9 We have yet to develop a consensus on 10 monitoring posttransplant, but I think we're close by 11 having consensus conferences. And we really need 12 validated biomarkers. This will obviously assist in 13 endpoint development and facilitate the identification 14 of new therapeutics in this unmet need in solid organ 15 transplant.</p> <p>16 Thank you. 17 (Applause.)</p> <p>18 DR. VELIDEDEOGLU: We thank Roslyn Mannon for 19 this excellent summary.</p> <p>20 And before moving on to the next talk, I have 21 a little reminder for our speakers except for the 22 patient representatives. Next to the podium, we have a</p> |
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| <p>1 are penalized for that, and you can still go into the 2 system and still have that time.</p> <p>3 There have been significant changes in KAS in 4 terms of it, but most importantly, there has been a 5 bolus of individuals that are highly sensitized. Some 6 of these patients do well, and some don't, and they are 7 clearly a high-risk patient population. There have 8 also been impacts on transplantation in African 9 Americans. There's been an increased rate in delayed 10 graft function across the country which is 11 statistically significant. There is also a lower 1- 12 year graft survival, although this did not reach 13 statistical significance.</p> <p>14 Finally, related to this conference, there is 15 the use of HIV-positive donor -- or unrelated is the 16 use of HIV-positive organs, the use of hepatitis C 17 treatment. Do we do it before or after? If we do it 18 after, it allows hepatitis C-positive patients to be 19 transplanted and get HepC kidneys. And then the whole 20 debate about the APOL1 mutations in individuals of 21 African American ancestry as either living donors or 22 recipient outcomes.</p> | <p>1 stand, and on top of the stand, we have a timer with 2 three lights on it, green, orange, and red. The green 3 light indicates that the speaker still has time. And 2 4 minutes before the end of the allocated time, the 5 orange light will come on. And the red light indicates 6 that the time has expired. But that doesn't apply to 7 our patient representatives, which have shorter 8 allocated time periods.</p> <p>9 So our next talk is by Peter Nickerson, from 10 the University of Manitoba, "A New Paradigm: HLA 11 Epitope-Based Donor/Recipient Mismatch Assessment." 12 A New Paradigm: HLA Epitope-Based 13 Donor/Recipient Mismatch Assessment</p> <p>14 DR. NICKERSON: Thanks very much, Ergun. And 15 I want to thank the organizers and the FDA for the 16 opportunity to come and speak and to share some of our 17 data and our thinking. And I'm looking forward to the 18 next day and a half. I think it's really -- it's been 19 7 years since our last time we've been talking, but I 20 think overall there has, as Ros just said, been a lot 21 of developments.</p> <p>22 So I'm going to talk about epitope- or</p> |

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| <p style="text-align: right;">Page 50</p> <p>1 Eplet-based donor/recipient mismatches. These are my 2 disclosures. I will not talk in this talk about off- 3 label. 4 And I don't think HLA matching is any new 5 thing. We've known since the beginning of transplant 6 that if you're an identical twin transplant, you don't 7 need any drugs, and so that's the ideal, if we could 8 ever get to that. There have been a lot of big names 9 in the field looking at, "How do we move HLA forward?" 10 And there have been multiple, I would say, top journal 11 publications on the science of HLA over the last 60 12 years. 13 So why do we need to talk about it now? Well, 14 it's really about beyond the whole molecule. So we've 15 always talked about an HLA mismatch for a given locus 16 as being a one whole molecule mismatch. 17 And Paul Terasaki, who is really one of the 18 grandfathers of this field, I think said it well. He 19 said, "We must now prepare for the second phase in 20 which more sophisticated measures of HLA compatibility 21 should be developed for more accurate prediction of 22 outcome." And that's what this is all about. And let</p> | <p style="text-align: right;">Page 52</p> <p>1 Duquesnoy developed a software package, a computational 2 software package, where he was basically looking at, 3 What are the polymorphic amino acids on the donor's 4 surface for a given donor/recipient mismatch? He's 5 identified the polymorphic amino acids that exist at 6 the site that could be a binding for the H3 CDR, the 7 specificity-determining target, and he has called those 8 amino acids the "Eplet," or what we would call the 9 functional epitope, and then there is the whole surface 10 binding here that we would call the structural epitope. 11 But his work is really based on this Eplet computation 12 that is looking at the functional epitope of where the 13 antibody could be binding. 14 So for a given HLA mismatch -- and I'm just 15 using this by way of example -- to really understand 16 this, you need to get the 4-digit or high-resolution 17 typing. And here's a DRB1*1101 molecule of the 18 patient, and here's a DRB1*0405 HLA molecule of the 19 donor. And in our current language, we would say these 20 are a 1DR mismatch. 21 But when we look at the Eplet level, we 22 actually see there are 11 potential areas of amino acid</p> |
| <p style="text-align: right;">Page 51</p> <p>1 us point out that Paul said this almost 50 years ago. 2 And so what have we been doing for 50 years? 3 And the answer is we've been really developing whole 4 fields in molecular biology, and with that knowledge, 5 we can now move forward. 6 So in the context of antibody-mediated 7 rejection, which is this workshop, what I really want 8 to talk about is, what does the antibody see on the 9 surface of the HLA molecule? So I'm giving you a 10 picture here in green of the cartoon of the surface of 11 an HLA molecule. And I'm showing you in highlighted 12 colors where the HLA antibody is actually going to bind 13 to the surface of this molecule. 14 And in particular, I'm highlighting the H3 15 region, which is the few amino acids that are the 16 polymorphic amino acids that the recipient is seeing on 17 the donor HLA, and this complement determining region 18 is determining the specificity of the antibody, and 19 these other areas in color, the other CDRs, really 20 stabilize that binding and lead to the affinity of the 21 antibody binding. 22 And it's with this framework that Rene</p> | <p style="text-align: right;">Page 53</p> <p>1 differences between these two HLA molecules. So the 2 degree of dissimilarity is actually quite distinct and 3 numerous. Whereas, if we look at another DRB1 mismatch 4 -- here's 1302 and 1119 -- again, we will call that a 5 1DR mismatch, but at the Eplet level, there is only one 6 amino acid residue difference. 7 And the importance here is we today treat 8 these two HLA mismatches as equivalent, but really the 9 first one is much more different compared to the second 10 one. And if we look at this over a whole population of 11 donors and recipients, we can see for a conventional 12 1DR mismatch, you can have a whole range of Eplet 13 mismatches, from as little as 1 or 2 up to as many as 14 50, almost 60, for DR, and the same is true for DQ. 15 So we have this broad range of different 16 polymorphisms that exist for a given 1DR or 1DQ 17 mismatch, and it's by getting to this level of 18 resolution that we can start thinking about, does that 19 give us better prediction of outcome? 20 So in this paper that Chris did in our group 21 during his graduate studies, he looked at, "What are 22 the independent predictors for forming antibodies</p> |

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| Page 54 | <p>1 against HLA DR?" And what he showed us here is that</p> <p>2 nonadherence DR Eplet mismatch load, so for every Eplet</p> <p>3 mismatch, your odds ratio goes up, and then if you have</p> <p>4 early clinical rejections preceding the antibody,</p> <p>5 that's also a risk factor.</p> <p>6 For DQ, it's nonadherence, it's the degree of</p> <p>7 Eplet mismatching at DQ and younger age. And so this</p> <p>8 is interesting because we a lot of times think that</p> <p>9 younger individuals are just being nonadherent, and</p> <p>10 what this multivariate is saying is independent of</p> <p>11 nonadherence, a younger age is actually a risk factor,</p> <p>12 and that's probably because they have a more robust</p> <p>13 immune system.</p> <p>14 Now, there are other ways of looking at</p> <p>15 immunogenicity, and this is the group from University</p> <p>16 of Cambridge in England where they looked at the</p> <p>17 electrostatic properties of the amino acid differences</p> <p>18 between donors and recipients. And so they used that</p> <p>19 to create an electrostatic score for the mismatches to</p> <p>20 try and see if that could predict immunogenicity</p> <p>21 better.</p> <p>22 And then they published this paper last year,</p> | Page 56 | <p>1 to hear a lot about transplant glomerulopathy at this</p> <p>2 meeting as one of the features that is leading to graft</p> <p>3 loss and is driven by de novo DSA formation. And,</p> <p>4 again, similar thresholds to what we saw for antibody</p> <p>5 formation, DQ above 18 and DR above 15, led to an</p> <p>6 increased risk for developing transplant</p> <p>7 glomerulopathy.</p> <p>8 How might we apply this in a clinical setting?</p> <p>9 Well, this was a clinical trial that we did sponsored</p> <p>10 by the NIH called the CTOT-09 trial where we were</p> <p>11 trying to look at minimization for our patients, trying</p> <p>12 to get them off medications. So we enrolled living</p> <p>13 donor transplants. These are pristine patients who</p> <p>14 were given standard of care immunosuppression. And for</p> <p>15 the first 6 months, these patients did outstandingly</p> <p>16 well. They had no rejections. On a protocol biopsy,</p> <p>17 had normal histology. And at 6 months they had no DSA</p> <p>18 formation.</p> <p>19 And we randomized these patients two to one to</p> <p>20 come off of the tacrolimus over a 3-month taper. And</p> <p>21 when we did that, what we found was that in those</p> <p>22 patients coming off tacrolimus, we had a lot of</p> |
| Page 55 | <p>1 where they evaluated amino acid mismatches, the Eplet</p> <p>2 mismatch method of Rene Duquesnoy, and their</p> <p>3 electrostatic mismatch tool. And all three of these</p> <p>4 were basically showing the same thing in multivariate</p> <p>5 models, that this higher degree of precision of</p> <p>6 understanding donor/recipient differences gives you a</p> <p>7 better prediction of who's at risk for developing</p> <p>8 antibodies towards Class II. And this was looking at</p> <p>9 DSA development after graft loss.</p> <p>10 So how can we use this information? Well, we</p> <p>11 can use it to get a risk prediction score, and we did</p> <p>12 it in our group using Eplet mismatch loads. What we</p> <p>13 found was that above 10 and above DR Eplet mismatches,</p> <p>14 there was an increased risk for the formation of HLA DR</p> <p>15 antibodies, as de novo antibodies, and above a</p> <p>16 threshold of 17, we had an increased risk of forming DQ</p> <p>17 antibodies.</p> <p>18 In a similar type of study, this is a group</p> <p>19 out of the University of Toronto, Joe Kim's group, and</p> <p>20 what they looked at was using the Eplet mismatch load</p> <p>21 idea to predict in a multivariate the risk of</p> <p>22 developing transplant glomerulopathy. And you're going</p> | Page 57 | <p>1 cellular rejections, and five of these patients</p> <p>2 developed DSA, either DSA alone or DSA in conjunction</p> <p>3 with acute cellular rejection. And in these patients,</p> <p>4 all the DSAs were against Class II DR or DQ, again</p> <p>5 highlighting the importance of Class II antibodies.</p> <p>6 So at that point, the DSMB halted the trial.</p> <p>7 They said you're having way too many alloimmune</p> <p>8 recognition events during tacrolimus weaning. And what</p> <p>9 this taught us was that quiescence wasn't low risk to</p> <p>10 minimize. We went back retrospectively and asked,</p> <p>11 Could we have predicted who was really at high risk for</p> <p>12 developing these antibodies?</p> <p>13 And so we went back for the DQ locus and</p> <p>14 looked at the Eplet mismatch load of these patients.</p> <p>15 And what we found was that those patients that formed</p> <p>16 the de novo DQ DSAs, all of them were above our</p> <p>17 threshold of 17, and those patients that didn't develop</p> <p>18 the DSA, only three were above that threshold.</p> <p>19 However, one of the patients, at the end of</p> <p>20 the study, decided they wanted to say off their</p> <p>21 tacrolimus, and subsequently, they went on and</p> <p>22 developed a DSA, so now six of eight above the</p> |

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| <p style="text-align: right;">Page 58</p> <p>1 threshold had a DSA.</p> <p>2 And one of the patients actually had an early</p> <p>3 cellular rejection, so they were restarted on their</p> <p>4 CNI, and I suspect that's partly why they didn't</p> <p>5 develop a DSA. And so that really only leaves one of</p> <p>6 our eight patients who were above our threshold who</p> <p>7 didn't develop a DSA, suggesting that this might be</p> <p>8 useful as a way of risk stratifying patients for who is</p> <p>9 at risk to developing a DSA if you're going to consider</p> <p>10 minimization trials.</p> <p>11 And, again, a similar type of point. This was</p> <p>12 switching immunosuppression from cyclosporine over to</p> <p>13 everolimus, and they had a higher rate of de novo DSA</p> <p>14 formation. And the Paris group went and showed that</p> <p>15 those patients that were forming DQ de novo DSA upon</p> <p>16 switch, they were again having a higher Eplet mismatch</p> <p>17 load compared to those patients that didn't form an</p> <p>18 antibody, again supporting the concept that the load</p> <p>19 may be a useful way of measuring or predicting risk.</p> <p>20 And then another paper looking at</p> <p>21 nonadherence, and this was a very interesting study out</p> <p>22 of the Minnesota group where they were using medication</p> | <p style="text-align: right;">Page 60</p> <p>1 late rejections in terms of DQ, and it wasn't leading</p> <p>2 to any diminishment in graft survival, again suggesting</p> <p>3 it's the HLA mismatch at this granular level, and</p> <p>4 understanding that degree of dissimilarity that can</p> <p>5 really be used to predict risk.</p> <p>6 So how much we use this thinking forward?</p> <p>7 Well, today we're here in empirical medicine, and we</p> <p>8 treat everybody in transplant the same. We look at HLA</p> <p>9 mismatches, and, yes, in the allocation system, if</p> <p>10 you're a good match, you can get some points in</p> <p>11 prioritization. So a zero DR mismatch gets 2 points,</p> <p>12 that leads to maybe you getting bumped up in your</p> <p>13 allocation scheme. But we treat all the patients</p> <p>14 pretty much the same in terms of the immunosuppression</p> <p>15 we use today.</p> <p>16 If we were to use DR or DQ Eplet mismatch</p> <p>17 load, or the electrostatic mismatch load of the</p> <p>18 University of Cambridge, and we knew that you were low</p> <p>19 for both, we could assign that priority in allocation</p> <p>20 points, we might consider these patients as individuals</p> <p>21 who might go through a minimization process in terms of</p> <p>22 their immunosuppression, and that's something that's</p> |
| <p style="text-align: right;">Page 59</p> <p>1 event monitoring systems, and in almost 200 patients,</p> <p>2 they found that almost a quarter of them were noting</p> <p>3 that they were dropping some of their doses in the</p> <p>4 early posttransplant period, in the first 2 months. So</p> <p>5 22 percent were missing 7 percent or more of their</p> <p>6 doses, and that led to more late acute rejections and</p> <p>7 more premature graft loss. And this was in the 1 to 2</p> <p>8 or the 3 to 5 year follow-up period.</p> <p>9 And we went back and retrospectively asked the</p> <p>10 question, Could we have predicted again who was at the</p> <p>11 most risk based on the Eplet mismatch load? And here</p> <p>12 what we're showing in the orange line -- and Ros had</p> <p>13 just shown this slide -- that those patients who were</p> <p>14 both nonadherent and with a high load actually were at</p> <p>15 the increased risk for DR for late rejection or the</p> <p>16 worse graft survival, and that was true also for DQ,</p> <p>17 late rejections in DQ graft survival.</p> <p>18 Now, what was interesting was if they were</p> <p>19 nonadherent and they had a low load, here in blue, in</p> <p>20 fact, those patients did quite well. So if you're</p> <p>21 missing your drugs, but you don't have the Eplet load</p> <p>22 to drive an immune response, this wasn't leading to</p> | <p style="text-align: right;">Page 61</p> <p>1 imminently testable in a clinical trial. And what we</p> <p>2 could say is if you're high for either, well, probably</p> <p>3 these are the individuals we should avoid trying to</p> <p>4 minimize them.</p> <p>5 And ultimately, what we really need to get to</p> <p>6 is not just understanding this kind of risk factor</p> <p>7 score using Eplet mismatches, but actually identify the</p> <p>8 specific epitopes that are commonly driving antibody</p> <p>9 formation, what we would call immunodominant epitopes,</p> <p>10 and if we had that, then we could really get into</p> <p>11 personalized immunosuppression, where if we knew that</p> <p>12 you had immunodominant epitopes, again we would avoid</p> <p>13 or give very low priority in our allocation scheme or</p> <p>14 we would certainly avoid minimization in the patients</p> <p>15 that have these immunodominant epitopes.</p> <p>16 And I think this is the next 20 years of our</p> <p>17 work, is really to identify, What are these</p> <p>18 immunodominant epitopes with reliability? And in the</p> <p>19 meantime, we can maybe start to work with some of our</p> <p>20 risk stratification scoring system.</p> <p>21 And with that, I'm going to stop and just</p> <p>22 acknowledge all the people that have contributed to</p> |

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| <p style="text-align: right;">Page 62</p> <p>1 this work, and, in particular, Chris Wiebe, who was in 2 our group doing his graduate studies at the time when 3 he was doing a lot of this work, and some of the work 4 that's ongoing with Arthur and the DeKAF Consortia, and 5 Peter Heeger and Don Hricik in our CTOT Consortia. 6 Thanks very much. 7 (Applause.) 8 DR. VELIDEDEOGLU: Thank you for this 9 excellent presentation. 10 Now it's time for our patient representatives. 11 And our first patient representative is Dawn Edwards. 12 The Voice of the Patient in Transplantation 13 MS. EDWARDS: Good morning. It certainly is a 14 pleasure to be considered to be presenting this 15 morning. It's really nice and it's really special that 16 patients' point of view and patients' experiences get 17 to be examined at these type of workshops. So I 18 appreciate the FDA and all of those responsible for 19 inviting me and bringing me out here. 20 I'm going to be talking about my kidney 21 journey and how the rejection episodes affected my 22 life.</p> | <p style="text-align: right;">Page 64</p> <p>1 but I know I didn't feel good. So we were rushed back 2 to the hospital. The family is all upset. And, you 3 know, we were told or we thought that once you get a 4 kidney transplant, everything was going to be okay 5 afterwards, you know, I was going to get the 6 transplant, and then I would be out having pizza and 7 beer with my friends, you know, and I was going to go 8 back to my regular life. However, we were certainly 9 mistaken. 10 I had several episodes with rejection, with 11 plasmapheresis and IVIG and bunny rabbit stuff and 12 horsy stuff and all kinds of different medications that 13 they were telling me about, and I had no idea what they 14 were all about. I just know that I was uncomfortable, 15 I was in pain. I also developed the -- what is it? 16 CMG. CMV. Thank you. The CMV infection as a result 17 of my donor. So that was pretty rough on my stomach 18 and my colon area. 19 The transplant was really a lot more than I 20 expected. It was not making me happy. Actually, at 21 some points I thought that I would have been better off 22 staying on dialysis.</p> |
| <p style="text-align: right;">Page 63</p> <p>1 I began dialysis 25 years ago at the age of 23 2 as the result of postpartum glomerulonephritis. Three 3 years later, after doing in-center dialysis, a doctor 4 convinced me to try peritoneal dialysis. And I was 5 afraid because I was told that peritoneal dialysis 6 caused infections that kill you. So I wasn't really 7 excited about it. But I did give it a try, and I loved 8 it. 9 Ten years later, after being on a waiting list 10 for 10 years, I did get called for a kidney transplant. 11 Very exciting. I was ready for it. I felt good about 12 it at the time. And we went in for the transplant. It 13 was a great thing. The family was excited about it. 14 And we were all very excited about having the 15 transplant. Boy, it's great to pee and it's great to 16 do all of those great bodily functions and everything. 17 So at the onset of the transplant, it was very 18 difficult for me. I received the kidney transplant on 19 September the 25th. I was sent home on September the 20 29th. And October 4th, I was back with a rejection 21 episode. I was in a raclimune (ph) study at the time, 22 and I don't know if that caused the rejection or not,</p> | <p style="text-align: right;">Page 65</p> <p>1 Yes, I began to hate this new kidney because 2 all of the attention was on the kidney, it wasn't 3 really about me. When I came to the hospital, it was 4 always the kidney, the kidney, and there was no Dawn 5 involved in my transplant experience. 6 The biopsies were constant. And I thought 7 that by the time they got finished snatching all of 8 those pieces out of the kidney, there wasn't going to 9 be any left. However, it just became a chore. The 10 medications were very difficult. 11 I was able to adhere, thanks to some 12 transplant organizations that sent us nice little 13 medication boxes and little alarm clocks to remind us 14 that every 12 hours you had to take that Prograf and 15 the CellCept 4 times a day. So I had a lot of 16 problems. 17 I developed colitis on several occasions. And 18 not only that, I was having problems with my bones. I 19 was having some body aches. The rejection episodes 20 just kept coming. For the first 3 years, I rejected 21 three times. And, again, plasmapheresis was just like 22 dialysis, only you get as many blankets as you want.</p> |

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| Page 66 | Page 68 |
| <p>1 I enjoyed the freedom of dialysis finally</p> <p>2 after 3 years. Everything began to settle down and I</p> <p>3 was able to go back to work, and I was very pleased</p> <p>4 about that. It's really nice to be able to contribute</p> <p>5 to the household again.</p> <p>6 I began working and I was traveling for my</p> <p>7 job. And one day during my travels, I stepped down off</p> <p>8 of a curb, and I felt a snap. And I knew that that</p> <p>9 just wasn't right. And this was in February of 2010.</p> <p>10 I was so nervous because the transplant center had</p> <p>11 called me that morning and told me to get home right</p> <p>12 away. And so off I went running back home to find out</p> <p>13 that I was having another rejection episode.</p> <p>14 During that episode, I was given</p> <p>15 Thymoglobulin, and I developed an anaphylactic reaction</p> <p>16 to the Thymoglobulin. And also my hip was fractured</p> <p>17 when I stepped off that curb. After the anaphylactic</p> <p>18 reaction with the Thymoglobulin, there was nothing else</p> <p>19 that they could do, and I just went into chronic</p> <p>20 rejection, and I ended up back on dialysis.</p> <p>21 This was 6 years. So I really expected more.</p> <p>22 I was very disappointed. I was hurt. My world was</p> | <p>1 then having a hip replacement.</p> <p>2 And not only that, but as a result, we also</p> <p>3 discovered that I had the early stages of colon cancer</p> <p>4 and needed to have my entire colon removed. And all of</p> <p>5 this, and I wasn't even 40 yet. That was very earth-</p> <p>6 shattering for me and devastating. There was nothing</p> <p>7 that was under my control at that point. Recovering</p> <p>8 from a hip replacement, the ostomy that was completely</p> <p>9 out of control, I don't wish that on anyone, and now</p> <p>10 I've discovered that I'm not going to be able to have a</p> <p>11 reversal.</p> <p>12 In conclusion, I'm now on home hemodialysis.</p> <p>13 And I don't like that too much either, but, you know,</p> <p>14 we have to do what we have to do to stay alive. And my</p> <p>15 outcomes are excellent. I'm very healthy, even though</p> <p>16 I'm not feeling well today. But I'm very, very</p> <p>17 healthy.</p> <p>18 And I'm just considering -- I'm not</p> <p>19 considering having a transplant again. I have not gone</p> <p>20 back active on the transplant list. I am absolutely</p> <p>21 afraid. I can't take the chance of something more</p> <p>22 happening to me and experiencing any of what I</p> |
| Page 67 | Page 69 |
| <p>1 shattered because I had begun a job. I had started to</p> <p>2 get my life back together. At the age of 23, I didn't</p> <p>3 expect to be on dialysis in the first place. And now I</p> <p>4 thought that I had an opportunity to reestablish my</p> <p>5 life and do some of the things that I wanted to do.</p> <p>6 And this was all taken away from me. And I went into a</p> <p>7 very deep depression. I'm actually still being treated</p> <p>8 for that, but we'll talk about that another time.</p> <p>9 And the depression was also something that I</p> <p>10 hadn't dealt with before. I actually felt like my life</p> <p>11 was over. I did not like dialysis from the first day</p> <p>12 that I did it, and I definitely didn't like going back</p> <p>13 to dialysis. However, I returned back to peritoneal</p> <p>14 dialysis. I thought that there would be more that</p> <p>15 could be done for me, but that was it. Back to</p> <p>16 dialysis I went.</p> <p>17 So eventually I returned to peritoneal</p> <p>18 dialysis, and that only worked for a few months because</p> <p>19 of the hip fracture that was deteriorating quickly.</p> <p>20 And before that, we had a MRSA episode after going back</p> <p>21 to in-center hemodialysis. So basically I spent the</p> <p>22 whole 2010 in the hospital recovering from MRSA and</p> | <p>1 experienced again. I am afraid.</p> <p>2 And it's great to be in a room full of people</p> <p>3 who want to make positive changes for patients that</p> <p>4 have these problems with kidney transplants,</p> <p>5 plasmapheresis, IVIG, and the horsy stuff and the bunny</p> <p>6 rabbit stuff. It's good for some people, and I'm</p> <p>7 really happy for those that it works for, but I would</p> <p>8 really, really like to see something for people who</p> <p>9 have these constant rejections. I would like to have</p> <p>10 an opportunity to have the life back that I so dream</p> <p>11 and so desire.</p> <p>12 So on that note, I thank you very much and</p> <p>13 thank you for your attention.</p> <p>14 (Applause.)</p> <p>15 DR. VELIDEDEOGLU: We thank Dawn Edwards for</p> <p>16 sharing her transplant experience with us.</p> <p>17 Our next patient representative is Michael</p> <p>18 Mittelman. We are running a little bit behind. So I</p> <p>19 request our patient representatives and the following</p> <p>20 speakers to try to wrap up within their allocated</p> <p>21 times, please.</p> <p>22 MR. MITTELMAN: Hi. Good morning. My name is</p> |

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| <p style="text-align: right;">Page 70</p> <p>1 Michael Mittelman, and I'm 35 years old. And I'm from 2 Philadelphia, Pennsylvania. I'm a three-time 3 transplant recipient, with the first being from 4 deceased donors. The most recent, the third, being 5 from a living donor, my mother. It was performed in 6 2001 at Johns Hopkins. And it was an ABO-incompatible 7 transplant. She was always a perfect match for me, 8 antigen-wise, my mother, but she never obviously had 9 the right blood type. So I can tell you that it was a 10 big relief when technology came along to be able to do 11 that.</p> <p>12 Both of my kidneys were removed when I was 5 13 years old. My original diagnosis at age 3 was 14 nephrotic syndrome, which subsequently was diagnosed 15 then as FSGS. So that has never recurred luckily. So 16 if any of you have some wood you can knock on, that 17 would be good. But it never recurred, so that's good. 18 I know it recurs in a lot of patients.</p> <p>19 During that time period before the first 20 transplant, I did have over 20 transfusions. I did 21 home PD, so I know I built up a number of antibodies 22 from the transfusions that I had at the time.</p> | <p style="text-align: right;">Page 72</p> <p>1 was on. I blame my being short on that because I was 2 kept on that for many years.</p> <p>3 I think during my second transplant, which was 4 in, like I said, 1990, I did not really have any 5 antibody-mediated rejection until about 8 years into 6 the transplant. It was a better match for me. I was 7 17 years old at the time when I started experiencing 8 the rejection again. The docs again, they jacked up my 9 dosage of prednisone. I also had a handful of biopsies 10 at the time period. They weren't exactly sure why I 11 was beginning to reject the kidney at that point.</p> <p>12 But it was during that time in 1998 at St. 13 Christopher's Hospital for Children that I was switched 14 over to what at the time was the new wonder drug known 15 as CellCept, which you all know about. The AMR 16 actually got worse, and the kidney function went almost 17 to nothing, so it decreased drastically.</p> <p>18 I think there is still debate I know among the 19 physicians that used to work at St. Christopher's about 20 whether or not we became toxic from the mycophenolate. 21 I know a number of kids lost their transplants from 22 being switched over from Imuran to mycophenolate. That</p> |
| <p style="text-align: right;">Page 71</p> <p>1 My first transplant was in 1988, like I said, 2 from a deceased donor, and it was in January '88. It 3 was a very poor match from the tissue typing 4 perspective, but the surgeons and the physicians at St. 5 Christopher's Hospital for Children wanted to get me a 6 transplant because I was very sick. I was a patient at 7 CHOP -- I had previously been a patient at CHOP, but 8 they did not have a transplant program back in the 9 early '80s, and St. Christopher's did.</p> <p>10 So my first experience with antibody-mediated 11 rejection was actually the same year, in 1988. I 12 became a lot more sluggish, bloated. I was given OKT3 13 at the time. The AMR actually became worse in 1989, 14 and in 1990, I received a second, and better, 15 transplant in December 1990, so the first did not last 16 that long of a time period.</p> <p>17 I was also given a lot of prednisone during 18 that time, so I obviously became a chunky little kid. 19 But I do remember during those time periods I would 20 gain a lot of weight. It was the protocol at the time 21 for pediatrics; they would jack up your prednisone. I 22 can remember the rates -- I'm sorry, the doses that I</p> | <p style="text-align: right;">Page 73</p> <p>1 was what was supposed to cause -- or stop a lot of our 2 rejection problems. But I do know liver patients, 3 heart patients, that all lost their organs, and I know 4 St. Christopher's transplant program subsequently fell 5 apart pretty shortly after.</p> <p>6 So I did lose that kidney. Again started 7 dialysis again in 1999 at my freshman year at 8 University of Pennsylvania. I did dialysis as an 9 outpatient at CHOP. They let me back into their 10 hospital after some fighting with them since I was a 11 student at Penn and I had been a patient and they had 12 turned me away because they didn't have a transplant 13 program.</p> <p>14 But luckily my mom read an article about this 15 new procedure going on at Johns Hopkins, the ABO- 16 incompatible transplants. Children's Hospital advised 17 against it. Almost every other hospital in the United 18 States advised against it as well. I was one of the 19 first in the United States done with the ABO- 20 incompatible transplants. Again, you know, obviously I 21 had to go plasmapheresis. I had IVIG post-surgery. 22 There was also fear of my getting CMV from the kidney.</p> |

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| <p style="text-align: right;">Page 74</p> <p>1 I did get it. It was pretty bad, so I think it was 2 meant to stop. 3 I have a pretty strong immune system, so every 4 time I get sick in that instance as well, my creatinine 5 went up. It continues to go up every time I get sick, 6 even though I am on a fairly low dose of all the drugs 7 that I'm on now. I'm not on prednisone anymore, thank 8 goodness for that. 9 But like I said, posttransplant, I was a 10 junior in college and in a fraternity, so I began to 11 live a pretty normal life again, if you can have one 12 being in a fraternity. The most difficult thing for me 13 I think was trying to remain compliant on my 14 medications while being a student with no regular 15 sleeping habits. You know, it was the first time I was 16 really away from family, and being in a fraternity and 17 all, you are out at all hours of the night. And I did 18 my best, obviously, to remain compliant. I have not 19 had any issues with compliance up to this anymore. 20 But subsequently I've been diagnosed with 21 Crohn's and epilepsy, and I worry about the other drugs 22 that I take as whether or not they're going to interact</p> | <p style="text-align: right;">Page 76</p> <p>1 drugs. 2 And I do believe in digital interventions that 3 can help. I work in the digital health field now. And 4 hopefully I will never need another transplant, at 5 least anytime soon. 6 Thanks. 7 (Applause.) 8 DR. VELIDEDEOGLU: Our next patient 9 representative is Jack Lennon. 10 MR. LENNON: Good morning, all. My name is 11 Jack Lennon, a lifelong kidney patient, born with post 12 urethral valves, and a three-time kidney transplant 13 recipient. And as you see, my slides today are photos 14 of my family and I throughout my life. To give you a 15 little bit of an insight into the life of a kidney 16 transplant recipient, and obviously feel free to ooh 17 and ah how cute I was when I was a baby. I'm not sure 18 what happened in the last 29 years. 19 My first transplant occurred at the age of 7 20 back in 1995, which was from my father and lasted 15 21 years. My second transplant was in 2008 from my mom 22 and only lasted 5 years due to a complicated first</p> |
| <p style="text-align: right;">Page 75</p> <p>1 with the drugs that I take now or if they're going to 2 be processed by the kidneys. 3 And I also worry about rejection because my 4 mother was diagnosed with ovarian cancer exactly a year 5 after donating a kidney to me. So I wonder if I have 6 any of that in me, and if there will be any of it 7 recognized by my body. 8 So like I said, right now I don't really have 9 any adherence issues. I did when I was younger. I 10 didn't want to take the liquid cyclosporine, which was 11 certainly a challenge. I did see a child psychologist. 12 And to this day, I do have a lot of damage in my joints 13 from long-term steroid usage. 14 But I would like to say that I do think that 15 if children and teens could be educated more about the 16 alternatives to not taking their medications, people 17 would probably be more compliant. But I know 18 compliance is a big challenge. I tend to see with the 19 support groups that I work with that it works best when 20 people have a support network behind them. I do know 21 people that rejected their transplants because they got 22 mad at their donor, and so they stopped taking their</p> | <p style="text-align: right;">Page 77</p> <p>1 couple of years characterized by significant cellular 2 and antibody-mediated rejection. 3 My most recent transplant, I actually hit my 4 3-year anniversary later this month, and I'm looking 5 for wood to knock on because this one is going to last 6 a very long time, as it's a perfectly matched kidney 7 from my older brother. But even so, I'm running out of 8 siblings, so family reunions become very interesting. 9 So obviously I've had this disease my entire 10 life, which means my family has had to deal with this 11 my entire life as well. And this is what happens in 12 pediatrics. Management of the disease is not only 13 influencing the behavior of the patient and helping the 14 child deal and cope with being a transplant patient and 15 being different, because kids notice when you're puffy 16 and you get hair on your face at a young age and when 17 you miss a lot of school, and they're too innocent not 18 to ask why, and the kid has got to come up with an 19 answer, and it can't be, "I'm sick," because then the 20 kids say, "I don't want to be around him." 21 So that's one part. And then we have to deal 22 with the caregivers and the parents, which is a whole</p> |

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| <p style="text-align: right;">Page 78</p> <p>1 nother ball of wax because we all know how much our 2 mothers worry about us. So even with a family affair 3 and them constantly, but nicely, nagging me to be 4 compliant or adherent -- and I don't like to use those 5 words, as they're used in manufacturing and insinuate 6 that you can control the environment in which you are 7 operating. And if anybody has kids, you know you can't 8 control the environment in which you live. 9 So real quick interactive session. Who here 10 takes medications for anything? 11 (Show of hands.) 12 MR. LENNON: Keep those hands up if you are 13 perfectly adherent, you never miss a dose, you're never 14 late, you take it with food when you're supposed to, 15 you take it on an empty stomach like you're supposed 16 to. Am I the only one with the hand raised anymore? 17 And I've got to put my hand down. All right? This is 18 the assumption, ask, and expectation of kidney 19 transplant recipients, is that we're perfect, that 20 we're robotic. But we're not. We're human. 21 So I had all the resources when I was growing 22 up -- I had a family, I spoke English, I had good</p> | <p style="text-align: right;">Page 80</p> <p>1 memories, and that's really the scary part. And my 2 challenge for the folks in the room is to change the 3 story for the next patient and have all these photos be 4 happy family photos and that maybe I can finally unpack 5 that bag in the back of my car. 6 Thanks. 7 (Applause.) 8 DR. VELIDEDEOGLU: We thank all the patient 9 representatives for sharing their transplant 10 experiences, their life experiences, and for their very 11 insightful comments. And we will move on with the 12 scientific presentations. 13 Our next speaker is Robert Colvin from 14 Massachusetts General Hospital. The title of his talk 15 is, "The Relationship Between Acute AMR and Chronic 16 AMR? Do Acute and Chronic AMR Represent a Continuum?" 17 The Relationship Between Acute AMR and Chronic 18 AMR? Do Acute and Chronic AMR Represent a Continuum? 19 DR. COLVIN: I would like to thank the FDA and 20 Ergun in particular for organizing this conference. 21 We're here to try to advance the field to address the 22 issues that we heard so eloquently encapsulated by our</p> |
| <p style="text-align: right;">Page 79</p> <p>1 insurance, all of the normal barriers you would think 2 of -- and yet I had issues with managing my care, is 3 what I like to call it. And ultimately it resulted in 4 me losing my first kidney transplant while I was in 5 college. 6 And I've been blessed, luckily, though, to be 7 able to receive two more transplants, as I mentioned, 8 from my mom, but without any solid explanation, marked 9 with significant cellular antibody-mediated, it only 10 lasted 5 years. And I started a habit anytime I would 11 go to the hospital to pack a bag. I didn't know what 12 the results were going to show. I didn't know if I 13 would have to stay in the hospital. And it's a 14 tradition that I keep going till today. And though I'm 15 blessed with a perfectly matched kidney, and I'm too 16 much of a realist to think it's going to last the rest 17 of my life, and I keep that bag packed in the back of 18 my car just in case, and that's the scary part. 19 You saw my pictures today, and they're 20 intermingled with happy family photos that you might 21 see in your own homes, but there might have been some 22 photos in there that for me bring back some pretty bad</p> | <p style="text-align: right;">Page 81</p> <p>1 patients here, and we're indebted to them for coming. 2 So my topic, the topic I was assigned, was, 3 "Acute and Chronic AMR: A Continuum or Distinct 4 Diseases?" And like the Yogi Berra expression, when 5 you get to a fork in the road, sometimes you have to 6 take it. And so my answer to the question, "A 7 continuum or distinct diseases?" is yes. 8 My financial disclosures. 9 So antibody has multiple effects on the kidney 10 ranging from hyperacute rejection, the first form of 11 antibody-mediated rejection recognized; acute antibody- 12 mediated rejection; and then a chronic form, which is 13 by far the most prevalent form of antibody-mediated 14 rejection. In addition, we've learned that there's a 15 form of injury, if you will, or resistance to injury, 16 called accommodation, where the antibody interacts with 17 the graft, but it doesn't cause any damage, and that 18 can be seen, for example, in ABO-incompatible grafts, 19 but it can also be seen in other settings. 20 And then there's a relatively newly recognized 21 form, which I like to call smoldering, which is 22 entirely below the waterline. Patients do not know</p> |

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| <p style="text-align: right;">Page 82</p> <p>1 they have it, the doctors do not know they have it. 2 The only way you know that it's going on in the kidney 3 is by doing a biopsy, at least that's the only way we 4 have now. And so this is characterized by a complement 5 deposition in the small vessels of the kidney. 6 In the case of chronic, you get the chronic 7 changes, fibrosis, duplication of basement membranes, 8 et cetera. In accommodation, there is no pathology at 9 all except the complement deposition. And in the 10 smoldering version, you get cells in the capillaries 11 and complement to varying degrees, but no immediate 12 loss of graft function. 13 Now, are these related? Are these the same 14 disease at different stages? And that's what I'll try 15 to address today. 16 The best definition of these diseases comes 17 from the Banff Consensus Conference, which has been 18 going on for many years. And they're separated by 19 their pathologic features by light microscopy and to 20 some extent by electron microscopy. 21 The acute version of this disease has acute 22 injury: microvascular inflammation, arteritis,</p> | <p style="text-align: right;">Page 84</p> <p>1 Well, what does it look like? In the case of 2 acute AMR, you have inflammation in the glomeruli, a 3 number of leukocytes, both mononuclear and neutrophils. 4 You have the same sorts of cells in the peritubular 5 capillaries, mononuclear cells, macrophages, NK cells, 6 neutrophils. You have thrombi in the capillaries of 7 the glomerulus sometimes, congestion, and, of course, 8 usually you have complement deposition in the 9 peritubular capillaries, and also the glomeruli. 10 You can have endarteritis in this setting with 11 polys underneath the endothelium and complement 12 deposited on the surface of the small arteries. 13 Now, the chronic form, which is by far more 14 common and probably accounts for about 60 percent of 15 late graft dysfunction, has quite a different 16 appearance. For one thing, there is something called 17 transplant glomerulopathy, which has duplication of the 18 basement membrane well seen by electron microscopy. 19 Here you see multiple new layers of basement membrane. 20 This is the original basement membrane, and all this 21 has been added to it. 22 The endothelial cell undergoes marked changes.</p> |
| <p style="text-align: right;">Page 83</p> <p>1 inflammation of the small arteries. It can have 2 thrombi. It can have acute tubular injury. 3 The chronic version has, of course, chronic 4 pathological changes, what's called transplant 5 glomerulopathy, which I will illustrate in a minute; 6 duplication of the basement membranes of the small 7 vessels of the kidney; or changes in the arteries. So 8 that's how we distinguish them. 9 They have in common two things. First, they 10 have evidence that antibody is interacting with the 11 endothelium originally in the form of C4d primarily. 12 Now we recognize the microvascular inflammation is an 13 indicator of that, although it's not as specific. And 14 we have the potential of molecular markers to detect 15 the endothelial response. 16 And, finally, we would like to detect the 17 antibodies in the circulation. These are almost always 18 HLA antibodies, but there is a possibility that other 19 antibodies, ABO, for example, but probably others as 20 well, can react with the endothelium. So this is how 21 we define it. If you have all three, that is 22 sufficient for the diagnosis.</p> | <p style="text-align: right;">Page 85</p> <p>1 It normally is fenestrated to allow filtration through 2 the glomerulus. This loses its specialized function 3 and looks very activated. This cell, of course, is one 4 of the targets of the antibody. 5 The capillaritis I mentioned before. The 6 peritubular capillaries also get these laminations. 7 These I think -- I've always thought of these as rings 8 on a tree reflecting past individual episodes of more 9 severe endothelial damage and repair. 10 This chronic disease goes through stages that 11 last many years. This is a patient we had who had 12 multiple protocol biopsies, started off at 3 months 13 with a normal biopsy, no antibody, and no C4d, normal 14 appearance by light and electron microscopy. But 11 15 months, there was antibody present in the circulation 16 and complement in the peritubular capillaries, but no 17 histologic evidence of injury. And this continued for 18 the next biopsy, which I think was about 15 months, if 19 I recall. 20 And, again, there is very little evidence, or 21 practically no evidence, of injury by light microscopy, 22 but you begin to see some changes by electron</p> |

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| Page 86 | <p>1 microscopy with thickening and duplication of the</p> <p>2 basement membrane.</p> <p>3 And, finally, 5 years after transplant, the</p> <p>4 creatinine is still reasonably good, and now you</p> <p>5 finally have the changes that we would call transplant</p> <p>6 glomerulopathy, well shown by electron microscopy.</p> <p>7 And we propose that this disease goes through</p> <p>8 stages. A slide was shown of this before, in which you</p> <p>9 begin by making antibodies. You then get some changes</p> <p>10 in the graft, C4d or capillaritis, glomerulitis, but</p> <p>11 this all occurs without any clinical evidence of</p> <p>12 disease, or for that matter, actual pathologic evidence</p> <p>13 of damage.</p> <p>14 Then you start to get damage that you can see</p> <p>15 histologically but still is not reflected by any</p> <p>16 clinical function, clinical renal function. Finally,</p> <p>17 you get graft dysfunction, and this, of course, is when</p> <p>18 we often get the biopsies, and you can tell that this</p> <p>19 is probably far too late to really effectively</p> <p>20 intervene. And the Wiebe study showed that this whole</p> <p>21 course typically takes about 8 years and progresses</p> <p>22 over 3 years once the graft dysfunction has occurred.</p> | Page 88 | <p>1 may have little or no complement deposition. Both have</p> <p>2 capillaritis. The acute tends to have neutrophils that</p> <p>3 the chronic does not.</p> <p>4 And recently a paper has been published to try</p> <p>5 to distinguish the molecular signature of these two</p> <p>6 forms. In this case, this is the acute, this is the</p> <p>7 early presensitized DSA, in which injury repair</p> <p>8 response is the primary molecular signal. And in the</p> <p>9 de novo, the late form, you have T-cell transcripts,</p> <p>10 NK, natural killer, cell transcripts, and gamma</p> <p>11 interferon-related transcripts. So the molecular</p> <p>12 signals are somewhat different, and I would like to</p> <p>13 think this can lead us to understanding differences in</p> <p>14 pathogenesis. This is really their most important</p> <p>15 role.</p> <p>16 Well, why are there these different effects of</p> <p>17 antibody? Let's just think in a general way why this</p> <p>18 might be. The first thing that comes to mind is the</p> <p>19 resistance and the effector strength, the resistance of</p> <p>20 the endothelium and the strength of the antibodies and</p> <p>21 the cells and the other things that mediate this</p> <p>22 damage. And you can imagine that these diseases are on</p> |
| Page 87 | <p>1 So this is a long disease.</p> <p>2 So what are the differences and similarities</p> <p>3 between acute and chronic antibody-mediated rejection?</p> <p>4 Acute antibody-mediated rejection is usually</p> <p>5 in presensitized patients, patients who have had</p> <p>6 exposure to blood products or pregnancies, et cetera,</p> <p>7 or a previous transplant.</p> <p>8 Chronic is usually de novo DSA, that is, the</p> <p>9 DSA was not present at the time they were transplanted,</p> <p>10 and it is associated with episodes of T-cell-mediated</p> <p>11 rejection, which will be discussed later by Dr. Gaston.</p> <p>12 Acute causes a rapid loss of function,</p> <p>13 measured in days, much like T-cell-mediated rejection.</p> <p>14 As I mentioned, this chronic disease is insidious,</p> <p>15 lasting months or years. And most of these cases are</p> <p>16 not associated with past episodes of acute AMR.</p> <p>17 The antibodies could be different. The acute</p> <p>18 AMR was originally associated with Class I antibodies</p> <p>19 by Phil Halloran, but now we know from the work of many</p> <p>20 that the Class II antibodies are the principal culprit</p> <p>21 in chronic antibody-mediated rejection. Acute AMR has</p> <p>22 widespread deposition of complement typically. Chronic</p> | Page 89 | <p>1 a continuum. At the beginning, where the effector</p> <p>2 strength is maximal and there is no resistance, you get</p> <p>3 hyperacute or acute antibody-mediated rejection. With</p> <p>4 time, I think the endothelium learns how to adapt their</p> <p>5 anti-complementary molecules on the endothelium, and</p> <p>6 there are other ways of resisting the effects of</p> <p>7 antibody. And so as the resistance strength increases,</p> <p>8 the effector strength may stay the same or go down, you</p> <p>9 begin to get the slower versions of these diseases. So</p> <p>10 that's one theory. It's the balance between effector</p> <p>11 and resistance.</p> <p>12 Another theory is the complement fixation</p> <p>13 theory. And this is nicely shown by the work of Loupy</p> <p>14 in Paris, who you've seen this slide before by Ros. In</p> <p>15 his studies, in their studies, the ability of the</p> <p>16 antibody to fix complement in vitro was correlated with</p> <p>17 a poor outcome, this red graph. And as you would</p> <p>18 expect -- let's see, I'm having trouble. I can't</p> <p>19 advance. Could you advance that for me? There. No.</p> <p>20 Yeah. Here we go.</p> <p>21 Another study, in this case, a preexisting</p> <p>22 DSA, a study from London, showed the ones that could</p> |

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| Page 90 | <p>1 fix complement in vitro on beads, in this case, C4d, 2 showed a much shorter graft survival. And this was 3 primarily in the first few weeks after transplant, as 4 you would expect. And it's nice to know that the C4d 5 stain in the tissue correlates very strongly with the 6 ability of the antibody to fix complement in vitro. So 7 this can be taken as a measure of this that we see in a 8 biopsy.</p> <p>9 And in this meta-analysis, the presence of C4d 10 was associated with inferior allograft survival 11 compared with DSA or histopathology alone.</p> <p>12 And, finally, in this theme, this study from 13 Hopkins suggests that patients who have C4d deposited 14 in the grafts -- and these are primarily early AMR -- 15 have a higher rate of graft dysfunction, an earlier 16 onset, and a higher rate of graft loss at 1 year. So 17 these are all arguments that complement is part of the 18 problem, but it may not be the whole story.</p> <p>19 You can think about mechanisms, and that's 20 what we do as pathologists a lot. And if we understand 21 the mechanisms, that can guide us to the right kind of 22 therapy. And we know that there are at least three</p> | Page 92 | <p>1 allografts. So there is evidence, at least in the 2 experimental studies, for each of these mechanisms.</p> <p>3 Finally, I just want to mention that there is 4 nothing unique about the kidney.</p> <p>5 Very sensitive, very sensitive. Sorry about 6 that. Why is that? This next one. Are you moving it, 7 too? Okay. All right. My hands are up.</p> <p>8 Just to make the point that there are common 9 features in all vascular organs for antibody-mediated 10 rejection, whether it's the kidney, the heart, the 11 liver, or the lung. And so these principles that we 12 are developing in kidney transplantation will probably 13 apply in other settings.</p> <p>14 So just to end, to summarize what I've said, 15 acute AMR, which is also called early or type 1, is 16 usually due to presensitization and involves both Class 17 I and Class II antibodies. It rapidly progresses 18 through renal failure, but it does respond to treatment 19 typically. It may be complement-dependent or not. And 20 I think this will be established by the drug therapy 21 trials more than anything else.</p> <p>22 C1q fixing antibody and C4d deposition are</p> |
| Page 91 | <p>1 ways that antibodies can interfere or damage the 2 endothelium. Antibody alone in tissue culture can 3 cause the endothelium to change, to proliferate, to 4 secrete procoagulant factors, and this has been shown 5 by Elaine Reed some years ago.</p> <p>6 Complement-mediated damage is well known, and 7 we know this through our studies of C4d and other 8 techniques. Complement not only kills endothelium, it 9 causes the endothelium to react and become activated.</p> <p>10 And, finally, a relatively, I would say, less 11 appreciated mechanism is cell-mediated injury of the 12 endothelium via Fc receptors on the surface of either 13 NK cells, macrophages, or neutrophils. And exactly 14 what this does to the endothelium we have less insights 15 on. So you would like to know in an individual patient 16 which of these mechanisms is most important.</p> <p>17 We know from animal studies -- and this will 18 be discussed later by Anita Chong -- that complement- 19 dependent mechanisms are important in acute AMR. And 20 we know in the setting of chronic rejection in mice 21 that NK and Fc mechanisms are very important, and 22 complement is irrelevant to the late damage of cardiac</p> | Page 93 | <p>1 associated with more severe course and argue that 2 complement is an important part of this.</p> <p>3 Chronic AMR, also called late or type 2, is 4 usually due to de novo DSA and related to Class II 5 antigens, and as Peter Nickerson eloquently so, just a 6 few amino acids on those Class II antigens. It's a 7 slow pace and it has a long subclinical phase, which we 8 need to detect better as clinicians. It progresses 9 through these stages over many years. And this may be 10 complement-independent and related to NK or macrophage 11 mediated mechanisms. But again, this is to be 12 established. And if I could think of a need for a 13 drug, it would be to affect this last mechanism, of Fc- 14 mediated endothelial damage.</p> <p>15 So why don't I stop there. Thank you very 16 much.</p> <p>17 (Applause.)</p> <p>18 DR. VELIDEDEOGLU: We thank Dr. Colvin for his 19 presentation.</p> <p>20 Our next speaker is Dr. Nickerson again. And 21 the title of his talk is, "Impact of Acute and Chronic 22 AMR on Graft and Patient Survival -- Is Acute AMR and</p> |

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| <p>1 Chronic AMR Related to Memory Versus De Novo DSA the</p> <p>2 Same Process or Fundamentally Different?"</p> <p>3 Impact of Acute and Chronic AMR on Graft and</p> <p>4 Patient Survival -- Is Acute AMR and Chronic AMR</p> <p>5 Related to Memory Versus De Novo DSA the Same Process</p> <p>6 or Fundamentally Different? HLA versus non-HLA</p> <p>7 Antibodies Causing AMR</p> <p>8 DR. NICKERSON: Thanks very much again to the</p> <p>9 FDA for this opportunity. I'm going to echo a lot of</p> <p>10 Dr. Colvin's discussion points in my talk. Again, I</p> <p>11 will talk a little bit about off-label in this</p> <p>12 discussion.</p> <p>13 Natural history of preformed antibodies or</p> <p>14 memory-related antibodies. And I think it depends on</p> <p>15 the context. Did you recognize that you had it or</p> <p>16 didn't you at the time of the transplant? And I think</p> <p>17 we're starting to recognize it more commonly, but in</p> <p>18 this paper, which came out of the University of Basel</p> <p>19 in Switzerland, they were doing transplants on the</p> <p>20 basis of a CDC-negative crossmatch pretransplant.</p> <p>21 And in retrospect, they went back and tested</p> <p>22 by the more sensitive single-antigen beads whether the</p> | <p>1 actual clinical event led to worse long outcomes.</p> <p>2 And this was also reiterated in a paper</p> <p>3 subsequently in 2015 by the Paris group where again if</p> <p>4 they did a protocol biopsy at 1 year in patients and</p> <p>5 found that they had ongoing subclinical antibody-</p> <p>6 mediated rejection, these patients had a much worse</p> <p>7 outcome. And many of these patients, 80 percent</p> <p>8 almost, were these ones that had antibodies at the time</p> <p>9 of transplant that they hadn't recognized and had gone</p> <p>10 across. So, again, making it really important to know</p> <p>11 whether you have the antibody when you're doing the</p> <p>12 transplant, and then ask the question, Can I mitigate</p> <p>13 that impact?</p> <p>14 And in this paper, a nice series of papers</p> <p>15 that came out of Mayo Clinic, and Dr. Stegall, who is</p> <p>16 here, was principal author on this group, these guys</p> <p>17 knew they had the DSA, and they asked the question, Can</p> <p>18 I overcome it with desensitization protocols? And it</p> <p>19 depended on how much antibody they had. And so as they</p> <p>20 went from weak flow crossmatches to strong flow</p> <p>21 crossmatches to cytotoxic crossmatch-positive</p> <p>22 transplants, and they put the patients through</p> |
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| <p>1 patient actually had a DSA that they had missed at the</p> <p>2 time of transplant because of the negative CDC</p> <p>3 crossmatch. And they found that there were patients</p> <p>4 that were positive for DSA by the more sensitive</p> <p>5 technique.</p> <p>6 And when they compared the rates of ABMR in</p> <p>7 these patients compared to those that had the negative</p> <p>8 single-antigen beads, what they saw was that those</p> <p>9 patients, almost 50 percent by 100 days were having a</p> <p>10 clinical onset of ABMR compared to those patients who</p> <p>11 were negative by the single-antigen beads.</p> <p>12 And I think because of this paper back in</p> <p>13 2009, many groups have now moved on to using single-</p> <p>14 antigen beads routinely in their practice. But this</p> <p>15 just shows you that if you didn't know it was there,</p> <p>16 you're actually at high risk for developing a clinical</p> <p>17 ABMR.</p> <p>18 Now, did that translate into worse outcomes?</p> <p>19 Well, yes, some of these patients, those who had a DSA</p> <p>20 and experienced an ABMR did worse compared to those</p> <p>21 patients who had a DSA and didn't experience an AMR.</p> <p>22 So clearly the combination of the antibody and an</p> | <p>1 desensitization, they still experienced ABMR in a</p> <p>2 number of these patients, and it really showed us that</p> <p>3 the higher the titer of the antibody, the more likely</p> <p>4 you were to have an antibody-mediated rejection even</p> <p>5 when you were trying to desensitize the patients.</p> <p>6 And a lot of interest was in, could you have</p> <p>7 predicted this based on the bead MFI? And others in</p> <p>8 this meeting will talk about the utility of that, but</p> <p>9 suffice it to say that the MFI didn't really predict</p> <p>10 who would or wouldn't have an ABMR, and this was 20</p> <p>11 percent basically we were experiencing in ABMR.</p> <p>12 And it didn't matter how strong your antibody</p> <p>13 was at the time of transplant, whether it was weakly</p> <p>14 positive or strongly positive, all of the patients were</p> <p>15 developing transplant glomerulopathy after the</p> <p>16 transplant in these desensitization protocols. And</p> <p>17 this really taught us a lot about -- and, again, I</p> <p>18 think what Dr. Colvin was just talking about, the</p> <p>19 smoldering nature of chronic antibody-mediated</p> <p>20 rejection.</p> <p>21 So that's memory, not recognizing it, or even</p> <p>22 recognizing it and trying to desensitize. And then now</p> |

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| <p style="text-align: right;">Page 98</p> <p>1 the question of de novo DSA and what's the etiology and 2 natural history? Well, in our case series, the first 3 315 patients, the majority of these patients had Class 4 II antibodies; 86 percent had de novo Class II either 5 alone or in association with Class I. And only 30 6 percent had a de novo Class I antibody; and only 14 7 percent, an isolated Class I antibody. And now we're 8 up to 600 patients and looking at, and we see the same 9 pattern. So dominantly Class II de novo DSA. 10 And throughout this whole series now of almost 11 600 patients, we've only had one patient with an 12 isolated Class I de novo DSA that's resulted in graft 13 failure out of almost 600. So really we think the 14 emphasis should be focused on the Class II DSAs. 15 That's where we're going to learn the most and 16 understand how to control process. 17 And I apologize for the use of nonadherence. 18 And my hand went down when the question came, do I take 19 all my medications appropriately? And the answer is 20 no, of course not. It's a really tough thing to do, 21 but it becomes critical in the context of a transplant 22 because we know that if you're adherent, the risk of</p> | <p style="text-align: right;">Page 100</p> <p>1 What was interesting is that we also found 2 that 61 percent of these patients also had TCMR. So it 3 wasn't just that they had pure ABMR, in fact, they had 4 a mixed rejection, and while half of these were 5 borderline, mild, TCMRs, half of them were actually 6 Grade 1 or higher TCMRs. So these were not occurring 7 in isolation. Only 18 percent of our biopsies at the 8 onset of a DSA had actually pristine histology. 9 Transplant glomerulopathy was uncommon, and 10 you would expect that to be the case. If the antibody 11 is leading the transplant glomerulopathy, and this is 12 the onset of the antibody, then you shouldn't see a lot 13 of transplant glomerulopathy, and we didn't at that 14 point in time. What we did see was a lot of 15 interstitial fibrosis and tubular atrophy at the time 16 of onset of DSA. And, again, I don't think we were 17 very surprised by that. 18 When we looked at what predicted the long-term 19 outcome in these patients on the biopsy, we found that 20 there were two independent predictors in a multivariate 21 model. One was transplant glomerulopathy. If you had 22 transplant glomerulopathy, that was a very strong</p> |
| <p style="text-align: right;">Page 99</p> <p>1 forming an antibody is really, in our series, about 2 2 percent per year. But if you're having trouble 3 complying with your regime, which it's absolutely 4 difficult to do in life, it certainly gets in the way, 5 you're at fourfold increased risk for developing an 6 antibody, and that really is a course once set on is 7 very difficult to control. 8 Now, once you have a de novo DSA, does that 9 always mean that you have ABMR? And so we did biopsies 10 at the onset of these DSAs. We were regularly 11 screening our patients from the time of transplant. 12 From the time of first detection, we would do a biopsy, 13 even if the function of the graft was fine. And we 14 found that three-quarters of our patients met the Banff 15 criteria for ABMR, and it was largely because of 16 peritubular capillaritis with C4d and glomerulitis. 17 Now, other case series, out of Vienna and out 18 of the Mayo Clinic, have shown that when they do 19 biopsies in these patients, they get about 50 percent 20 ABMR detected. And so I think the range is anywhere 21 between 50 and three-quarters we'll have ABMR when you 22 have a de novo DSA.</p> | <p style="text-align: right;">Page 101</p> <p>1 predictor that your graft was at risk for premature 2 failure, but, again, only 13 percent had this at the 3 onset of the antibody. Tubulitis was actually a very 4 strong predictor of eventual graft loss, and I think 5 it's giving us some indication of the strength of the 6 immune response that's ongoing in these grafts. 7 We did see that the Banff CG score would 8 increase by one grade per 3 years of follow-up after 9 the onset of antibody, so this was actually something 10 that was a strong correlation. 11 What was interesting was that microvascular 12 inflammation grade, in other words, how much g+ptc you 13 had, if you had mild g+ptc or you had more severe forms 14 of g+ptc, that really didn't differentiate who would go 15 on to graft loss, and I think that's partly because 16 most patients had some degree of g+ptc, and once you 17 have it, there is probably spottiness in the biopsy 18 that you're doing, it doesn't really help you to 19 predict who's going to be more accelerated in their 20 graft loss, nor did C4d positive or negative have any 21 prediction on who would go on to subsequent graft loss. 22 So not to say that they're not important, I'm</p> |

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| <p style="text-align: right;">Page 102</p> <p>1 saying that a lot of times these are telling us that 2 there's a process underway, but the degree of that 3 process is not predictive of the outcome. 4 And as already shown, if you are clinical at 5 the onset, in other words, you already had graft 6 dysfunction when you first had the antibody, on 7 average, you lost your graft at about 3.3 years, but if 8 you had stable graft function when the antibody first 9 showed up, on average, it was taking 8.3 years to lose 10 the graft. When you did lose the graft, there was a 11 lot of transplant glomerulopathy and there was a lot of 12 interstitial fibrosis and tubular atrophy. And again 13 in multivariate models, the only thing that predicted 14 the CG was the antibody, and what predicted the IFTA 15 was early cellular rejection and if you had had 16 nonadherence. Antibody did not predict IFTA. And we 17 think that the nonadherence is really a surrogate 18 marker of ongoing smoldering cellular rejection in the 19 graft that's leading to IFTA. 20 So the model that we've derived from our de 21 novo DSA studies is that graft loss is really the 22 composite of IFTA and CG, that IFTA can be caused by</p> | <p style="text-align: right;">Page 104</p> <p>1 accelerate on to graft failure. 2 So the question of, de novo versus memory, 3 what's the differences? Again, a nice paper that just 4 came out of the Paris group, where they basically 5 showed that the onset of ABMR related to preexisting 6 was very rapid, within the first year largely, and 7 within the first few years, for almost all the cases 8 that they had documented. 9 De novo DSA was a much more slower onset of 10 cases of antibody. They also noted that those that had 11 preexisting DSA tended to have slightly better graft 12 survival than those that had de novo onset of DSA. 13 When they looked at the pathology differences, 14 it was actually quite interesting. The de novo DSA 15 ABMRs had more transplant glomerulopathy, TCMR, IFTA, 16 and proteinuria at diagnosis, and I think in part, 17 that's because they likely had delayed recognition of 18 the process with de novo DSA. When they looked at how 19 many were subclinical in the de novo DSA, it was only 20 8.8 percent. So I think the cases that they were 21 documenting of de novo DSA-associated ABMR were these 22 late cases, which they weren't recognizing by</p> |
| <p style="text-align: right;">Page 103</p> <p>1 multiple things. It could be drug toxicity, older 2 donors, ischemia reperfusion injury that occurs at the 3 time of deceased donation, and then TCMR. And we've 4 stolen shamelessly from Dr. Colvin in using the term 5 "smoldering" because we believe that there is a 6 smoldering cellular rejection, and many times this is 7 much more subclinical than clinical that's leading to 8 IFTA. 9 And CG is driven by, again, ABMR, which, 10 again, we also like the term "smoldering" and I would 11 refer to this as predominantly subclinical rather than 12 clinical that's leading to transplant glomerulopathy, 13 and this is driven by de novo DSA formation. 14 And we'll hear later the linkages between 15 cellular and DSA formation. And all of this is driven 16 by HLA mismatching, and, hence, the importance of 17 matching for HLA, and, in particular, Class II. 18 Under immunosuppression, whether that's 19 because of difficulty with adhering to our regimes or 20 us, because we're prematurely or minimizing our 21 patients, leads to basically taking the brakes off of 22 the immune response and allows this whole process to</p> | <p style="text-align: right;">Page 105</p> <p>1 screening, but they were recognizing by the onset of 2 graft dysfunction. Whereas the early preexisting 3 antibodies had a lot more subclinical, and I think 4 that's because they were much more attuned into doing 5 protocol biopsies in these patients anticipating the 6 risk for early ABMR. 7 What was also interesting and I think also 8 deserves emphasis is that the de novo DSA, they noted 9 at the molecular level a lot more TCMR transcripts as 10 compared to the preexisting DSA. So the preexisting 11 DSAs seem to occur predominantly as an antibody 12 phenotype whereas the de novo DSA much more commonly 13 had this mixed phenotype with T-cell transcripts, NK, 14 and interferon gamma transcripts. 15 In another paper, by Dr. Haas, who is here, 16 and his group with Stan Jordan, they looked at again 17 type 1, where these were really ABMRs associated with 18 preexisting antibody or type 2, which were de novo DSA- 19 associated antibody-mediated rejections. And what they 20 also noted here, 72 percent of the de novo antibody- 21 mediated rejections had a concomitant TCMR Banff 1a or 22 borderline compared to only 27 percent in the</p> |

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| <p style="text-align: right;">Page 106</p> <p>1 preexisting DSA. They had more transplant 2 glomerulopathy in these patients compared to the 3 preexisting DSA. 4 And in terms of the activity, 70 percent were 5 acute or active whereas in the de novo DSA-associated, 6 60 percent were chronic and active. So, again, similar 7 to what you heard from Dr. Colvin's discussion, and, 8 again, predominantly Class II in the de novo DSA- 9 associated types. 10 In terms of response to therapies, this is a 11 nice paper from Steve Woodle and his group at 12 Cincinnati, and what they were looking at is treating 13 ABMR, and they were basically looking at refractory 14 ABMR, and how do we actually overcome these and how 15 responsive are these patients to using additional 16 agents? And in this case, they were using proteasome 17 inhibition as a last ditch effort to try and quiet down 18 the ABMR. 19 And what they found was that if this was 20 within 6 months of the transplant, they were actually 21 pretty good at settling things down. They had a good 22 immune response documented by a drop in the MFI within</p> | <p style="text-align: right;">Page 108</p> <p>1 differential effect of what we're seeing on the 2 pathology. Certainly nonadherence is pretty good in 3 the preexisting. You don't really have nonadherence 4 because you're under tight monitoring at that point in 5 time, whereas it tends to be a bigger problem in the de 6 novo DSA patients. ABMR tends to be more severe in the 7 preexisting, less so in the de novo. And the TCMR, I 8 think we're starting to appreciate more and more this 9 really is a cardinal feature of the de novo DSA 10 phenotypes, and the response to therapy is much 11 different, it's a lot better chance to get a response 12 with the preexisting than it is with the de novo. 13 So that summarizes my HLA part. Now, I was 14 also asked to just briefly talk about non-HLA 15 antibodies, and are they playing a role? And I'm 16 giving you a cartoon here just to really identify what 17 we're talking about when we talk about non-HLA. Now, 18 in this context, I'm referring to an HLA antibody 19 targeting HLA leading to inflammation in the graft, but 20 this could be any kind of inflammatory process in the 21 kidney leading to spreading of revealing epitopes 22 inside the tissues. So we get collagen, perlecan,</p> |
| <p style="text-align: right;">Page 107</p> <p>1 14 days of treatment in three-quarters of the patients, 2 histologic response in almost 90 percent, and 3 improvement in graft function. But if these ABMRs were 4 occurring after 6 months posttransplant, the response 5 to therapy was much less dramatic, and again showing 6 the unmet need that we have in this patient cohort. 7 So in summary of, "What's the difference 8 between preexisting DSA and de novo DSA-associated 9 ABMR?" I think it's fairly similar to the summation 10 that Dr. Colvin gave, the HLA DSAs and preexisting are 11 Class II, maybe a little bit more or equal to that of 12 Class I compared to de novo, where it's dominantly 13 Class II. 14 One of the things we haven't really 15 highlighted is the level of immunosuppression in 16 preexisting DSA. We're anticipating this. We're 17 giving a lot of immunosuppression. We're doing 18 induction depletion therapies and pheresis, IVIG, 19 whereas in the de novo onset, we're really at baseline 20 immunosuppression. So there's a real difference in the 21 immunosuppression at the time that we're diagnosing 22 these processes, and I think that also leads to a</p> | <p style="text-align: right;">Page 109</p> <p>1 MICA, other targets, AT1R, all getting expressed in the 2 context of inflammation leading to antigens being shed, 3 being processed, and within the regional lymph node 4 then getting plasma cell production of antibodies 5 hitting these targets that are being revealed through 6 the inflammatory process. 7 So there have been data supporting constructs 8 like anti-LG3, anti-perlecan, collagen IV, AT1R, MICA, 9 and anti-endothelial antibodies that can then come back 10 into the graft and cause their own inflammatory 11 processes. And the real question for a lot of us is, 12 To what role are these non-HLA antibodies playing a 13 role in causing an antibody-mediated like inflammatory 14 response in the tissues? 15 And there's some data coming out more and more 16 certainly supporting a role for anti-angiotensin I 17 receptor antibodies. Preexisting, and this may be 18 revealed from the processes that led to kidney failure 19 in the first place and at the time of transplant then 20 being a risk factor for acute rejection and graft loss. 21 Anti-perlecan antibodies, again associated with 22 vascular rejection or more chronic allograft rejection.</p> |

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| Page 110 | Page 112 |
| <p>1 And anti-collagen IV and fibronectin antibodies, 2 leading to transplant glomerulopathy and associated 3 with chronic allograft rejection. 4 The problem with a lot of these studies, 5 though, is that they're frequently confounded by 6 preexisting HLA DSA, and so to separate what these non- 7 HLA antibodies are doing relative to the HLA antibodies 8 is very difficult. 9 And the other problem with a lot of these 10 studies, because a lot of them are older studies now, 11 is that there was inadequate assessment for HLA DSA 12 using the solid phase technology to really rule out 13 that there wasn't an HLA antibody there that was 14 driving the process as opposed to the non-HLA antibody. 15 So I think this is a field certainly ripe for 16 investigation, but to actually attribute that these are 17 absolutely driving processes with great frequency I 18 think is the problem that we have today in the field. 19 And with that, I've already given my 20 acknowledgements before. I'll stop. Thank you very 21 much. 22 (Applause.)</p> | <p>1 first talk. Is the ability to measure those amino acid 2 epitopes, is that something that routine clinical labs 3 can now do, or is this something strictly being done at 4 research centers? 5 DR. NICKERSON: Yeah. So certainly the 6 software package that is used to do this is freeware, 7 so it's downloadable from the Web, there's nothing 8 magic about the software. What it requires is for you 9 to do higher resolution HLA typing on the donor and the 10 recipient, and that's really up to the labs, what 11 they're prepared to do or not to do. 12 Certainly we do that already for bone marrow 13 transplant, we do matching at a very high-resolution 14 level. We've not really brought that into kidney 15 transplant because we haven't really had a reason to do 16 that until now. 17 I think we're going to see as the technology 18 evolves and as the recognition of the utility of such 19 an approach evolves, more and more labs will start 20 doing higher resolution typing. 21 There has been a lot of discussion about even 22 just using what we know about HLA frequencies to impute</p> |
| Page 111 | Page 113 |
| <p>1 Public Comment and Discussion Part I 2 DR. VELIDEDEOGLU: Okay. We thank Dr. 3 Nickerson. Now, this concludes our Part I 4 presentations. 5 Now we will start the discussion session 6 following Part I. And we are running approximately 10 7 to 15 minutes behind schedule. And the first 8 approximately 10 minutes will be devoted to the 9 questions from the audience or from the speakers 10 specific to the presentations if they have any 11 clarifying questions. And we will follow by our 12 preformulated question afterwards to steer the 13 discussion related to the presentations. 14 And I request all the audience members and the 15 speakers who plan on asking questions to introduce 16 themselves first before each question. Since this 17 workshop is being webcast live, this is important. And 18 so if anybody has any questions related to the 19 presentations, Part I presentations, they can ask now. 20 Please, go ahead. 21 DR. KNOLL: Greg Knoll, from the University of 22 Ottawa. It's a question actually for Peter from your</p> | <p>1 what the high-resolution typing would be. Although my 2 colleagues would frown on that, I think that's actually 3 a bad thing to do because using imputation, you're 4 going to introduce a lot of error, and I think 5 introducing error introduces noise, and if we keep 6 doing that, we're not going to be able to get the 7 associations we need. So I think you really do need to 8 get to high-resolution typing. 9 Can we do this today? Absolutely. There is 10 nothing preventing us from doing this today and 11 assessing what the epitope mismatched degrees are 12 between -- or the Eplet mismatched degrees are between 13 donor and recipient. Anyone can do that. 14 DR. KNOLL: And just a follow-up then. Is 15 there much cost to the high-res typing if you're not 16 currently doing, the additional cost a lot? 17 DR. NICKERSON: Yeah, again, as the evolution 18 of the technology occurs, a lot of times you are 19 getting high-res or close to high-res typing, and I 20 think that it will become very cost effective. Yes, 21 there is some additional cost to do that, but 22 ultimately to risk stratify your patients into whether</p> |

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| <p style="text-align: right;">Page 114</p> <p>1 you're at high or low risk, and then how you would 2 treat them accordingly, it's a minimal investment to 3 make. 4 DR. VELIDEDEOGLU: Okay. Any other questions? 5 Okay, Anat Tambur. 6 DR. ROITBERG-TAMBUR: Thank you. I want to 7 stay on the same topic and definitely echo Peter with 8 the newer agents that we have in the market right now 9 that will allow significantly higher resolution with 10 minimal added cost. And just to clarify, I definitely 11 think that that is a great way for risk stratification. 12 Where I see a little bit of a problem is when 13 you look at the different papers, everyone comes up 14 with their own different thresholds, and where I'm not 15 sure that we can actually take it and implement it 16 right now, as a community, as an approach, even though 17 we definitely get way better resolution of how 18 different the donor and the recipient are by taking 19 that approach, is, how do we go with thresholds? 20 And you'll hear me talking about MFI cutoffs 21 and my aversion to that, and I just want to caution 22 about jumping into something using a threshold that may</p> | <p style="text-align: right;">Page 116</p> <p>1 about the other technologies, the subclasses, the C1q 2 assays from Anat and Dr. Gebel in their presentations. 3 And, yes, I think what Anat has nicely shown is that 4 you can start looking at titer and, how does titer have 5 predictability? 6 Again, there is mixed literature out there. I 7 think it really depends and you have to look very 8 carefully at who is reporting what in what context. 9 Chris Wiebe from our group is going to show some data 10 where we had tried to look at titer or C1q. 11 And certainly in a univariate analysis, both 12 of those, the higher the titer and the higher -- 13 whether you were C1q-positive, that did correlate with 14 graft outcome, but we also saw that that correlated 15 with clinical phenotypes. In other words, if you had 16 clinical rejection at the onset of your ABMR or if you 17 were known to be having nonadherence in the mix, that 18 seemed to associate very strongly with high titer and 19 C1q-positive. And so those all interacted, and 20 basically the clinical phenotype had as much prediction 21 as any ancillary diagnostics would have had in that 22 construct of de novo DSA.</p> |
| <p style="text-align: right;">Page 115</p> <p>1 be the best for one population, and then you go to 2 another population where they're more heavily Hispanic 3 donors or African American donors, and you're talking 4 about a whole different universe, and your thresholds 5 will be different. 6 And thank you, Peter, for nodding for this 7 because I think it's an important issue. 8 DR. VELIDEDEOGLU: Okay. The member from the 9 audience at the microphone, please. 10 DR. CHONG: Hi. My name is Anita Chong. I'm 11 from the University of Chicago. I wanted to ask a 12 question related to the chronic as well as the acute 13 AMR and whether there are any new technologies that are 14 looking at whether the quality of the antibody 15 responses are different in terms of the subclasses, the 16 titers, the avidity, as the immune response sort of 17 develops over time with T-cell help. 18 DR. VELIDEDEOGLU: Well, to whom do you want 19 to direct your question? 20 DR. CHONG: Probably to Peter as well as Bob 21 Colvin. 22 DR. NICKERSON: Certainly we're going to hear</p> | <p style="text-align: right;">Page 117</p> <p>1 In terms of subclasses, I think there really 2 needs to be a lot more work done on subclasses at this 3 point to correlate with outcomes. 4 DR. VELIDEDEOGLU: Okay. Thank you for the 5 questions. Now we are running quite a bit behind, so 6 we will move on to the FDA questions. 7 And the first question for discussion is: Are 8 early acute AMR and late acute AMR the same regardless 9 of whether they are related to preformed or de novo 10 DSA? Do either or both represent a continuum to 11 chronic AMR? Discuss how. 12 So if anybody volunteers to make a comment or 13 question, please you are welcome to do so. 14 Dr. Haas? 15 DR. HAAS: Yeah. I think that the late AMR, 16 the differences between late AMR and early AMR I think 17 are primarily due to whether this is a memory response 18 or whether this is a de novo DSA. We do a lot of 19 presensitized patients at our center and at Johns 20 Hopkins, where I was previously at, and the rebound, 21 the memory effect, can occur as late as 3 or 4 years 22 posttransplant, where if you type the donor-specific</p> |

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| Page 118 | Page 120 |
| <p>1 antibodies, they're the same donor-specific antibodies</p> <p>2 that were present pretransplant, and these can be type</p> <p>3 1, anti-Class I or anti-Class II, and these tend to be</p> <p>4 pure antibody-mediated rejection responses. They're</p> <p>5 not mixed rejections.</p> <p>6 By contrast, when we're dealing with de novo</p> <p>7 donor-specific antibodies, I think as was highlighted</p> <p>8 by Peter and by Bob, these are primarily anti-Class II</p> <p>9 antibodies. They're often preceded by and occur</p> <p>10 together with cell-mediated rejection. The gene</p> <p>11 activation that occurs in these responses is different</p> <p>12 in that instead of this being a pure antibody humoral</p> <p>13 type response, this is a mixed T-cell-mediated</p> <p>14 antibody-mediated response. So I think it's not a</p> <p>15 matter of time posttransplant, but whether we're</p> <p>16 dealing with a memory response versus a de novo DSA.</p> <p>17 DR. VELIDEDEOGLU: Okay. Thank you.</p> <p>18 Any other comments?</p> <p>19 DR. STEGALL: I'll comment on that.</p> <p>20 DR. VELIDEDEOGLU: Okay. Dr. Stegall.</p> <p>21 DR. STEGALL: I think that when you do a</p> <p>22 biopsy, they look a lot alike, but the early acute ABMR</p> | <p>1 DR. VELIDEDEOGLU: Okay. We thank Dr.</p> <p>2 Stegall.</p> <p>3 DR. COLVIN: Could I make one?</p> <p>4 DR. VELIDEDEOGLU: Dr. Colvin, please, go</p> <p>5 ahead.</p> <p>6 DR. COLVIN: I think that late acute AMR is</p> <p>7 quite unusual to be present just alone. The cases I've</p> <p>8 seen have almost always had a component of a chronic</p> <p>9 process, transplant glomerulopathy in particular. So I</p> <p>10 think the acute AMR in the late phase is just a flare-</p> <p>11 up of a chronic process rather than something</p> <p>12 different, and more related to what occurs early on.</p> <p>13 DR. STEGALL: But the difference is that</p> <p>14 you're seeing biopsies for cause, so more than protocol</p> <p>15 biopsies. So when we see protocol biopsies, you almost</p> <p>16 always see the peritubular capillaritis and</p> <p>17 inflammation first. There's not a lot of C4d. There</p> <p>18 is commonly not transplant glomerulopathy by light</p> <p>19 microscopy. So I think it's the only time you ever</p> <p>20 biopsy that person is when they've already progressed</p> <p>21 to something.</p> <p>22 If you do an EM, endothelial cell activation</p> |
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| <p>1 in a sensitized patient usually occurs if there is a</p> <p>2 crescendo rise in antibody, and you can actually</p> <p>3 usually get through that. And many of these patients</p> <p>4 actually will never develop transplant glomerulopathy</p> <p>5 long term, especially if they're Class I. So it's a</p> <p>6 different clinical situation.</p> <p>7 One of the confusing things about this is</p> <p>8 Banff looks at antibody-mediated rejection as the same</p> <p>9 thing, which it sort of is histologically, but</p> <p>10 clinically, being a clinician, it's not even close to</p> <p>11 being the same scenario. You'll do a year later biopsy</p> <p>12 on someone who's had an early acute ABMR episode, and</p> <p>13 they won't have any peritubular capillaritis or CG, but</p> <p>14 if you do a year biopsy on anybody, and they have</p> <p>15 peritubular capillaritis, your next question, almost</p> <p>16 always it will progress at some point to CG, it just</p> <p>17 depends on how long you're looking at it.</p> <p>18 So the question is the same. Of course,</p> <p>19 nothing in biology is exactly the same, but the</p> <p>20 histology is the same, but the clinical scenarios are</p> <p>21 very different, and I think the treatment of those two</p> <p>22 scenarios are very different.</p> | <p>1 is there, it's like one of the first things that ever</p> <p>2 happens, it's just that you don't see that. The</p> <p>3 process of duplication of the glomerular basement</p> <p>4 membrane follows the chronic inflammation.</p> <p>5 DR. COLVIN: Right. Can I respond, Ergun?</p> <p>6 DR. VELIDEDEOGLU: Yes.</p> <p>7 DR. COLVIN: Yeah, I agree with you</p> <p>8 completely, and your protocol biopsies are telling us</p> <p>9 an awfully lot about the underlying pathobiology of this</p> <p>10 condition. There's a gap in the Banff classification</p> <p>11 for what I like to call smoldering. And I don't know</p> <p>12 if Mark would like to comment on this, but this is what</p> <p>13 you're seeing in your protocol biopsies, and it isn't</p> <p>14 necessarily associated with any change in renal</p> <p>15 function. And whether you call that acute or chronic,</p> <p>16 I think probably either one is not the right term, but</p> <p>17 we need another term. "Smoldering" would be one of</p> <p>18 them.</p> <p>19 DR. HAAS: Yeah. I mean, one of the problems</p> <p>20 with the Banff is we divide antibody-mediated rejection</p> <p>21 into what's called acute active and chronic active.</p> <p>22 And acute active is a little bit of a misnomer because</p> |

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| <p style="text-align: right;">Page 122</p> <p>1 it implies that it's always acute. And if you look at 2 the footnotes from the original, you know, the 2013, 3 Banff, it actually states that the process may be acute 4 or smoldering, and may be clinical or subclinical. 5 So at the last 2017 Banff meeting, which was 6 held in Barcelona just a couple weeks ago, there was a 7 move afoot to remove the word "acute" from the acute 8 active category to reflect that this may be acute or 9 smoldering, that it's just active and it doesn't have 10 TG. The problem with that, of course, is that it 11 assumes that the cases that are truly acute and the 12 cases that are more smoldering are the same so long as 13 they don't have transplant glomerulopathy, which is 14 probably not the case. 15 So there may in fact be really three 16 categories of antibody-mediated rejection: the true 17 acutes, which are usually a memory response to rebound 18 of preexisting donor-specific antibodies occur very 19 early on posttransplant, can occur later, but are 20 usually seen in highly sensitized patients; the more 21 smoldering cases, which are not yet reached the stage 22 of chronic active, but may have more in common with</p> | <p style="text-align: right;">Page 124</p> <p>1 if not in the biopsy, that the patient has ongoing 2 injury, proteinuria, for instance, is one of the things 3 we tend to see in these patients. 4 Also, the combination of the antibodies. Are 5 we dealing only with a Class I antibody, with a Class 6 II antibody, or Class I and Class II? We know that 7 Class II fare the worst. Those patients have a 8 component of noncompliance even if you cannot detect 9 them immediately, because patients are smart, they know 10 how to make their numbers and their drug levels look 11 good before they come to clinic. What happens in 12 between, we do not know. 13 So it's important to have that concept because 14 you want to select the right patients for trials. You 15 want to select patients that will respond to therapy, 16 where the process is early enough that you can stall it 17 or, if possible, eliminate it. 18 Once antibody-mediated rejection is going on 19 for a while, it becomes independent. It doesn't matter 20 what you do with it. If you want to block complement, 21 if you want to eliminate antibody, the response is so 22 robust that you will not be able to have those patients</p> |
| <p style="text-align: right;">Page 123</p> <p>1 chronic active than actually the acute phase; and then 2 the ones that are truly chronic with transplant 3 glomerulopathy. So there may be really three forms of 4 ABMR rather than two, as the Banff states. 5 DR. VELIDEDEOGLU: Okay. And I want to invite 6 Dr. Samaniego to the microphone, please. She's been 7 standing there. 8 Dr. Samaniego, you have an assigned seat at 9 the table if you would like to. 10 DR. SAMANIEGO-PICOTA: Thank you. I will come 11 to the table later. I think that everything I pretty 12 much agree with everything that Dr. Stegall said. And 13 we see exactly the same biology in our program, where 14 we also do protocol biopsies. In my opinion, there are 15 two things to look at. One is the tissue. If the 16 patient has chronicity, that is a different type of 17 process that is going on. Response to therapy is 18 completely different. Outcome is completely different. 19 If the patient has history of noncompliance 20 regardless of where it is happening, the prognosis is 21 not going to be good. And even if we don't see 22 chronicity in those patients, there may be indication,</p> | <p style="text-align: right;">Page 125</p> <p>1 to respond to anything, it's just getting ready for 2 another transplant. 3 DR. VELIDEDEOGLU: Dr. Haas? 4 DR. HAAS: Yeah. Excuse me. With regard to 5 treating patients with transplant glomerulopathy, is 6 there something out there that enables us to tell which 7 patients who have transplant glomerulopathy on the 8 biopsy can be treated with some improved outcome, 9 whether it be some improvement of function or at least 10 slowing the rate of decline of function versus those 11 patients who unfortunately are inevitably going to 12 progress to graft loss regardless of treatment. 13 I think the biopsy can give us some 14 information. Joe Kahwaji, from our group, published a 15 small study a couple of years ago where he looked at 16 the level of microvascular inflammation, glomerulitis 17 and peritubular capillaritis, and found that when there 18 was moderate to severe microvascular inflammation, that 19 treating these patients with IVIG and rituximab did 20 tend to stabilize the patients and that their 21 progression was less. Whereas in patients who had no 22 or only mild microvascular inflammation, the treatment</p> |

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| Page 126 | <p>1 had no effect on the rate of progression. But this was 2 a very small study. 3 I think this is also an area where the 4 molecular diagnostics can contribute to whether we're 5 dealing with really an active lesion. How much 6 endothelial activation, NK cell transcripts, are there? 7 Measures of kidney injury transcripts, which the 8 Halloran group found, were very, very important 9 regardless of etiology in predicting outcomes. So 10 there's a lot we need to learn about this, but not all 11 patients with transplant glomerulopathy I believe have 12 a death sentence for their graft, that some patients 13 with TG can be treated and at least stabilized or their 14 progression slowed. 15 DR. VELIDEDEOGLU: Okay. Dr. Woodle has the 16 last word on this question. We need to move on to the 17 next question. So we are really running quite behind. 18 DR. WOODLE: So, one, we agree completely with 19 Mark in the description of these early anamnestic 20 responses being very treatable. They're really 21 treatable if you pick them up early. And if you wait 22 until the antibody is so high that the graft is</p> | Page 128 | <p>1 the ones that do respond and show a 50 percent 2 reduction in DSA have better survival than those that 3 don't. 4 And so within that big group of late AMR that 5 is really hard to sort out, are there different ones? 6 They're not all the same clearly. That's one predictor 7 that I think is out there that is starting to help us 8 sort out some of them. 9 So we don't believe it's totally untreatable, 10 it's just a very refractory form of rejection that we 11 don't have drugs. The drugs and stuff we're using now 12 is woefully inadequate, and we need better drugs for 13 that. 14 DR. ALLOWAY: I just want to make one comment 15 before, as Mark said, we give a death sentence to the 16 patients that have TG. I think that a lot of people 17 here refer to nonadherence and the impact that it has 18 on this and how it drives it. I think that we need to 19 be just as disciplined to give the patients and 20 identify them a precise prescription for nonadherence 21 to try to address those issues if there is enough 22 kidney function there to salvage. And I think that</p> |
| Page 127 | <p>1 threatened to rupture, then you're looking at 2 eculizumab or splenectomy or potentially taking the 3 kidney out. 4 This is something that's been known for a long 5 time. When we wrote the paper that was referred to, 6 our early versus late paper with proteasome inhibitor 7 treatment, I was at Toronto General with Carl Cardella, 8 who many of you know, and Carl goes, "Steve, we've 9 known this for a long time, for 20 or 30 years, that 10 early antibody-mediated rejection is easy to treat, it 11 does well long term." 12 And so this is not novel. Although there's 13 not much in the literature, there were only two papers 14 in the literature when we did that. 15 So we've looked at an endpoint that we defined 16 just arbitrarily and picked it, and it's turned out to 17 be fairly reliable, and that is a 50 percent reduction 18 in the level of immunodominant DSA MFI within 14 days 19 predicts outcome. And we'll present data at ATC. It's 20 the strongest predictor for outcome in AMR that we've 21 found to date, and it even works in late AMR. And it 22 appears to us that not all late AMRs are the same, that</p> | Page 129 | <p>1 what we see is the patients that are nonadherent are 2 not going to change unless we make a definitive 3 intervention. 4 And as Dr. Nickerson has referred to before, 5 and I'll steal words from him, your first shot is your 6 best shot. And so we need to maximize that if we can. 7 DR. VELIDEDEOGLU: Okay. Thank you. We only 8 have 10 minutes for the next question. And the next 9 question is, as you see on the screen: If acute AMR 10 and chronic AMR is a continuum, then can we predict who 11 will or will not progress to chronic AMR? Are acute 12 AMR and acute mixed AMR distinct entities? What is the 13 significance of the presence of cellular rejection 14 component in a biopsy demonstrating AMR? 15 Comments, please. 16 Dr. Stegall? 17 DR. STEGALL: I'll take the second one. So 18 when we get a biopsy, a patient comes back, and they 19 have combined cellular and humoral rejection, so this 20 is like the clinical approach to this. You probably 21 treat the cellular component first, right? That's what 22 you do. And then you also sort of make a judgment,</p> |

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| <p style="text-align: right;">Page 130</p> <p>1 what's the primary process that's -- maybe the 2 creatinine is elevated, what's the primary thing that's 3 driving the creatinine elevation? 4 If they end up with borderline cellular 5 rejection on the biopsy, I really can't believe that 6 that's -- and if they end up with transplant 7 glomerulopathy is the next biopsy they get, I think 8 that most of these patients will end up, if they get 9 back on immunosuppression for whatever reason, maybe 10 you decreased it because they had polyoma, they're not 11 all nonadherent, that the primary thing that they're 12 left with is an antibody-mediated rejection that's 13 smoldering, it's not this acute rise. I think the 14 nomenclature is confusing us more than actually the 15 biological process. 16 So I think that it's significant obviously to 17 have cellular rejection. And I think that if there's 18 an association with cellular rejection and bad outcome, 19 there's no question. What's driving the bad outcome is 20 not known. It could just be associated with people who 21 just didn't take any immunosuppression and that are 22 going to end up with higher levels of antibody.</p> | <p style="text-align: right;">Page 132</p> <p>1 First, the biopsy is just a single time point, and if 2 you have a cell-mediated component, T-cell-mediated 3 component, and you have an antibody-mediated component, 4 we can't tell from the biopsy which was there first and 5 which was there second. 6 So we don't necessarily know if the -- 7 although there is clearly data out there from the 8 Manitoba group and others that cell-mediated rejection 9 is a risk for later development of de novo DSAs, we 10 don't know in each case if the cell-mediated rejection 11 preceded the antibody, if the antibody preceded the 12 cell-mediated component, or if they occurred at the 13 same time. We don't know that. Again, we have a 14 hard -- 15 The other thing is that peritubular 16 capillaritis is very hard, if not impossible, to 17 diagnose in the context of T-cell-mediated rejection 18 because the cells have to get there somehow into the 19 interstitium and into the tubules, and the way they get 20 there is through the peritubular capillaries. So 21 peritubular capillaritis, which is an important 22 diagnostic tool for antibody-mediated rejection is</p> |
| <p style="text-align: right;">Page 131</p> <p>1 So I don't think that you -- the cellular 2 component of this, there are a lot of T cells in these 3 grafts, but I'm not sure that it's garden variety T- 4 cell rejection, and I'm not sure that it's driving the 5 chronic process as much as people would say. 6 I do think that they all look like the same at 7 the end. They all look like they get transplant 8 glomerulopathy. And I think it is a continuum, the 9 acute and chronic is a continuum. And I do think that 10 hopefully the way out of this is to treat as much of 11 the cellular rejection as possible, but you're still 12 left with people who have peritubular capillaritis and 13 develop CG and lose their graft to antibody over time. 14 That's what I think. 15 So probably in my mind this leans more to an 16 antibody-mediated process than not. 17 DR. VELIDEDEOGLU: Thank you. 18 Any other comments? 19 Dr. Haas? 20 DR. HAAS: I mean, from a pathology 21 standpoint, and I'm a pathologist, the diagnosis of 22 mixed rejection is difficult for a number of reasons.</p> | <p style="text-align: right;">Page 133</p> <p>1 pretty useless in terms of cell-mediated rejection. 2 And with late rejections, these are not infrequently 3 C4d-negative. 4 So it's a diagnostic conundrum. The whole 5 borderline category is a diagnostic conundrum. Is this 6 really rejection? And how can we tell the borderlines 7 that really are rejection from the borderlines that are 8 due to another lesion? 9 And, again, I think we really need to go 10 beyond pure histology here to really understand the 11 true implication of mixed rejections. Some kind of 12 molecular diagnostic biomarker studies are ultimately 13 going to be necessary before we really understand that. 14 And then there is, finally, as Ros Mannon 15 pointed out, the whole issue of interstitial 16 inflammation in areas of fibrosis. Banff does not 17 grade this as cell-mediated rejection. There's a move 18 toward putting i-IFTA as sort of a chronic or chronic 19 active cell-mediated rejection, but that is sort of 20 purely a consensus at this point. 21 We know it's bad, and we know it occurs, and 22 so we can call it rejection, but is this really related</p> |

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| <p style="text-align: right;">Page 134</p> <p>1 to the acute T-cell-mediated rejection that we see? 2 Again, we don't know, and we need to go beyond 3 histology. Histology is good as far as we can tell, 4 but it's not the be all to end all. 5 DR. VELIDEDEOGLU: Dr. Woodle? 6 DR. WOODLE: Mark, we were bothered by this a 7 long time ago, and so one of the things we did early on 8 when we were looking at mixed rejections, and this was 9 several years ago, is we asked a simple question. 10 Forget the Banff criteria for AMR. If you just look at 11 the predictive power of the single-antigen bead assay 12 denoting a DSA, that alone discriminates almost as 13 effectively as using Banff criteria. 14 And I don't want to make you and Bob feel that 15 you're not necessary, but in our program, if you have a 16 cellular rejection and you meet Banff criteria and you 17 have a DSA and you have mixed rejection, you get 18 treated as such. 19 DR. COLVIN: Could I respond? I think there 20 is no doubt that pathologists undercall T-cell-mediated 21 rejection in the late biopsies. Our criteria are not 22 very good, and hopefully they will improve. The</p> | <p style="text-align: right;">Page 136</p> <p>1 measure that risk? And you've done a DSA, of course, 2 to get that far, but do you need to do a biopsy at that 3 point? And how can the biopsy guide your therapy? I 4 think that's the question, how you monitor these 5 patients after they've been transplanted and appear 6 with a DSA. 7 DR. GASTON: Bob, I was going to change it to 8 the last question in addressing that, and that is, to 9 me, I think all of these questions have to be addressed 10 in the context of the immunosuppressants that we have 11 patients on and the mechanisms by which they block 12 alloresponses. And so I think it's very possible in a 13 patient to use adequate dosing of the immuno- 14 suppressants we have available to us and have them 15 still develop antibody and AMR. 16 I think, however, the presence of cellular 17 rejection always means inadequate immunosuppression, 18 whether it's patient induced or whether it's physician 19 induced. And so I think that's the significance of the 20 cellular piece in it, is inadequacy of immuno- 21 suppression. 22 DR. VELIDEDEOGLU: Dr. Haas.</p> |
| <p style="text-align: right;">Page 135</p> <p>1 molecular tests pick this up very easily, and I've been 2 impressed with how striking the T-cell signal is in 3 some of these. And, of course, you can do it with an 4 immunohistochemical stain for T cells as well. So I 5 think we're going to learn a lot more about the 6 component of the cellular aspect. And you have to, of 7 course, remember that B cells don't make antibodies on 8 their own, they need the T cells, and there is some 9 evidence that local production of the antibody is 10 occurring in the graft in some settings with helper 11 cells, et cetera. So that's one issue. 12 I want to just mention, I just want to mention 13 one other thing in the first part of this question. If 14 acute AMR and chronic AMR is a continuum -- well, I 15 don't think it necessarily is a continuum. We've heard 16 that acute AMR usually responds to therapy, and chronic 17 AMR is not usually preceded by acute AMR. 18 I think the salient question is when a patient 19 comes in at year 1 or 2 and has antibodies in the 20 circulation, how do you decide what to do with that 21 patient? You know that patient is at risk for getting 22 chronic antibody-mediated rejection, but how do you</p> | <p style="text-align: right;">Page 137</p> <p>1 DR. HAAS: Okay. Well, three responses. One 2 to Dr. Gaston. I agree 100 percent that the cell- 3 mediated component is indicative of under- 4 immunosuppression. And there was actually a good deal 5 of work presented at the most recent Banff meeting, 6 that whether i-IFTA is truly chronic active cell- 7 mediated rejection or not, it seems to be a marker for 8 inadequate immunosuppression, and whether by the time 9 we detect it, it's too late to correct that or not, we 10 really need clinical trials to determine the response 11 of i-IFTA to correcting immunosuppression, but it 12 clearly is associated with under-immunosuppression. 13 The second point, raised by Bob Colvin and 14 others in terms of the continuum between acute and 15 chronic antibody-mediated rejection and whether these 16 are not a continuum, I think points out to maybe the 17 inadequacy of the current Banff classification, which 18 only has two forms of antibody-mediated rejection. 19 There's an acute form and there's a chronic 20 form. And maybe acute and chronic may not be a 21 continuum in all cases, but that maybe the active 22 smoldering form, which clinically is not acute, but in</p> |

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1 the Banff classification is graded as acute, may be on
 2 a continuum with the chronic form.
 3 So some acute is on a continuum with chronic,
 4 and that's the smoldering form, but other acute, which
 5 is the rebound kind of effect that's more easily
 6 treated, may not be a continuum with chronic antibody-
 7 mediated rejection.
 8 DR. VELIDEDEOGLU: Just one question. As far
 9 as I've seen in the publications, one of the
 10 overlapping areas between antibody-mediated rejection
 11 and cellular rejection I believe might endarteritis or
 12 intimal arteritis.
 13 DR. HAAS: And this I think also points out
 14 some of the limitations of histology because if you
 15 look at endarteritis, especially isolated endarteritis,
 16 where you see endarteritis with little or no tubulitis,
 17 this has traditionally in the Banff been called cell-
 18 mediated rejection, although there is data that has
 19 come out from the Paris group that has found that some
 20 of these cases appear to be associated with antibody,
 21 and the combination of antibody and endarteritis tends
 22 to have a worse prognosis than endarteritis alone.

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1 But where I think we're really dealing is that
 2 if we look at endarteritis from a molecular standpoint,
 3 and there was a very nice paper that was published I
 4 believe in the JASN from the Halloran group just a year
 5 or two ago where they looked at their TCMR classifier,
 6 molecular TCMR classifier, and molecular antibody-
 7 mediated rejection classifier in lesions with
 8 endarteritis, particularly isolated endarteritis, they
 9 found that some of their lesions were strong in the
 10 TCMR classifier and some were stronger in the antibody-
 11 mediated rejection classifier, yet histologically these
 12 lesions look the same. And the ones that were stronger
 13 in the T-cell-mediated classifier tended to be more the
 14 early isolated endarteritis, whereas later isolated
 15 endarteritis was almost always antibody-mediated
 16 rejection.
 17 So, again, you can have the same lesion or
 18 virtually the same lesion histologically be
 19 predominantly a T-cell-mediated rejection or an
 20 antibody-mediated rejection or both, depending on the
 21 time posttransplantation that this occurs. So, again,
 22 we need to take into account more than histology, but

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1 also the clinical course of the patient. And hopefully
 2 the molecular classifiers will be coming online, too,
 3 because these clearly, as I'll show in my talk
 4 tomorrow, seem to add to the predictive ability of
 5 histology to predict the patient's clinical course.
 6 DR. VELIDEDEOGLU: Thank you for all the
 7 comments. Now we have to stop here in the interest of
 8 time. And we have actually now it's down to 12
 9 minutes. We have a 12-minute break. And we will try
 10 to reconvene sharp at 10:40 if possible, please.
 11 DR. ALBRECHT: As people go to their break, I
 12 would like to mention to the invited speakers,
 13 including our patient representatives, we do have a
 14 speaker-ready break room for you. It's room 9224,
 15 9225, it's outside the door to my right here. This is
 16 for the invited speakers and patient representatives.
 17 Hi. I would just like to ask the invited
 18 speakers and patients to listen for a second. We've
 19 been told by the conference center that for the invited
 20 speakers and patient representatives, they do have an
 21 offer for a boxed lunch, four choices, smoked turkey,
 22 Caesar salad, chicken Caesar salad, sliced roast

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1 sirloin, or veggie, and these boxed lunches are
 2 available for \$20. And if you're interested, please
 3 order them in front of the room, there's a gentleman
 4 named Devon (ph) who is sitting at a table and can take
 5 your orders. Again, this is for our invited speakers
 6 and patient representatives. People can go now.
 7 (Break.)
 8 Part II
 9 DR. VELIDEDEOGLU: The time is 10:50 now, and
 10 we are starting the Part II of Session 1. And the
 11 first two talks are going to be given by Dr. Mark
 12 Stegall, from Mayo Clinic. And I believe he combined
 13 two topics into one talk. In brief, it's about the
 14 utility of protocol biopsies in the follow-up of acute
 15 AMR and tailored immunosuppression based on routine DSA
 16 monitoring.
 17 The Utility of Protocol Biopsies in the
 18 Follow-up of Acute AMR and in the Detection of Chronic
 19 AMR
 20 DR. STEGALL: I want to say thank you to the
 21 FDA for having this workshop. And I'm also thanking
 22 them to give my talks today. I'm not going to be here

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| <p style="text-align: right;">Page 142</p> <p>1 tomorrow, I know it's breaking everybody's heart, but 2 actually my wife is making me go to England. Her 3 goddaughter is getting married, and we tried to move 4 the wedding, but we just couldn't pull it off. 5 (Laughter.) 6 DR. STEGALL: My disclosures is also the 7 largest amount of money I've received recently is the 8 FDA flew me to D.C. It has nice lodging. So if I say 9 anything about the FDA, you have to take that into 10 consideration. 11 The goals of the workshop have been 12 delineated. I thought I would actually, since I'm not 13 going to be here tomorrow, I would actually comment on 14 this, get my comments out of the way. And the idea of 15 nonadherence and the development of de novo DSA and 16 antibody-mediated rejection, I would say that from the 17 Mayo Clinic we agree, but also remember that not all 18 patients are nonadherent who have this process. 19 And the nonadherent patients, I think that 20 we've actually been able to treat their cellular 21 rejection and get them back on immunosuppression. And 22 in many cases, their primary problem is persistent</p> | <p style="text-align: right;">Page 144</p> <p>1 understand the pathologic process better than we have. 2 So this is a meeting on antibody-mediated 3 rejection, right? And it's kind of amazing, when I 4 look back to think about this talk, a decade ago, Jim 5 Gloor and our group, we wrote this paper on transplant 6 glomerulopathy, and it was a big deal at the time 7 because we were really trying to figure it out. Most 8 people were interested in interstitial fibrosis at the 9 time. And over here we said that originally classified 10 as a variant of chronic allograft nephropathy of 11 unknown etiology, TG is now recognized, yada yada yada. 12 Actually, we were just beginning to figure out 13 what transplant glomerulopathy was, what the histology 14 was, and then we figured out that there was this 15 spectrum, that there was this peritubular capillaritis. 16 I think Mark Haas was one of the first people to write 17 about this, and Alexandre Loupy's group coming from 18 Paris. And amazingly this was all done prior to DSA 19 testing. We were really groping around in the dark 20 about a decade ago, and I think even 3 years later when 21 we had this meeting, we were just in that really foggy 22 phase where we didn't have a lot of data.</p> |
| <p style="text-align: right;">Page 143</p> <p>1 ABMR, and that's kind of my comment on that. 2 The other goal of the workshop was to discuss 3 new developments such as non-HLA antibody and the 4 routine posttransplant DSA monitoring. And I think the 5 status of this has been mentioned. A lot of our 6 sensitized patients don't have a lot of DSA floating 7 around, but it's very difficult to show, that we almost 8 never find non-HLA antibodies, so we're sort of 9 skeptical about that. 10 We do a lot of posttransplant DSA monitoring. 11 And I say it would be a lot more important if there was 12 actually effective therapy for it, but we see a lot of 13 stuff that we can't treat, and a lot of people treat a 14 lot of stuff because they get nervous about it. So 15 there's that. 16 The other goal of the workshop was to discuss 17 the natural course of acute ABMR continuum and its 18 temporal association with cellular rejection and 19 changes in GFR. And actually Mark Haas and a few 20 people set me up because what I want to talk about is 21 it's a major source of confusion. I think that most of 22 it is just the terminology is poor. I think we</p> | <p style="text-align: right;">Page 145</p> <p>1 And I think what's happened is in the last 2 decade is there's a consensus that this acute active 3 antibody-mediated rejection, this peritubular 4 capillaritis and glomerulitis, which, of course, is not 5 totally specific for antibody, but if you see it in a 6 patient who's had antibody, et cetera, that this 7 microvascular inflammation is pretty highly correlated 8 with whatever you want to call it terminology-wise, but 9 it's antibody-mediated injury. And the other thing is 10 that the demarcation between acute and chronic really 11 is the presence of transplant glomerulopathy. It's not 12 a clinical scenario, it's basically a biopsy finding, 13 and that came out I think the jungle of Brazil at a 14 Banff meeting that I did not attend, so we're still 15 skeptical about how that actually came to occur. 16 So, again, this is the Banff criteria, and 17 again the difference between acute active -- and you 18 have to have all three features, and our patients don't 19 tend to read this paper, so they tend to have all sorts 20 of variants of this. So we try to give this to the 21 patients at time of transplant so they'll come back 22 with the right diagnosis, but they don't. And then the</p> |

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| <p style="text-align: right;">Page 146</p> <p>1 chronic active is basically transplant glomerulopathy. 2 But we do have a paradigm I think that is 3 emerging in this field, and the paradigm starts like 4 this, is that there is donor-specific antibody of some 5 sort, and that leads to microvascular inflammation, 6 peritubular capillaritis, and glomerulitis. Our 7 protocol biopsies have probably shown us that that can 8 actually precede the development of transplant 9 glomerulopathy, but if you look closely enough, if you 10 look electron microscopically, you can actually see 11 ABMR ultrastructurally before you can see it by light 12 microscopy because it's 1,000 more times sensitive. 13 And then at some point, you get declining GFR and graft 14 loss. 15 And, again, patients don't read the books. 16 They get lots of different things in addition to this 17 one isolated problem. They get a bad kidney or they 18 get polyoma virus or they get a lot of other things 19 going on. But this is the paradigm. 20 The other thing that's important as we talk 21 about this at a meeting like this is sometimes we get a 22 little sloppy in our clinical scenarios and</p> | <p style="text-align: right;">Page 148</p> <p>1 So much more commonly, but I think it becomes 2 much more of a mixed bag of patients, is a couple of 3 years to 5, 6, 7 years after transplant, somebody comes 4 in with an elevated creatinine or for some reason they 5 get a protocol biopsy, and that biopsy shows active 6 ABMR, it looks a lot like early acute ABMR actually, 7 and these patients, of course, tend to be de novo DSA 8 patients. We also see it in our presensitized patients 9 when they get protocol biopsies down the line. The DSA 10 levels can be kind of all over the place. 11 And I say this over and over again, the fact 12 that we're here today is the fact that there is no 13 effective treatment for this. So you can have your 14 ideas about how to treat it, but it's just not very 15 commonly treated. Histology, again, it's commonly 16 mixed ACR and ABMR. Again, nonadherence. A lot of 17 these people show up and they haven't been taking their 18 meds, but some of them show up and they have been 19 taking their meds. 20 And the thing about this is there is a bit of 21 a controversy about the incidents, but if it's greater 22 than 10 percent by 5 years in tacrolimus-treated</p> |
| <p style="text-align: right;">Page 147</p> <p>1 terminology. And I think it's important to remind this 2 group that there are really different clinical 3 scenarios where you have somebody who's diagnosed with 4 antibody-mediated rejection. There is this early acute 5 ABMR, which a lot of people have written a lot papers 6 around the table here. We definitely have, which is 7 that early rise in creatinine in the first 14 days 8 after transplant, this is almost always in 9 presensitized patients who have high levels of DSA 10 either going in or at some point. It's quite 11 reversible because it tends to be due to plasmablasts 12 that jump up the antibody levels, and sometimes the 13 antibody levels most of the time will come back and be 14 manageable. And, again, it's more of a pure ABMR on 15 biopsy that you see. 16 This is actually kind of rare except for a few 17 crazy programs that do desensitization. Most places 18 will see maybe one or two of these a year. So it's 19 hard to do a clinical trial where kidney transplant 20 programs are seeing one or two patients a year because 21 someone like Arjang has to be there for that weekend to 22 get that patient enrolled.</p> | <p style="text-align: right;">Page 149</p> <p>1 patients, then I think you probably should follow your 2 patients closer because I think that this should be 3 about that. 4 So you have these two different clinical 5 scenarios. And what happens is the histology of these 6 early acute and late active or late acute look a lot 7 alike, and I think that that's a bit of the confusion 8 that goes along in the terminology. And, again, the 9 difference between late active and chronic is the 10 presence of transplant glomerulopathy. 11 Okay. So that's a little bit, because I'm 12 supposed to be talking about histology, right? And 13 when you talk about histology, when you talk about the 14 Banff 2013 criteria, there are these three things that 15 are used. The first one, histologic evidence of this 16 acute -- that's the PTCitis Gitis score. And I think 17 that in our hands, we would say that that's very 18 important in prognosis. 19 And, again, I think that the biopsies are 20 basically a biomarker to look forward to see how the 21 patient is going to do after they get their biopsy. 22 This C4d staining is actually quite variable</p> |

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| <p style="text-align: right;">Page 150</p> <p>1 especially if you do late biopsies, protocol biopsies, 2 but it's in there. Almost all of the early ABMRs that 3 we see in sensitized patients with C4d-positive, and 4 it's not the case with late ones. 5 And then serologic evidence of donor-specific 6 alloantibodies is actually not histology at all, it's 7 that they would like to have something else to 8 corroborate this. And I think that our group and the 9 Hopkins group said back in the day, even in positive 10 crossmatched patients, a lot of those patients will 11 lose their antibody in the serum in a year, and I don't 12 think that they have actually lost the antibody, it's 13 probably in the graft. 14 So nothing is perfect, right? And it's not 15 going to be. This is clinical medicine. 16 So microvascular inflammation has the highest 17 correlation with graft loss. We use this combination 18 of graft loss, or 50 percent decline in eGFR in the 19 following 2 to 5 years. So that's something. It's not 20 perfect, but it's something. 21 If you look at DSA development, DSA, by the 22 currently FDA-approved assay, has a relatively lower</p> | <p style="text-align: right;">Page 152</p> <p>1 get some therapy that would be treatable for ABMR. 2 So the talk I was supposed to give is, "The 3 Utility of Protocol Biopsies in the Follow-up of Acute 4 AMR and Detection of Chronic ABMR." And I think I may 5 be on time. So the question came up, Does early acute 6 lead to late chronic? And we get papers back reviewed 7 that everybody knows that it does. And we thought it 8 might. But the question really is, is it just an 9 association? Are the same people who get early acute 10 the same people who get late chronic, but it's not 11 causal? 12 And we did a little study with eculizumab a 13 few years ago, and then we did a follow-up paper, and 14 we basically can summarize it saying preventing early 15 acute clinical ABMR does not prevent chronic ABMR in 16 patients with preexisting DSA. This is in AJT. Lynn 17 Cornell put a bunch of this together. 18 And just to run through it quick, we had 19 eculizumab, 30 patients, control group, it was a 20 historical control group. They had a fair amount of 21 antibody. Their total antibody at the time before we 22 started pheresis was about 10,000 MFI. So I think</p> |
| <p style="text-align: right;">Page 151</p> <p>1 correlation with outcome. In fact, not all people with 2 DSA have inflammation. Non-HLA antibody possibly is 3 out there, but is it possibly just the case where you 4 can no longer detect a lot of serum DSA? 5 And then there are these other biopsy issues 6 that I talked about, which C4d has a high correlation 7 with outcome, Bob Gaston showed that, but it also 8 misses a lot of patients. So if you're looking for a 9 biomarker, you don't want to be missing a lot of 10 patients that will progress. 11 And I agree that all DSA is a product of T- 12 cell-dependent immune response, but we really may not 13 detect ACR on biopsy in a lot of these patients. T 14 cells, homes to sites of inflammation in ABMR. And I 15 do throw it out there for discussion, that if you 16 really have borderline or a small amount of T-cell- 17 mediated rejection by itself, that generally has a 18 pretty poor -- pretty good prognosis actually, and 19 compared to ABMR, which has a very dismal prognosis. 20 So it's really a matter when you're a 21 clinician, is, what are you going to treat? And I 22 think that if we were designing therapy, I would try to</p> | <p style="text-align: right;">Page 153</p> <p>1 these patients were truly sensitized. 2 They got eculizumab for the first month, all 3 of them. If the B flow crossmatch was less than 200, 4 we stopped it, and if it was greater than 200, we 5 continued it because at the time we didn't know 6 anything about what we should be doing, we just wanted 7 to get them off this really expensive drug and also 8 possibly not have the risk of infection. 9 So it turns out that when we did this, we had 10 biopsy-proven acute clinical rejections, in the paper, 11 which is an increase in creatinine over .3, so this is 12 clinical, we call this clinical. You had to have a 13 biopsy. The first 3 months, the control group had 40 14 percent rejection, and eculizumab had 6.7 percent 15 rejection. 16 And there have been other studies that do, but 17 the problem is they didn't have a high enough rejection 18 rate in the control group to show a difference, but I 19 think those of us who have used eculizumab are fairly 20 impressed with what it can do in these patients. And, 21 again, eculizumab was given for a minimum of 1 month 22 and continued if the antibody levels were persistent.</p> |

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| <p style="text-align: right;">Page 154</p> <p>1 And what happened was we prevented antibody-</p> <p>2 mediated rejection, which was actually a good thing.</p> <p>3 These patients became much easier to take of. Long-</p> <p>4 term graft survival was not changed in these patients.</p> <p>5 And as we looked at it, the problem is, is that we</p> <p>6 didn't prevent this smoldering antibody-mediated</p> <p>7 rejection, if you want to call it that.</p> <p>8 And so if you look at the peritubular</p> <p>9 capillaritis, moderate to severe in these patients,</p> <p>10 control is in that sort of crimson color, and the blue</p> <p>11 is the eculizumab patients. And so they still have</p> <p>12 this smoldering -- they never had that early acute</p> <p>13 rejection, but they do have the smoldering.</p> <p>14 Transplant glomerulopathy was actually higher</p> <p>15 in the control group, but it was not prevented in the</p> <p>16 eculizumab group. So you can avoid this early</p> <p>17 catastrophic event and still get long-term injury.</p> <p>18 And the C4d is another thing. I throw this in</p> <p>19 here. Why we're not in love with C4d is because,</p> <p>20 again, it seemed to be a lot lower than the other</p> <p>21 histologic lesions.</p> <p>22 So this is Figure 7 of this paper that Lynn</p> | <p style="text-align: right;">Page 156</p> <p>1 levels of DSA needed complement activation in order to</p> <p>2 cause the inflammation and the graft damage to get</p> <p>3 transplant glomerulopathy, where if you had high</p> <p>4 amounts of antibody, it didn't matter whether you had</p> <p>5 complement blockage or you had complement, the kidney</p> <p>6 was going to get damaged.</p> <p>7 So I think that lessons learned from</p> <p>8 eculizumab -- and it was asked from me, "What can you</p> <p>9 learn from protocol biopsies?" And I think that you</p> <p>10 can learn a lot from protocol biopsies. I think that</p> <p>11 you can learn that preventing early clinical ABMR does</p> <p>12 not prevent chronic ABMR. And, again, these are</p> <p>13 subclinical cases almost all the time.</p> <p>14 You learn that complement blockade may prevent</p> <p>15 injury in patients with low levels of DSA, but high</p> <p>16 levels of DSA patients are not as complement-dependent.</p> <p>17 So I think that you can learn a lot. I think that give</p> <p>18 you some sort of signpost of where to go with some of</p> <p>19 this research in small numbers of patients, because</p> <p>20 you're never going to get a big prospective randomized</p> <p>21 trial to teach you all of this, at least not at the</p> <p>22 beginning.</p> |
| <p style="text-align: right;">Page 155</p> <p>1 Cornell wrote, is a great figure in my mind that I</p> <p>2 like, and nobody else likes, but it's pretty common</p> <p>3 nobody likes my ideas. So what it was is we looked at</p> <p>4 the control patients, and if you had at 6 months a B</p> <p>5 flow crossmatch that was less than 200 -- let's see if</p> <p>6 I can show this.</p> <p>7 So let's look at this. So you had a B flow</p> <p>8 crossmatch in the control groups less than 200. A fair</p> <p>9 number of these patients got transplant glomerulopathy</p> <p>10 by 1 year. So they had low levels of antibody at 6</p> <p>11 months. They should have done well, right? But they</p> <p>12 went ahead and got transplant glomerulopathy.</p> <p>13 When you looked at the eculizumab-treated</p> <p>14 patients, you still got transplant glomerulopathy in</p> <p>15 the people at high levels of DSA because these patients</p> <p>16 are pretty wound up and are going to have transplant</p> <p>17 glomerulopathy eventually. But even if you got a short</p> <p>18 course of this, you actually didn't get transplant</p> <p>19 glomerulopathy, which was counterintuitive because we</p> <p>20 thought those patients maybe should have never gotten</p> <p>21 eculizumab, they never had rejection, and therefore</p> <p>22 they didn't the drug. But it could be that the low</p> | <p style="text-align: right;">Page 157</p> <p>1 And I think that, more importantly, protocol</p> <p>2 biopsies help us delineate progression of chronic</p> <p>3 injury in many different facets of transplant. They</p> <p>4 can actually provide some indication of who to treat.</p> <p>5 And now it's a question about, Do we have the drugs to</p> <p>6 treat patients?</p> <p>7 So the other question is, Discuss the natural</p> <p>8 course of acute/chronic AMR continuum and its temporal</p> <p>9 association with cellular rejection and changes in GFR.</p> <p>10 And I think that there is an emerging paradigm, a</p> <p>11 different group of patients, not this early, on the</p> <p>12 left side of that graph, but the ones on the right side</p> <p>13 of that figure that I made, that late after transplant,</p> <p>14 many patients present with a combination of ACR and</p> <p>15 ABMR on biopsy, and this is a real clinical entity.</p> <p>16 And ACR may be the primary cause of the acute rise in</p> <p>17 creatinine in these patients. Also, they just could be</p> <p>18 dehydrated or their Prograf level got high, and you</p> <p>19 call that a biopsy for cause; half the time that's it.</p> <p>20 But I think what's happened is if at some</p> <p>21 point ABMR becomes the primary cause of late graft loss</p> <p>22 in this setting, in a nonadherent patient, they're</p> |

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| <p style="text-align: right;">Page 158</p> <p>1 having an acute cellular immune response against the 2 graft, which you actually might be able to treat, but 3 what you're left with at the end of the day is a 4 patient who has persistently high DSA, just like you do 5 in that positive crossmatch patient 14 or 16 days after 6 kidney transplant, and that leads to that paradigm of 7 PTCitis, CG, and graft loss.</p> <p>8 So the mechanism of DSA development. I do 9 believe it's T-cell dependent. Its nonadherence 10 actually definitely must play a role, but I think that 11 it may persist after the treatment or resolution of 12 cellular responses. I think Matt Everly has a paper 13 that he did from East Carolina that the biggest risk 14 factor in that patient population was polyoma virus, 15 and that was the reduction of immunosuppression to 16 treat polyoma.</p> <p>17 So there are multiple pathways to having the 18 immune system become activated. I think we've just 19 become so accustomed to being able to block cellular 20 rejection that we forget that it actually has evolved 21 over hundreds of millions of years.</p> <p>22 Planned reduction immunosuppression, such as</p> | <p style="text-align: right;">Page 160</p> <p>1 getting this paradigm of chronic injury due to 2 antibody.</p> <p>3 So let's talk about de novo DSA. I'll go over 4 this real quick. The incidence varies with the patient 5 population studies, somewhere at 13 to 22 percent. I 6 think that some of these older publications included a 7 lot of patients on cyclosporine. They also included a 8 lot of patients who were never tested at the time of 9 transplant for single-antigen beads and DSA because it 10 was a different era. So I think overall we're 11 transplanting patients with less antibody, probably a 12 cleaner population today.</p> <p>13 And I think that we've gone through this all, 14 but the last one is DSA-positive patients who do not 15 develop ABMR on biopsy. I think more and more it's 16 getting to be they do pretty well in the short term, 17 but if you get a person with de novo DSA and you do a 18 biopsy -- and the way that we handle these patients, 19 our standard of care is to monitor antibody yearly, and 20 if a person has antibody, a new antibody, in the 21 circulation, we'll bring them in and do a biopsy. And 22 if the biopsy shows this, we get nervous.</p> |
| <p style="text-align: right;">Page 159</p> <p>1 polyoma virus, cancer, minimization/tolerance protocols 2 are also another way you get there.</p> <p>3 And I think that at Mayo Clinic we actually 4 have people who come back for their appointments and 5 take their medicines, a unique group of patients, I 6 guess, but we'll take any of those that you would like 7 to refer to us. And some of those people come in with 8 antibodies to their graft. And I actually believe them 9 that they are taking their medicines, I don't think I'm 10 trying to undercut them. So nature finds a way.</p> <p>11 And I think the other thing is treating acute 12 cellular rejection does not prevent late graft loss 13 from antibody-mediated rejection. I think we've got to 14 figure that out.</p> <p>15 So what you're left with, you're left with 16 patients with DSA, and other problems are taken care 17 of. And so maybe now we can go to work. Maybe there 18 will be a lot of other people in this room will work on 19 adherence and a lot of other things. I'm a surgeon, I 20 usually don't get to go to those kind of clinics, which 21 is good. And what we end up with is this, a patient 22 who already has DSA, and they're on their way to maybe</p> | <p style="text-align: right;">Page 161</p> <p>1 And the paradigm here I think is that 50 2 percent of patients with DSA will develop ABMR within 3 about a year of developing it. It's definitely more 4 common with all the things that's been talked about 5 this morning, but none of those assays are FDA 6 approved, so we're not really doing a lot of those.</p> <p>7 But I think the last one is that if you're 8 DSA-positive and ABMR-negative, it doesn't mean you're 9 never going to get in trouble, it just means in the 10 short term you're going to do pretty well. And I think 11 that from a clinical trials perspective, if you treat 12 everyone with de novo DSA, you won't have an endpoint 13 that you can really measure outcomes out there very 14 well.</p> <p>15 So Carrie Schinstock, who is Jim Gloor's 16 replacement, came and has put together our de novo DSA 17 data, and it uses protocol biopsies, which I guess is 18 one of the reasons I'm here. And so this paper in AJT 19 is 967 patients that are in 2007 to 2014. So the 20 reason this era was chosen is because they're all 21 tacrolimus patients and they all had single-antigen 22 bead testing throughout their transplant, so they had</p> |

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| <p style="text-align: right;">Page 162</p> <p>1 it at the time of transplant. So this is kind of state 2 of the art. 3 We actually only had 54 patients in a mean 4 follow-up of 4.2 years, and they also got surveillance 5 biopsies and included everything else. So 54 patients 6 who had de novo DSA. So a pretty low incidence. And 7 if you look at it, it's about, I think conservatively, 8 about 2 percent per year developed de novo DSA today. 9 That's still 10 percent incidence at 10 years. And I 10 do think that, is de novo DSA lower in tacrolimus- 11 treated patients? And also, but it also may be a 12 function of our DSA testing. Again, low levels of DSA, 13 people with memory, finally get up and have a response. 14 So it's not good to have de novo DSA, 15 everybody knows that. Even in compliant patients, they 16 do less well. And if you do surveillance biopsies 1 17 year after the detection of de novo DSA, 50 percent of 18 those patients had acute active ABMR and a normal 19 creatinine, but what happened is 37 had already, Bob, 20 had cABMR, had some transplant glomerulopathy. Usually 21 it's pretty mild at this stage, but it nevertheless 22 does exist.</p> | <p style="text-align: right;">Page 164</p> <p>1 other etiologies. 2 So I'm sort of saying that we're going to 3 catch most of the patients that are going to do poorly 4 if we do de novo DSA testing and then do a biopsy once 5 they have de novo DSA. Make sense? So this is kind of 6 getting toward, "How do we get there?" 7 Tailored Immunosuppression Based on Routine 8 DSA Monitoring (both in sensitized and nonsensitized 9 patients) 10 DR. STEGALL: So then people ask -- the next 11 talk I was supposed to give is "Tailored 12 Immunosuppression Based on Routine DSA monitoring." 13 And the answer is nothing works. So the treatment of 14 ABMR, again, no proven therapy exists. Why else would 15 we be here? If there was therapy, we would be here for 16 some other reason. 17 So what we do at Mayo Clinic primarily is we 18 optimize tacrolimus and MMF. We only use IVIG or 19 plasma exchange if there is acute graft dysfunction. 20 And some might treat it if it occurs early after 21 transplant or if the biopsy shows a little chronic 22 injury.</p> |
| <p style="text-align: right;">Page 163</p> <p>1 And I think that this is the slide -- this is 2 the figure from the table. I would say that every 3 paper has one table that's the entire paper, and this 4 is that from this paper, and it tells you basically is 5 2-year outcomes after de novo DSA detection. So this 6 is possibly a timeframe when we could do a clinical 7 trial, is you could detect de novo DSA and follow the 8 patients for a couple years. And 34.5 percent of the 9 patients who had de novo DSA who actually had antibody- 10 mediated rejection on their biopsy at either the time 11 of detection or within a year, 34.5 percent of those 12 had graft failure or 50 percent decline in GFR by 2 13 years. So now you're getting to numbers that might 14 actually have an endpoint that you could follow. Now, 15 not everybody had graft loss. Only 20 percent had 16 graft loss. 17 Over here, there were no graft losses in the 18 people who had de novo DSA and no AMR, but actually 19 some of them probably did develop something over time 20 because 18 percent of those had a decline in GFR over 21 time. The people with no DSA, there are still people 22 who have a decline in GFR over a 2-year period from</p> | <p style="text-align: right;">Page 165</p> <p>1 I think the desire to treat in this area is 2 because that you know the kidney is not going to do 3 well long term, and yet there really isn't a lot that's 4 that effective. I think we all kind of know that 5 plasma exchange, IVIG, and all the rest is probably not 6 doing a lot to these grafts. So, again, did I say no 7 proven effective therapy? There's no proven effective 8 therapy. 9 And there's more than one study. And people 10 kind of have a nickel's worth of effects sometimes in 11 this area. Really, patients don't need a nickel's 12 worth of effect, right, guys? You need your kidney to 13 work a lot longer than that. You need it to kind of go 14 away. And so we need better therapy. 15 So the goals of the workshop were to discuss 16 unmet medical needs and trial design. So I have 5 17 minutes and 22 seconds to talk about this, about what a 18 clinical trial would look like. And I think the 19 problem in this, again, gets back to this thorny issue 20 about these patients are a mixed bag, and which 21 patients aren't. Fifty percent is caused by 22 nonadherence, some have these other problems. You have</p> |

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| <p style="text-align: right;">Page 166</p> <p>1 this.</p> <p>2 So how do you get patients in a study? And we</p> <p>3 suggest that you have to get all those other problems</p> <p>4 cleared up before you can start the study, but that's</p> <p>5 okay, I think we can do a lot to get patients to the</p> <p>6 point where we can look at them.</p> <p>7 And I think a conservative estimate, many</p> <p>8 studies in transplant overestimate the patient, the</p> <p>9 incidence of the problem, and then they end up with no</p> <p>10 enrollment, which is not good. And so we think 2</p> <p>11 percent per year is probably good, 10 percent incidence</p> <p>12 at 5 years.</p> <p>13 And I'm asking the FDA at some point if they</p> <p>14 would help us out with this combined endpoint of graft</p> <p>15 loss and a 50 percent decline in eGFR as our clinical</p> <p>16 endpoint for this study.</p> <p>17 So surrogate endpoints, I'm advocating the</p> <p>18 histologic changes of cABMR are a good surrogate marker</p> <p>19 -- or ABMR, excuse me -- for allograft loss because</p> <p>20 they precede allograft loss by years. And they're</p> <p>21 pretty specific. Obviously there are other things that</p> <p>22 go on. And, alternatively, we could just use DSA</p> | <p style="text-align: right;">Page 168</p> <p>1 I think we're going to be talking about in the next</p> <p>2 couple of years that it's going to be a 50 percent</p> <p>3 reduction in MFI. That's not validated.</p> <p>4 So the incidence of graft loss with MFI at</p> <p>5 1,000 at 2 years is 18 percent. That's not a really</p> <p>6 huge endpoint. And C1q might be better, but, again,</p> <p>7 it's not yet approved. So if you look at the numbers</p> <p>8 for a DSA trial, if you look even for 50 percent of the</p> <p>9 patients who have a complete resolution of their DSA,</p> <p>10 just to study one drug, you would need 116 patients to</p> <p>11 just study one drug for the surrogate endpoint, and</p> <p>12 probably hundreds of patients to study the 2-year</p> <p>13 endpoint, and that's not feasible, we're not going to</p> <p>14 find those patients.</p> <p>15 The other study that might get done -- so the</p> <p>16 other thing I say, too, is DSA can resolve without</p> <p>17 treatment, it kind of goes away in these patients, and</p> <p>18 the rate of graft loss is low. So intervention trial</p> <p>19 number 2 that I would like to talk about is patients</p> <p>20 with de novo DSA that get a biopsy, following a little</p> <p>21 bit what Carrie Schinstock showed, and if they have</p> <p>22 antibody-mediated rejection on the biopsy, would go in</p> |
| <p style="text-align: right;">Page 167</p> <p>1 alone. And I think that what we're trying to do</p> <p>2 ultimately is prevent graft loss decline in GFR.</p> <p>3 And so chronic irreversible changes that need</p> <p>4 to be considered, this is another thing. If a biopsy</p> <p>5 has a lot of chronic changes, at Mayo, we're a lot less</p> <p>6 likely to treat. I wouldn't put those patients in</p> <p>7 clinical trials. Retransplant is probably a better</p> <p>8 option.</p> <p>9 And I think that Peter and his group have</p> <p>10 looked at this before. And the 5-year timeframe for</p> <p>11 DSA is probably pretty real. Eventually these patients</p> <p>12 with de novo DSA will lose their grafts, but 5 years is</p> <p>13 a long time for follow-up. So I think that we can</p> <p>14 probably use other clinical endpoints.</p> <p>15 I would talk about the surrogate being</p> <p>16 resolution of DSA versus resolution of antibody-</p> <p>17 mediated rejection on biopsy. If you use DSA's</p> <p>18 inclusion criteria, you're going to have to pick some</p> <p>19 MFI that's reasonable, yes/no. If you use 1,000, and</p> <p>20 then you have 6 months, treat, and recheck the DSA, and</p> <p>21 then the endpoint would have to be, as a surrogate</p> <p>22 endpoint, the resolution of the DSA, right? I don't</p> | <p style="text-align: right;">Page 169</p> <p>1 the trial; if not, you just follow and rebiopsy. And</p> <p>2 then the numbers start looking a lot better.</p> <p>3 And, again, I think that the power</p> <p>4 calculations for these, I would like to suggest that we</p> <p>5 might use complete resolution of antibody-mediated</p> <p>6 rejection or complete histologic response as the</p> <p>7 endpoint. If you look at that, you only need 28</p> <p>8 patients to show efficacy with one drug and a clinical</p> <p>9 study showing a clinical endpoint, you would have 90</p> <p>10 percent chance showing a Phase 3 clinical trial with</p> <p>11 just 128 patients in each group. So, again, these</p> <p>12 numbers are a little more feasible.</p> <p>13 And I was going to go through adaptive trial</p> <p>14 design, but I think that's the next phase that we</p> <p>15 should be looking at in this area where we basically</p> <p>16 have parameters for changing the trial. Small numbers</p> <p>17 of patients. And I think again we showed that as few</p> <p>18 as eight patients can be used to decide if a therapy is</p> <p>19 ineffective.</p> <p>20 And another thing is it enhances the efficacy</p> <p>21 that a single ongoing control group, where you can have</p> <p>22 multiple experimental groups, and therefore the vast</p> |

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| <p style="text-align: right;">Page 170</p> <p>1 majority of patients can be assigned to an experimental 2 group. 3 And minimizes the number of patients receiving 4 ineffective treatments and limits unnecessary treatment 5 risks. I think the FDA has gone on record saying they 6 like that aspect of it. 7 And it's cheaper. Drug companies don't have 8 to have people coming all the time wanting to do a 9 Phase 3 prospective randomized clinical trial in this 10 area, and I think that that's not the way to go. 11 And I'm frozen. There you go. 12 So remember this, you have 14 patients in each 13 arm. You actually can do a study where you have one 14 control arm and three treatment arms, and if they're 15 all ineffective, you only have to have 32 patients. If 16 they're all ineffective and you want to use combination 17 therapy, if one of the combos is working, you can 18 actually do the whole study with 74 patients, the whole 19 Phase 2 clinical trial with 74 patients. So we're kind 20 of thinking that that might be a smart way to do these 21 kind of studies. 22 So in summarizing, there are different</p> | <p style="text-align: right;">Page 172</p> <p>1 causes of graft injury. 2 You can assess the amount of chronic injury, 3 whether or not it's really worth putting this patient, 4 who's had polyoma and everything else, through another 5 round of therapy because maybe that's not the way to 6 go. 7 And in my mind, it's just a biomarker. That's 8 what a biopsy does. And it might assess response to 9 treatment, which I think is unknown, but it's something 10 that we need to try to approach. 11 So I think, most importantly, is if your 12 biopsy is normal, your chance of graft loss is low. So 13 we probably shouldn't be treating a lot of people with 14 normal biopsies or near normal biopsies. I don't think 15 you're going to have a very good endpoint for clinical 16 trials, and you probably aren't going to do a lot for 17 the patient. 18 So our conclusion is developing therapy for 19 antibody-mediated rejection is a major unmet need in 20 kidney transplantation. Validated surrogate markers 21 are needed. I think histology is a very good one. I 22 think clinical trials are feasible. And it's best to</p> |
| <p style="text-align: right;">Page 171</p> <p>1 clinical scenarios that antibody-mediated rejection 2 occurs. There is this early acute, late acute active, 3 and I think that we have to keep those in mind when 4 we're talking terminology. 5 I would also say that the first ones are 6 really hard to enroll. And we can talk about those in 7 a lot of different studies, but if you're looking at 8 all comers, that's going to be a hard study to do. I 9 think that the chronic injury is a much more pressing 10 need for transplant patients overall in this with 11 respect to ABMR. 12 This paradigm actually I think has some merit, 13 and I think the protocol biopsies are showing that that 14 is something that has emerged from those papers from 15 2007 to get to this point. I think that Jim Gloor and 16 I would have argued about this paradigm a lot back in 17 those days, but I think it really is emerging. 18 I think the biopsies are very important in 19 this field. And people talk a lot about genomics, and 20 we do genomics, but I think biopsies are really 21 important because you can rule out other causes of 22 graft injury. We have a lot of interest in other</p> | <p style="text-align: right;">Page 173</p> <p>1 employ adaptive trial design. 2 Thank you. 3 (Applause.) 4 DR. VELIDEDEOGLU: Our next speaker is Howard 5 Gebel, from Emory University. And the title of his 6 talk is, "Scientific Aspects: A General Overview of 7 the Currently Used Antibody Measurement Methods, Issues 8 of Standardization, Validation." 9 Scientific Aspects: A General Overview of the 10 Currently Used Antibody Measurement Methods, Issues of 11 Standardization, Validation 12 DR. GEBEL: Well, thank you to the organizers 13 for the opportunity to present here. I have no 14 financial relationships related to this presentation. 15 It's been about 50 years since Paul Terasaki 16 published his seminal paper that showed an overwhelming 17 association between positive crossmatches and 18 hyperacute allograft rejection. For the next 30 to 40 19 years, the assay that was used to detect those 20 antibodies was shown in this slide. And it's a 21 cytotoxicity crossmatch. 22 I'm showing you this slide specifically</p> |

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| <p style="text-align: right;">Page 174</p> <p>1 because half the cells are alive and half the cells are 2 dead. This is what we had to deal with. And what does 3 that mean? You can use the right kidney, not the left 4 kidney? Or that half the cells fix complement and the 5 other half don't? Of course, the answer is no. We 6 were just obligated to use this test because nothing 7 better existed.</p> <p>8 And we had numerous problems that we knew 9 right from the beginning. The sensitivity wasn't 10 optimal. We had false negative results. Specificity 11 was also not optimal with false positives. We got to 12 compose our own panels. Cells needed to be viable till 13 the end of the study. And typically we were restricted 14 to identifying Class I antibodies. And as we've heard 15 throughout this morning, Class II antibodies are very 16 relevant.</p> <p>17 So over the ensuing time, there has been a 18 dramatic evolution of the types of tests that became 19 available. And on the upper right side, the test that 20 has become the most used one today is a solid phase 21 assay that takes microparticles and coats them with HLA 22 antigens. And in this situation, we don't have to</p> | <p style="text-align: right;">Page 176</p> <p>1 the role of that antibody in a clinical situation.</p> <p>2 Now, what we thought is we could begin using 3 these assays to identify the pathogenicity of these 4 antibodies. And, in fact, we've seen this slide 5 multiple times already from Mark Stegall. And on the 6 right side, we see that we had some ability, we 7 thought, to quantify what the antibodies where, and 8 that once we got even over no DSA at all, between 5,000 9 to 10,000 and greater than 10,000, there was a 10 likelihood of antibody-mediated rejection. And one 11 began to think that we could compare these assays from 12 laboratory to laboratory. But it's not as simple as we 13 thought.</p> <p>14 So here is some data from a publication that 15 Elaine Reed led a couple of years ago. There are 16 numerous people who are on this publication. It 17 involved seven different HLA laboratories. And what I 18 want to show you highlighted in blue is what we looked 19 like before we attempted any standardization. We all 20 tested, as it turned out, sera that we each had in our 21 possession, the same exact sera, and we were all asked 22 to just perform the assay. And what you see is while</p> |
| <p style="text-align: right;">Page 175</p> <p>1 worry about other cell membrane-bound antigens that are 2 attached to a cell. We're looking exclusively at HLA 3 targets.</p> <p>4 And here are two types of assays that are 5 utilized. On the left side is an assay that's a 6 screening assay, and it's typically simply a yes or a 7 no. There's a little extra data in there. That bell- 8 shaped curve on the left side in purple indicates what 9 a negative reaction looks like. There are no 10 antibodies whatsoever. To the right of that, in pink, 11 are reactions from a patient who had antibodies, and in 12 this case, we say they reacted with 99 percent of the 13 beads. It tells us that there is a positive reaction; 14 it doesn't tell us what's positive. That's on the 15 right side of the slide.</p> <p>16 And here we're looking at a suspension array. 17 And as you look along the X axis, each one of those 18 numbers refers to a different bead, and each bead is 19 coated with a different HLA antigen. And as you go 20 from bottom to top, you are going up a scale that's 21 numerical from zero to about 25,000. And in general, 22 the stronger the antibody, the stronger, we think, is</p> | <p style="text-align: right;">Page 177</p> <p>1 we identified the same HLA antibodies in every case, 2 the coefficient of variation was 62 percent, and that's 3 not particularly impressive.</p> <p>4 There are a lot of reasons why laboratories 5 don't get identical results when testing the same 6 samples. We use different vendors for the source of 7 the beads. The antigen source on the beads is 8 different, it could be native or recombinant. The 9 expression of the antigen can differ from bead to bead, 10 whether it's confirmationally correct, how much is 11 there. I'm going to be talking about this in a while, 12 interfering factors that can bother us in terms of 13 interpreting a result. The reagents that we use aren't 14 standardized. There is certainly tech-to-tech 15 variation that will impact the outcome of the result. 16 And, finally, the protocols that are used from 17 laboratory to laboratory aren't truly standardized. 18 And so the assay conditions, even things such as 19 ambient temperature, can begin to affect our outcomes.</p> <p>20 So how did we do, once we did standardize 21 everything that we could, we used the same reagents, we 22 used the same protocol, the same technologists did the</p> |

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1 assay in each of these seven different laboratories --
 2 on the left side and right side are looking at single-
 3 antigen beads Class I and Class II with the
 4 standardized protocol. And you see under those
 5 circumstances that we got to a point where our CV was
 6 20 percent; still not particularly impressive, it
 7 wouldn't pass a chemistry test, but much, much better
 8 than we had.

9 Now, the fact is we could do this, we can
 10 standardize, but we don't. Right now, each laboratory
 11 is still using their own protocols, and we're not using
 12 standardized reagents across the board.

13 Now, one of the things that we have to
 14 consider is the other things that can impact our test
 15 results, and in particular, so-called interfering
 16 factors. And in its simplest form, interfering factors
 17 are going to interfere with our ability to detect
 18 antibodies.

19 Here is one example of an interfering factor.
 20 So shown on this slide is we have a matrix that's going
 21 to be your bead, and we have antigen on the bead, and
 22 in yellow is the patient's antibody binding to the

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1 bead. And here the interfering factor is complement.
 2 Complement fixes to the bead. Complement and
 3 the molecules that are deposited are big and they block
 4 the ability of that blue antibody to bind to the
 5 immunoglobulin that's attached to the bead. We can't
 6 see it, and it looks like there is no antibody there
 7 whatsoever.

8 If we do something to remove the complement,
 9 break up the complex so that instead of it binding to
 10 the bead itself, the red, green, and blue molecules are
 11 now dissipated, the antibody has the ability to bind to
 12 the bead. And in these circumstances, we've eliminated
 13 the interfering factor.

14 Here is just an example of how these
 15 interfering factors can present. And if you look in
 16 the middle of this complex slide, you see that there
 17 are lines that have gone from low to high, and what
 18 that means is as those interfering factors were
 19 removed, the ability to detect the antibodies are
 20 present. So something that had zero MFI, once it was
 21 treated to remove the interfering factor, came up to
 22 20,000. So you totally missed an antibody if you

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1 didn't get rid of the interfering factor.
 2 These are examples of the different things
 3 that can be used to remove interfering factors, such as
 4 EDTA, which will chelate the calcium, a necessary
 5 component of complement activation. We can heat and
 6 activate the complement. You can add dithiothreitol.
 7 You can heat and activate it, as I said. There are a
 8 number of different ways. There is no standardization
 9 and no mandate to do this from laboratory to
 10 laboratory.

11 So we've seen this slide multiple times, too.
 12 It's interesting that complement can block the ability
 13 to detect antibody, and at the same time, it has been
 14 reported that complement-fixing antibodies are the ones
 15 that we have to worry about the most.

16 So here we are just looking, comparing DSA to
 17 no DSA, and when you look at the DSA that fixes
 18 complement versus the DSA that doesn't fix complement,
 19 there's a huge difference. And so the interpretation
 20 is that it's due to the complement-fixing ability of
 21 these antibodies to cause the rejection.

22 If you look at little deeper into the

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1 supplement of this paper, there is some data I want to
 2 point out. And, in particular, the red line and the
 3 blue line indicate individuals who lost their graft,
 4 and the brown line and the yellow line are patients who
 5 did not lose their graft.

6 When you take a look more carefully, you see
 7 of the ones that did not lose their graft, 90 percent
 8 of the patients were made up of individuals who had MFI
 9 values of less than 6,000. And when you look at the
 10 ones who did lose their graft, 70 percent were greater
 11 than 6,000. And as I'll be showing you in a minute,
 12 greater than 6,000 could mean greater than 6 million.
 13 So it's not necessarily the complement-fixing ability,
 14 it's the level of MFI values.

15 Here is some data to back that up. This was
 16 done by Tom Ellis at the University of Wisconsin. And
 17 on the left side, we find out what happens when you
 18 take complement-fixing antibodies and dilute them. If
 19 you dilute them to a lower MFI value, they no longer
 20 fix complement. Alternatively, on the right side, if
 21 you take those same antibodies that did not fix
 22 complement and concentrate them, you can find that you

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| <p style="text-align: right;">Page 182</p> <p>1 can elevate their MFI values. Once you do that, they 2 fix complement. 3 Other things that are appearing in the 4 literature are focusing on subclasses of 5 immunoglobulin. And here there is a recent study that 6 came out of Carmen Lefaucheur's center where they were 7 breaking down the different subclasses of 8 immunoglobulin and associated them with either no ABMR, 9 acute ABMR, or subclinical ABMR. And on the right 10 side, you're seeing the subclasses that are associated 11 with the rejection or lack of it. 12 However, when you go a little bit deeper into 13 what these slides are actually showing, these 14 overlapping Venn diagrams will show you unequivocally 15 that the likelihood of finding any subclass by itself 16 is pretty remote. Everything is contaminated for the 17 most part with other subclasses. 18 And another important component of this is 19 when you look at these data, there were a total of 125 20 patients that were studied. Twenty-one of them did not 21 have a positive subclass at all, they couldn't find 22 one. Now, there are only four subclasses of</p> | <p style="text-align: right;">Page 184</p> <p>1 say even though all these antibodies were less 1,000, 2 there's something about them that makes us believe 3 there's a real antibody. Using the terminology that 4 everybody else is using, they share an epitope that is 5 common. 6 If we look at another assay, even though it 7 wasn't positive by this criteria, this is our screening 8 assay, under these conditions, the screening assay was 9 clearly positive, and using another flow-based assay, 10 flow cytometric-based assay, everything over the 11 vertical line is positive, you see several beads that 12 do show up as being positive. They're all part of that 13 reactive group, they're all part of the group that 14 expresses an antibody I'm concerned about. 15 What we think is happening when you have a 16 limited amount of antibody and a lot of target, like 17 you see on the right side, these are the single-antigen 18 beads, you are not looking at one bead, you're looking 19 at hundreds of beads at the same time, you're diluting 20 that antibody over a large surface area, and you don't 21 get a strong enough signal on any one bead. On the 22 left side is a positive reaction just using the</p> |
| <p style="text-align: right;">Page 183</p> <p>1 immunoglobulin, so this is something that did not work. 2 And so my question is, What are these? You have 3 several assay concerns under these conditions: that 4 the reagents that you're using aren't necessarily 5 appropriate, that they're not sensitive enough. And 6 from personal experience, I can tell you that these 7 reagents are very, very cross-reactive. And while I 8 believe there might be something here, I think it's 9 premature to use this in a fashion that we can rely on 10 100 percent of the time. 11 Recently, I published a personal viewpoint on, 12 "The Road to HLA Antibody Evaluation: Do Not Rely on 13 MFI." And what you need to remember is that beads were 14 never meant to be quantitative, they weren't approved 15 to be quantitative. Semi-quantitative, yes; 3,000 is 16 less than 4,000. But it is not quantitative because 17 what you have is an MFI value that reflects a given 18 bead's fluorescence, but it's not compared to a 19 standard. 20 So here's an example of a reaction where less 21 than 1,000 is not considered a positive response. And 22 I and some of my HLA colleagues can look at these and</p> | <p style="text-align: right;">Page 185</p> <p>1 screening beads, where is less target. 2 Finally, what about the MFI value itself? 3 Here, again from Tom Ellis, what we see is MFI values 4 that are virtually identical, about 14,000 in each 5 case. But we see when we begin to dilute them, there's 6 a big difference between the two subjects. The one on 7 top winds up staying at 14,000 no matter how much we 8 dilute it. The one on the bottom serially goes away. 9 Dr. Tambur I'm sure is going to be going over this in 10 much more detail in her presentation. 11 So I believe that we have a test that is 12 better than anything we've had in the past, but it's 13 not necessarily at the point where it's perfect. I do 14 believe that we can use this information, but we have 15 to know what its limitations are. We have a long way 16 to still go to make it more standardized. And we all 17 know the beginning of the Charles Dickens novel, A Tale 18 of Two Cities, the best of times, the worst of times. 19 Well, it was the best of tests, it was the worst of 20 tests. And my apologies to Dickens, I'll stop there. 21 Thanks. 22 (Applause.)</p> |

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| Page 186 | Page 188 |
| <p>1 DR. VELIDEDEOGLU: Our next speaker is Anat 2 Tambur, from Northwestern University. And the title 3 is, "Consideration of Quantitative Use of HLA Antibody 4 Assays and a Summary of the 2017 AST/ASHI Antibodies in 5 Transplantation Consensus Conference." 6 Consideration of Quantitative Use of HLA 7 Antibody Assays and a Summary of the 2017 AST/ASHI 8 Antibodies in Transplantation Consensus Conference 9 DR. ROITBERG-TAMBUR: Thank you. And being 10 Howie's student, I think it is very appropriate that I 11 am going to be speaking after him. And Howie called me 12 a few weeks ago, and I was like, "Our talk is going to 13 be very redundant. What do you think?" And, yeah, 14 there will be some redundancy, but I told Howie I'm not 15 concerned about this at all because I think there are 16 some points that we really need to make sure that the 17 message goes across to the clinician and how they are 18 using this. 19 So I hope there will be some new things here 20 and that I can strengthen some of the message. 21 These are my disclosures here. 22 And my topic was specifically to talk about</p> | <p>1 posttransplantation when we're thinking about, do we 2 have an antibody-mediated rejection or not? And when 3 we're treating it, to monitor those responses. 4 And a lot of people are talking about the 5 strength of antibody as a predictor for long-term 6 outcome. And let me tell you, coming from Chicago, 7 this is going to be even more difficult from trying to 8 predict the weather in Chicago, not just for 5 years 9 down the road, but sometimes also for tomorrow. Only 2 10 weeks ago we had a 70 percent day followed by a 50 -- 11 sorry -- 70 degrees day followed by a 50 degrees day 12 followed by a 30 degrees day. 13 The antibody, the transplant, everything 14 surrounding it is a very active process with a lot of 15 moving parts to it. And I think we will be amiss if 16 we're trying to look at a snapshot and try to make 17 predictions with this. But I do think antibodies can 18 help us as a monitoring tool in conjunction to a lot of 19 other things. 20 So what is realistic to expect from the assay? 21 And I know Howie talked about the assay. And I want to 22 very quickly kind of go through this. We have the</p> |
| Page 187 | Page 189 |
| <p>1 trying to quantify the assays. And I was trying to 2 think about, when will be the times that we need to 3 quantify the assay? And I know a lot of centers, all 4 they want to know is, "Do I have an antibody or not? 5 Can I go ahead with this transplant?" But I think 6 there are a lot of times that we do need to quantify 7 the antibodies. 8 So part of it -- and I apologize, it doesn't 9 project very well -- is really for the pretransplant 10 testing period. And this is something that we might 11 want to use immediately to make a decision whether we 12 go into transplantation. 13 But I think when we are talking about 14 measuring antibodies, it's really important to try to 15 get a sense of how much antibody we have, because it's 16 not a yea or a nay, or a black and white, we're talking 17 about a very significant gray scale, is to look at a 18 patient and say, "Are we going to be successful in 19 treating those antibodies?" where we're talking about 20 desensitization and then how to monitor their response 21 to desensitization. What are we talking about? A 22 diagnostic aid for biopsy or a clinical presentation</p> | <p>1 beads, we have the patient's serum, we have the 2 detection antibody, eventually we're getting MFI 3 results. 4 And the reason that I wanted to schematically 5 show this is because we have one detection antibody 6 binding to one HLA-specific antibody, and the 7 expectation as a result of this, even though this is 8 not an assay that was released to be quantitative, is 9 that it will be quantitative, right? We have a one-to- 10 one relationship. So why are we not using MFI as a 11 tool that can give us antibody strength? And I think 12 the vast majority of us realize that this is not a 13 reliable tool for antibody strength. 14 So I want to talk about, why is it not working 15 as we would have expected? And Howie talked about 16 reagents issues, and I'm not going to repeat this at 17 all. 18 I think we have to appreciate the 19 manufacturing issues. And I'm not trying to provide 20 any excuses to the manufacturers, they know, they've 21 heard from me many, many times, but what we need to 22 appreciate is that the reagents that are going into</p> |

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| <p style="text-align: right;">Page 190</p> <p>1 those assays, those are not DNA probes that were 2 synthesized in a laboratory. The ability to 3 manufacture those reagents is really, really difficult. 4 We have to have 100 different analytes for a Class I, 5 100 different analytes for a Class II. We want to 6 extend the panels. And all the HLA community comes and 7 talks about having more and more of them, but 8 generating them is not an easy thing. 9 So, again, I would like to get a way better 10 assay, but I think we need to appreciate this part as 11 well. 12 On top of this, we are talking about a very 13 small market. We have about 200 laboratories in the 14 United States, maybe 1,000 around the world. We're 15 talking about huge expenses. So the question is, How 16 can we make that assay to work better for us with those 17 limitations? 18 Another limitation -- and Howie touched upon 19 this a little bit -- is this particular slide. I have 20 a little different spin to show you about this. We're 21 talking about assays that are performing in very, very 22 small volumes, and they are multiplexed. And I think</p> | <p style="text-align: right;">Page 192</p> <p>1 us to step away from MFI as a particular number on its 2 own. 3 But really where I want to spend more time 4 today are serum-specific issues that we need to be 5 aware of. 6 So Howie mentioned inhibition, and I want to 7 show a slide about this. I want to talk about issues 8 of saturation of the assay. I want to mention the 9 shared epitope phenomenon. I'm not going to talk much 10 about this because I don't think we have a solution for 11 this right now. 12 And most of you know that I've been using 13 titration studies for a long time. We started using 14 this pretty much when I arrived to Northwestern, so 15 we're talking about at least 12, 13 years ago, and 16 we've been using this clinically for many, many years. 17 And the thing is that the antibody assay, like 18 a lot of other immunological assays, mostly 19 agglutination assays, have been using titration studies 20 since its creation. This is how we're referring to 21 antibodies to blood groups, to antibodies to other 22 antigens, to antibodies to response to vaccinations.</p> |
| <p style="text-align: right;">Page 191</p> <p>1 we all thought this is a wonderful thing, but like a 2 lot of other things, this is a two-edged sword. And 3 taking you back to your days in medical school, if you 4 need to pick 5 microliters, and you look at the outside 5 of your pipette, there will be a film with some liquid 6 on it, and if it's 1 microliter compared to the 5, 7 there you go, here's the 20 percent variability or the 8 CV that we received in the assay despite the fact that 9 we were trying to standardize it. 10 And Peter and Howie and myself and the others, 11 in this assay, we spent probably more time trying to 12 standardize the assay than actually executing the 13 assay. We still couldn't get there. 14 And I think this is a very important thing to 15 appreciate because if what we're trying to get is a 16 particular MFI value, and we're going to have 20 17 percent variability, that there is no way to get around 18 this. And we tried with automation. We never 19 published that part of the study. I think many of us 20 had tried this internally. There is just no way to get 21 anything better than this because of the design of the 22 assay. And if we appreciate this, I think it will help</p> | <p style="text-align: right;">Page 193</p> <p>1 We don't have an MFI to put our hats on. 2 But all of us have done this going through med 3 schools. You dilute the serum and you figure out when 4 the response stops becoming positive, and you know what 5 is the strength of the antibody. So why not apply this 6 to HLA antibodies? And this is what we've been doing 7 at Northwestern. 8 This is one slide to talk about, inhibitory 9 factors. And what you're seeing here are on the left, 10 the MFI values. And you see result of one serum 11 sample, one patient, one assay, 10 different beads. 12 Okay? 13 Let me see if I can point here. On the very 14 left, you see the responses that we get in the regular 15 assay. This is what I call the neat assay. Okay? You 16 run the assay following the manufacturer's 17 recommendations, and this is what you get, and you see 18 that that patient has some antibodies that are fairly 19 strong and some antibodies that are actually negative. 20 And what we did and what we're doing when we 21 need to get the strength of the antibody is we dilute 22 the serum sample. Unknowingly at that time, we</p> |

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| Page 194 | <p>1 actually dilute also the inhibitory factors. So now 2 we're removing inhibition. 3 And we can start seeing that some of the beads 4 will dilute, as we expect them, right? The MFI values 5 will go down, and you seeing doubling dilutions coming 6 up here. Some of them will actually increase in MFI 7 values. 8 And I do want to point here that there are 9 actually two different patterns of dilutions. So this 10 is one patient, one serum sample, one assay. Some 11 beads will be affected by inhibition, and some will 12 not. And I think it's an important point to make 13 because people sometimes kind of jump over this when 14 they look at an overall statistical data instead of 15 looking at an individual patient. 16 And again, the fact that the different 17 antibodies can be affected by the inhibition 18 differently I think is also very important. So at the 19 end of the day, what we see is this patient is really 20 very highly sensitized. 21 We can remove inhibition by other means, not 22 just by titrations, and Howie showed multiple ways to</p> | Page 196 | <p>1 will return to inhibition a little bit later. I think 2 this is something that needs to be a must as we're 3 moving forward, and this is something that we need to 4 keep very close to our minds when we're interpreting 5 the assays, that we not remove the inhibition. 6 And now we're saying there is no correlation 7 between the level of the antibody and what we're seeing 8 clinically because if you don't remove the antibody and 9 you think you have no -- sorry, you do not remove the 10 inhibition and you think you have no antibodies while 11 in reality you have a lot of antibodies, I think that 12 can change the way you interpret things. 13 Something else that I think goes currently 14 underappreciated a lot is the fact that we saturate the 15 beads. There is a limited amount of antigens that is 16 attached to the beads. This is a paper that is now in 17 press in Transplantation. 18 And what we've done here, you can see the 19 separation to the different loci and the number of 20 beads that we were looking at, at each and every one of 21 those loci. And what I'm providing here is the median 22 MFI value of each and every one of the groups of beads</p> |
| Page 195 | <p>1 do this. In this particular study, we used EDTA. We 2 used a C1q assay as a comparison. If we're talking 3 about EDTA, in this particular case, the inhibition was 4 not removed from all the beads, especially those that 5 had the strongest inhibition there. So knowing what 6 protocol you're using for the EDTA is important, but 7 even when you remove some of the inhibition, it really 8 doesn't tell you how strong the antibody is. It tells 9 you there is an inhibition, there is something that is 10 masking the response, but how strong that is I think is 11 definitely not revealed by using EDTA. 12 When you're doing the C1q assay -- and I've 13 kind of numbered the beads here so you can see the 14 correlation -- you're actually getting them fairly 15 neatly organized by the strength of the antibody, and 16 this is mostly I think because there is a step of 17 dilution when you're running the C1q assay, there is a 18 step of heat inactivation. 19 So if you want to know as a quick and dirty 20 thing, "Do I have a lot of antibodies, yes or no?" and 21 you run the C1q assay, I think you're getting a good 22 response, and that's a way to remove inhibition. And</p> | Page 197 | <p>1 that ended up to have a particular titer. So the 2 titers are going up here. And as you look at the low 3 titer antibodies, you can see that there is an increase 4 in the median MFI. This is really what we would 5 expect. 6 But you reach a point where you reach a 7 plateau, and if you take, I don't know, a value of 8 19,000 MFI, you can find antibodies with a titer of 512 9 and antibodies in a titer of all the way up to 65,000, 10 which I don't know what else is in those patients' 11 serum when they have so much antibodies. 12 And by the way, I think, Steve, going into 13 your comment before, if you have a 50 percent reduction 14 of antibody, you must be somewhere here in order to see 15 it because otherwise, you are beyond saturation. 16 And I know Steve had seen this before, but I 17 wanted to mention it here because really what we're 18 talking about, the strength of the antibody, and you 19 get to a point where you just don't see the difference 20 in the amount of antibodies. So saying we have 21 responses some of the times and don't have responses 22 some of the times, and I'll show you some examples, I</p> |

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| <p style="text-align: right;">Page 198</p> <p>1 think it's really dependent more on how much antibody 2 you have there. 3 So this I believe is underappreciated. We 4 have the same data for the CIq assay going to a little 5 bit higher titer because of the nature of the assay. 6 And this is still coming from that same paper. 7 And what I've done is I took the median MFIs 8 and I've plotted them here because a lot of my 9 colleagues will tell me, "We can get with MFI 10 everything that you're saying with titers. We really 11 don't need to do this," which is true when you're 12 talking statistically, at the median of large groups, 13 and it's true to a certain point, and I think 14 everything that falls beyond 10- or 15,000 MFI, 15 statistically speaking, correlates pretty nicely to the 16 titer. But when you go beyond that, you're losing that 17 correlation. 18 So, again, for statistics, this is wonderful, 19 but if you have a patient -- so this is the raw data 20 from which we derived this information. And let's say 21 we have a patient with an MFI of 15,000 on the B locus, 22 how strong that antibody is, is really important to see</p> | <p style="text-align: right;">Page 200</p> <p>1 recognize a target that is shared by all of them? And 2 we recognize that shared thing all the way from the 3 days of CREG, right? This is simply a CREG antibody 4 that recognize something on all those beads. What 5 would that do to the MFI? Right? 6 So it's very difficult to take an MFI as it's 7 being spit out of the computer and just assume this is 8 good enough to do a clinical study. It really needs to 9 go through a more rigorous analysis. And right now we 10 don't have a good solution for this. We can run 11 different approaches. Howie had shown an example, 12 which I thought was great to do this, but at least we 13 can get a better sense to say the MFI is not indicative 14 of the antibody strength. We cannot give you a 15 different MFI, but we can tell you there is an antibody 16 there that we are not seeing. 17 Just to share some examples, I actually showed 18 this in the previous FDA workshop. I want to repeat 19 this, as we've been using titers to make clinical 20 decisions. So this is a study of patients that were 21 undergoing desensitization using rituximab and then 22 cycles of plasmapheresis, low-dose IVIG.</p> |
| <p style="text-align: right;">Page 199</p> <p>1 with the MFI. 2 So if you want to desensitize this patient, if 3 you're trying to treat AMR for this patient, you really 4 don't know whether your titer falls here and your 5 patient is likely to respond to treatment, or your 6 titer falls here, and you can treat that patient 7 endlessly and make him even more sick, but the level of 8 antibodies won't go below what should be clinically 9 significant. So I think this is really something that 10 is adding a lot of information to the way we can treat 11 patients. 12 I'm going to very briefly talk about this. 13 Howard mentioned this before. I just use a very 14 cartoon form to this. But this is another reason why I 15 think we should not rely on MFI as a number. 16 And I want to talk about the shared epitope 17 phenomenon. So let's say we have five beads and we 18 have antibodies that recognize the bead. We come with 19 our secondary antibody. And now we have an MFI of 20 5,000 for the blue bead. No MFIs associated with the 21 other ones, right? Very, very simple. 22 What would happen if we have an antibody that</p> | <p style="text-align: right;">Page 201</p> <p>1 So this is one patient, and we were monitoring 2 all the antibodies before and after treatment, and 3 we've seen results like this from multiple papers over 4 time. If we use the CIq matrix to look at those 5 results, we see a trend down at everything, but 6 different gradations of reduction. But if we convert 7 to a titer metrics, we see a very unified response of 8 the antibodies. And what I compare to this is to the 9 delta, the difference, between the pre and the post, 10 and you can see that the delta titer is very neat, very 11 narrow. 12 And this is the complete study. And again you 13 can see that the delta titer runs within the 20 percent 14 CV of the assay pretty much. So you can measure. You 15 can quantify the antibodies pretty well by converting 16 them instead of an MFI metric to a titer metric. 17 And let me just walk you through a patient. 18 This is actually in collaboration with Johns Hopkins. 19 And we are looking at three different metrics of 20 measuring the antibodies and looking at four different 21 serum samples with the color codes, the pretreatment, 22 the posttreatment immediately pretransplant. This</p> |

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| <p style="text-align: right;">Page 202</p> <p>1 patient received additional treatment immediately 2 posttransplant. And this is a 3- to 6-month follow-up 3 of all the patients that we've been looking at. 4 And what I want to show you here is two groups 5 of beads that have the same MFI. But if you look 6 closer, this group of beads, or antibodies, responded 7 very nicely to treatment, maybe not sufficient, but 8 responded very nicely to treatment, versus this one 9 that did not. 10 If we look at the titer metrics, it's clear 11 from the get-go that this group of antibodies will 12 respond to treatment, and the same goes with the C1q, 13 those that responded versus those that did not, and you 14 can see that that correlates very nicely with titers. 15 So, again, this is something that can help you predict 16 this. 17 And I think this is the last slide of data 18 that I want to show here. This was accepted as an 19 abstract for ATC again in collaboration with Johns 20 Hopkins. And what we've done here, we blindly took 21 patients that were treated -- and this is going all the 22 way back to 2001 -- they were treated based on the</p> | <p style="text-align: right;">Page 204</p> <p>1 something that can be removed by 6, 7 cycles of 2 plasmapheresis, those can be removed. If your antibody 3 is stronger than this, if you need to use more cycles, 4 don't even attempt because it will not go there at all. 5 So what do I think should be the remediation 6 of everything that we have presented right now? I 7 think we need to adjust our expectations from the 8 assay. I think the assay is good. I think we're 9 trying to force it to give us something that I don't 10 think it can. I definitely -- and I've been saying 11 this for a long time -- do not use strict MFI as a 12 cutoff. 13 We need to put our thinking caps together and 14 find something that the community feels comfortable 15 with. But a strict MFI is not the route to go. We 16 need to use additional tools to assess presence and 17 strength of antibody. And I'll talk about STAR in a 18 minute. We definitely need to make sure that we're 19 removing inhibition. 20 And just as food for thought, patients' serum 21 samples are very different than -- transplant patients, 22 I should clarify this, that patients that receive</p> |
| <p style="text-align: right;">Page 203</p> <p>1 center's standard of care. So they didn't have the 2 information as they determined how many cycles of 3 plasmapheresis they want to go, and those are listed 4 separately for Class I and Class II on the X axis. 5 And on the Y axis, you see the log₂ or the 6 delta reduction in the titer. The size of the circle 7 represent the amount of data points that we had for 8 each and every one of the individual data that you are 9 seeing there. 10 And when I look at the data, I think there is 11 a very nice linear correlation of delta reduction with 12 increased number of cycles up to a certain point. And 13 I remember I talked with Bob about this, and I was 14 like, well, I knew this all the time, right? I knew 15 that there are some patients that have so much 16 antibodies that if I need to use that extra cycles of 17 plasmapheresis and IVIG, it's probably not going to be 18 that great, and many of those patients eventually had 19 rebounds of those antibodies. 20 But I think by using this approach, you can 21 determine up front that patients that have -- depending 22 on how much antibody you want to remove, up to</p> | <p style="text-align: right;">Page 205</p> <p>1 transfusions, that multiparous woman, they have so many 2 other things in their serum samples that affect how 3 those assays work. 4 And I just want to throw there, I know it's 5 not going to be an easy thing to do, but I would want 6 to throw, there is some collaboration between the -- I 7 don't know if the FDA regulatory bodies and the 8 vendors, that allow the vendors access to transplant 9 patients' serum samples so they can QC and improve 10 their assays better, and I think that can really help 11 us with this. 12 So very, very quickly I want to take you 13 through the STAR. Ros had mentioned this, the STAR 14 workgroup that we had. I just want to acknowledge a 15 lot of the people that were a part of this. This is 16 not the full group. We had about 40 people that were a 17 part of this. I definitely want to acknowledge very 18 much Peter Nickerson, who helped me drive that meeting. 19 We have several goals going into this, and 20 really I think we put a lot of focus trying to start 21 thinking differently about patients that are 22 immunologically, alloimmunologically, naive versus</p> |

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| <p style="text-align: right;">Page 206</p> <p>1 those that have a potential memory. And I know this is 2 an area that can have a lot of discussions, but we were 3 trying to separate it to those that have sensitization 4 against allo and nothing else to this.</p> <p>5 We had several guiding principles that were 6 listed here, and we really were trying to be very 7 strict to state-of-the-art clinical diagnostics and 8 trying to provide grade of evidence as we were moving 9 forward.</p> <p>10 Our goal was to come up with four 11 deliverables. The first is the technical primer, and 12 that we tried to finalize before going into the 13 meeting, so this is where I will show you a little bit 14 more information.</p> <p>15 We had a section, and Howie Gebel and Frans 16 Claas were the ones leading this, that were really 17 trying to narrow down the definitions of what is 18 immunologically versus naive patients. And Howie will 19 talk about this later, so I'm not going to mention this 20 at all. And we had two major groups that were trying 21 to come up with clinical applications and 22 recommendations.</p> | <p style="text-align: right;">Page 208</p> <p>1 we know today because the conclusions might be 2 different. But the important thing is that we really 3 need to try to get comprehensive typing of the donor 4 and the recipient.</p> <p>5 And as I commented earlier, we are having now 6 new reagents in the field that would allow not next 7 generation sequencing, but fairly high resolution, at 8 least at the level that we have the reagents to test 9 for antibodies, for donor and recipient that can be 10 done in a few hours and not a huge added cost. And I 11 think we really need to adopt this because we can learn 12 a lot of things on multiple levels definitely going 13 into the Eplet route. Molecular methods is something 14 that was adopted in the United States a long time ago. 15 We just kept this here.</p> <p>16 And really for antibody assessment, we need to 17 look at all the different loci. And I listed here very 18 specifically the DQ alpha/beta together, the DP 19 alpha/beta together. I think this will be an important 20 angle to look at antibodies the way they are expressed 21 on the cell surface and not the way they are expressed 22 on the molecular level.</p> |
| <p style="text-align: right;">Page 207</p> <p>1 And, again, I'm not going to read all of this, 2 you can see that information. The memory group was 3 divided into the four different organs, so we had 4 heart, lung, kidney, and liver groups. We did not 5 separate the pancreas outside of this. And then the 6 immunologically naive -- and Ros mentioned there isn't 7 a lot of data on this -- was separated for thoracic and 8 abdominal moving forward.</p> <p>9 The groups are finalizing their recommendation 10 as a result of that meeting, but I think we had a very 11 fruitful day, a lot of discussions. Many of the people 12 in the room were actually part of this. We had invited 13 to the room together with us representatives from the 14 FDA, from NIH, and from UNOS, because I think they're 15 significant shareholders in the discussions, and I 16 think we had very good discussions with them thinking 17 about this.</p> <p>18 So what I can present to you today is really 19 the recommendation for testing. I think this is really 20 critical, and I really want you to remember this as 21 you're rereading papers that were published 5, 10, 15 22 years ago when we didn't know a lot of the things that</p> | <p style="text-align: right;">Page 209</p> <p>1 And I think the most important thing is we 2 will recommend that inhibition must be removed. We're 3 not going to recommend which methods need to be used to 4 do this, but it needs to be removed, and the labs have 5 to be able to prove that they are able to remove the 6 inhibitions, so at least we won't miss those patients 7 that we think they don't have antibodies and actually 8 have much stronger antibodies.</p> <p>9 And then there should be some mechanism in 10 place to detect the phenomenon of potential epitope 11 sharing because I think this is another place where 12 we're underappreciating the strength of the antibodies.</p> <p>13 So I think with this I'll end. Thank you. 14 (Applause.)</p> <p>15 Public Comment and Discussion Part II 16 DR. VELIDEDEOGLU: Thank you for the excellent 17 presentations. Now we just completed the Part II, the 18 scientific presentations, and Part II of Session 1. 19 And we will move on to the Public Comment and 20 Discussion session. If anybody has any specific 21 questions about the presentations, please ask your 22 question.</p> |

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| <p style="text-align: right;">Page 210</p> <p>1 Dr. Haas?</p> <p>2 DR. HAAS: I had a question for Mark actually.</p> <p>3 There was something in the eculizumab study that I</p> <p>4 guess maybe it's my naiveté, but the fact that the</p> <p>5 eculizumab seemed to prevent development of TG in</p> <p>6 patients who have low titer antibodies. Now, the low</p> <p>7 titer antibodies I guess, as I understand it, are the</p> <p>8 ones that are most likely to be C1q-negative in terms</p> <p>9 of the C1q binding. So one might expect that</p> <p>10 complement inhibition might have the least effect with</p> <p>11 these antibodies, yet it seemed to have the most</p> <p>12 effect. Am I missing something or are we dealing with</p> <p>13 the fact of the imperfections in the assays?</p> <p>14 DR. STEGALL: Yes, you're missing something.</p> <p>15 (Laughter.)</p> <p>16 DR. HAAS: Yeah.</p> <p>17 DR. STEGALL: So I think that these antibody</p> <p>18 levels are higher than most. These are sensitized</p> <p>19 patient, positive crossmatch patients, so these weren't</p> <p>20 low level of antibodies. I think it's small numbers of</p> <p>21 patients, so it's just a signal that you kind of think,</p> <p>22 well, maybe there is something to complement inhibition</p> | <p style="text-align: right;">Page 212</p> <p>1 no question. So if you try to say that IG3 is a C1q-</p> <p>2 negative antibody, I think the rest of the immunology</p> <p>3 community is going to say you don't know what you're</p> <p>4 talking about kind of thing. And so the idea is the</p> <p>5 C1q assay is an assay that it's a little bit arbitrary,</p> <p>6 right? It's just an assay. It has some sort of</p> <p>7 correlation with outcome, and mostly it has to do with</p> <p>8 level of antibody, right? If you make enough antibody,</p> <p>9 you'll be IG3-positive. So the C1q piece is a tool,</p> <p>10 but it's not a biological phenomenon that immunologists</p> <p>11 talk about. Does that make sense?</p> <p>12 DR. HAAS: I think actually you could look at</p> <p>13 your question a little differently and kind of turn it</p> <p>14 around and suggest that maybe those low-level</p> <p>15 antibodies wouldn't have ever developed TG, and that</p> <p>16 the eculizumab is really maybe not doing anything with</p> <p>17 the low-level antibodies, but it may be preventing AMR</p> <p>18 with the really strong antibodies.</p> <p>19 And I think your control group suggested that</p> <p>20 the antibodies that were below 200 with or without</p> <p>21 eculizumab didn't seem to correlate with chronic</p> <p>22 rejection.</p> |
| <p style="text-align: right;">Page 211</p> <p>1 in chronic injury, was the kernel of the hypothesis</p> <p>2 that we're working on.</p> <p>3 And the way I kind of look at it is that the</p> <p>4 final end result we see clinically is the tip of the</p> <p>5 iceberg, right? A lot of things are working underneath</p> <p>6 that, moving that clinical endpoint forward. And a lot</p> <p>7 of it is -- our interpretation of that is undercut by</p> <p>8 all the limitations of histology, the assay, and</p> <p>9 everything else, right?</p> <p>10 But there is at least hypothesis that there</p> <p>11 are certain antibodies that -- that you have a certain</p> <p>12 amount of antibody that truly is going to injure the</p> <p>13 graft and cause transplant glomerulopathy without any</p> <p>14 other -- with complement, right? Direct activation or</p> <p>15 -- it's large enough that it causes proximal C3</p> <p>16 activation because it's only C5 you're blocking, but</p> <p>17 that the immune system, the way it works, is that it</p> <p>18 evolved complement for a reason, it probably augments.</p> <p>19 So if you have lower levels -- lower affinity</p> <p>20 antibodies, they may need C5 activation to move</p> <p>21 downstream.</p> <p>22 IG3 activates complement, it binds complement,</p> | <p style="text-align: right;">Page 213</p> <p>1 DR. STEGALL: No, I mean, I've kind of got to</p> <p>2 stop presenting that slide to tell you the truth. It</p> <p>3 just talks more discussion than it is. But I think</p> <p>4 that it -- the control group that had low level -- that</p> <p>5 had a B flow crossmatch less than 200 at 6 months,</p> <p>6 right? I don't know if that's low-level antibodies or</p> <p>7 not -- had transplant glomerulopathy, they developed</p> <p>8 transplant glomerulopathy, and the same sort of range</p> <p>9 of patients who had 1 month of eculizumab at a year</p> <p>10 didn't have transplant glomerulopathy.</p> <p>11 So it's just an observation. I throw it in</p> <p>12 there more as starting discussion that antibody-</p> <p>13 mediated injury is a spectrum, right? And there's a</p> <p>14 reason why some people with DSA don't develop</p> <p>15 peritubular capillaritis or at least to a significant</p> <p>16 degree.</p> <p>17 And I think every study shows the more</p> <p>18 antibody you have, the more injury you have, right?</p> <p>19 And if you can get around the acute part, the more</p> <p>20 chronic injury you have, the more antibody you have.</p> <p>21 And I think that's just the biology of the system. And</p> <p>22 I'm sure there is something to do with the kidney's</p> |

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| <p style="text-align: right;">Page 214</p> <p>1 ability to accommodate the antibody, too. 2 But I think the eculizumab -- just say 3 complement is probably important to chronic injury, 4 too, we just don't measure it very carefully. 5 DR. VELIDEDEOGLU: Okay. Any other specific 6 questions related to the presentations, clarifying 7 questions? 8 DR. WOODLE: So I had a couple of questions 9 for Howie Gebel if I could. 10 DR. VELIDEDEOGLU: Oh, okay. 11 DR. WOODLE: Howie, if you take just single- 12 antigen bead strength, antibody strength, and use that 13 as predictor, can it replace C1q or can it be as good 14 as C1q? 15 DR. GEBEL: I think I'll just answer it a 16 different way, which is at my center we don't do the 17 C1q assay. So we believe in the MFI value as the 18 cutoff. So in our center, that's how we operate, yes. 19 DR. WOODLE: And my next question pertains to 20 the isotype-specific assays. One of the issues with -- 21 as you know, IgG3 has been advocated to some degree, 22 but in our center, we don't see IgG3 in early antibody-</p> | <p style="text-align: right;">Page 216</p> <p>1 As I alluded to, when we were trying to 2 develop this assay ourselves several years ago, we took 3 commercial reagents, we coated Luminex beads with IgG1, 4 2, 3, or 4. We came back with supposedly monoclonal 5 antibodies specific for IgG1, 2, 3, or 4. And there 6 was a ton of cross-reactivity. And so it's not that I 7 don't believe that there might be nuggets of good 8 information in there, but I think it deserves much more 9 attention to reliably create the secondary reagents and 10 then determine the integrity of the assay itself. 11 DR. VELIDEDEOGLU: Anat Tambur. 12 DR. ROITBERG-TAMBUR: So just to add to, first 13 of all, the comment about C1q versus strength of 14 antibody. I think we showed very, very clearly not -- 15 Tom Ellis definitely had shown it by either 16 concentrating the antibody or diluting the antibody, 17 that there is a correlation, but I think we've shown 18 very clearly that there is an actual titer cutoff, if 19 you will. Very strong correlation from you get to a 20 titer of 1 to 16 or 1 to 32, you suddenly get to cC1q 21 binding. 22 So it's very strongly correlated with a titer</p> |
| <p style="text-align: right;">Page 215</p> <p>1 mediated rejection, and we see it in about half of the 2 late rejections. And so it's actually only in a small 3 -- it's only in a minority of the population, and 4 that's problem number 1. 5 Problem number 2 is that -- I think you 6 pointed this out very well with the Venn diagrams, it's 7 never in the context of where there is just an IgG3, 8 it's in the context of other antibodies. Problem 9 number 2. 10 And problem number 3 I'd like you to comment 11 on, which I don't think you did, was that when you 12 assay for IgG1, 2, 3, and 4, you use a different 13 secondary antibody. So it's really the sum of the 14 isotypes and the amount that you have in each isotype. 15 How do you get over that problem and getting at a 16 summary when most patients actually have multiple 17 isotypes? 18 DR. GEBEL: There's no argument with me at 19 all, Steve, because I agree with what you've said. I 20 think the reliability of the assays as they currently 21 stand is quite questionable because of the cross- 22 reactivity of your secondary reagents.</p> | <p style="text-align: right;">Page 217</p> <p>1 of antibody, and I think quite a lot of centers right 2 now, instead of running all the titration studies, will 3 run a dilution, whatever they pick as a dilution, as a 4 measure to say whether they have a strong antibody or 5 not, and I think it removes inhibition and it gives you 6 a lot of information. 7 For the subtype, the IgG subtype question, I 8 totally agree with Howie. I don't think that we have 9 very good reagents, to talk about that point and how we 10 had indicated several other things. But I still want 11 to remind everyone, those subtypes is a dynamic 12 process, and the snapshots that we take today are not 13 necessarily going to tell us where that patient will be 14 in a month or 2 months and 3 months. So we need to 15 take that part into consideration as well. 16 DR. WOODLE: Yeah, I think that's a good 17 point. We have data that we'll present at ATC that 18 indicate that the amount -- the quality or the quantity 19 of IgG3 isotypes goes down when you treat with 20 proteasome inhibitor therapy. So that subclass goes 21 down, as does the FcR binding capacity of the 22 antibodies. And so what you start with may be totally</p> |

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| <p style="text-align: right;">Page 218</p> <p>1 different than what you have at the end after you 2 finish treatment. 3 DR. VELIDEDEOGLU: Ros Mannon, please. 4 DR. MANNON: Yeah. So my question is 5 tangential to that and for Mark. In this hypothetical 6 trial, since we're talking about DSAs, how do you 7 envision it if you've got people with multiple? And, 8 granted, usually in my personal experience, the early 9 acutes have more multiples than the late, but the late 10 can have multiples. So how would you deal with that? 11 And that's going to come into number 3. Do we do this 12 MFI some or what? 13 DR. STEGALL: So I think that's the reason 14 that I think that we're in this era today -- right? -- 15 looking at DSA as a screening tool. And it doesn't 16 matter, one, two, ten, it doesn't matter. That's not 17 what's going to determine whether I think that we 18 should try to then develop therapy for patients at that 19 juncture. 20 So we allow the tissue-typers to say this 21 person has an antibody. It's probably real. You can 22 do dilutions and do whatever you want. And then we'll</p> | <p style="text-align: right;">Page 220</p> <p>1 agreeable. 2 DR. STEGALL: That trial cannot be done. In 3 my opinion, that trial cannot be done. You can't use 4 DSA as an entry criteria -- as a surrogate endpoint for 5 a clinical trial today. We crossed that bridge a few 6 years ago, and that's the reason that we're not 7 proposing that. 8 I only threw that out just purely to point to 9 the limitations because people want to use DSA for a 10 clinical trial, I guess, and I think that the assay is 11 not quantitative, it's unrealistic to think you're 12 going to be able to measure a 50 percent decline in 13 MFI, just for all those -- there are going to be 1,000 14 reasons. And also for another reason, because you 15 don't want to treat all those people. They're not all 16 going to do poorly for a lot of different reasons. 17 So you use it as a screening tool. You screen 18 people, you can't biopsy people necessarily every year. 19 You use it as a screening tool. And I think a lot of 20 the peripheral assays that are being used, a lot of the 21 tools used for acute cellular rejection will be 22 screening tools to tell you who to biopsy. And then</p> |
| <p style="text-align: right;">Page 219</p> <p>1 biopsy the patient. That's what we want to do. And 2 then we're going to use the biopsy for the -- the 3 biopsy then becomes the entry into the clinical trial. 4 You get around all of these ASHI kind of 5 meetings, arguments, and that's fine with me. I know 6 that it's important to do quantification and all the 7 rest, and someday we'll probably get there, at least 8 for certain things, but today -- and also really what 9 matters is the histology anyway. 10 So I'm not worried about quantification, 11 that's not what we're -- the trial I put up -- I put up 12 trial number 1 primarily to condemn trial number 1 13 obviously. 14 DR. MANNON: But you mentioned one potential 15 surrogate endpoint was dropping DSA and understand the 16 effect and -- 17 DR. STEGALL: Correct. Again, that was 18 mentioned to basically -- 19 DR. MANNON: Yeah. So that's my question, is, 20 Do we say were going to take the highest? And do we 21 really know it's the -- you know, I mean, and I don't 22 want to be contentious because I want us to be</p> | <p style="text-align: right;">Page 221</p> <p>1 there is going to be a different -- indication biopsy 2 is not going to be for elevated serum creatinine, it's 3 going to be for some sort of other test that turned 4 positive, whether it's a peripheral blood assay for T- 5 cell activation or serum. 6 So I wouldn't worry about -- the 7 quantification is not the issue, the issue really is 8 who you biopsy. And the thing about that, even with a 9 C statistic of like .9, you're still going to biopsy a 10 lot of people who don't have the disease, but you're 11 not going to biopsy everybody. 12 DR. VELIDEDEOGLU: Peter Nickerson? 13 DR. NICKERSON: Yeah. So a couple comments 14 just to come back to Steve's original question, and it 15 sort of echoes Anat's question, point, about titer. So 16 when Chris actually looked at EDTA-treated serum, so we 17 removed inhibiting factors, there was a very tight 18 correlation between the MFI and the C1q positivity, and 19 I think that this goes to titer. 20 But I thought one of the most important things 21 that Chris had in the paper was that if you were C1q- 22 negative with the antibody, and you did the biopsy, 40</p> |

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| <p style="text-align: right;">Page 222</p> <p>1 percent of those biopsies were C4d-positive. In other 2 words, in the biopsy, you were getting complement 3 activation despite the fact that your in vitro test was 4 C1q-negative. 5 And what that tells me is that -- and a lot of 6 people have tried to use the language that the in vitro 7 test tells you whether you have a complement-fixing 8 antibody or not, and that is not true. In vivo, you 9 can very well have a complement-fixing antibody, which 10 is physiologically the important question, that tests 11 negative in vitro. And I think we have to get this 12 language and concept clarified in our thinking. 13 DR. VELIDEDEOGLU: Robert Montgomery. 14 DR. MONTGOMERY: So I disagree with Mark. 15 When I was at Hopkins, we found that actually there was 16 a very tight correlation between semi-quantitative 17 report of DSA and what we would find on the biopsy, to 18 the point that after 5 or 6 years of doing that, we 19 would just treat on the basis of the tissue typing 20 data. 21 And I think that, you know, if you go to a 22 barber, you're going to get a haircut, right? At the</p> | <p style="text-align: right;">Page 224</p> <p>1 that's the group of patients I'm talking about. 2 So, yeah, posttransplant, obviously early 3 posttransplant the levels are very high and correlate 4 very well with the histology, but in 5 years, when the 5 MFI is 2,000, and it's a de novo DSA, then the 6 histology and the DSA do not correlate, and that's the 7 reason I think at that point you need to do the biopsy. 8 So it's a different patient population. And, 9 again, that's the reason I made those slides, to try to 10 tell you that it's not -- yeah, histology and DSA do 11 correlate, but it just depends on the time 12 posttransplant -- right? -- and the setting. That's 13 all I was saying. 14 DR. WOODLE: So to try to mediate this -- 15 (Laughter.) 16 DR. STEGALL: No, it's just a clarification of 17 what I'm trying to -- actually, I never said what he 18 said. 19 DR. WOODLE: No, I understand. Bob is right, 20 you've got to have an HLA lab that pays attention to 21 the precision of their measurements. So we do ours 22 robotically, and our CV percent is 10 percent, it's</p> |
| <p style="text-align: right;">Page 223</p> <p>1 Mayo Clinic, they biopsy, right? I think that it's a 2 very good idea to have some redundancy in terms of 3 being able to determine the level, the quality, of 4 information that you're getting, so I think biopsying 5 is a great thing, you should do it a lot, I totally 6 agree with it, but when you're getting really high 7 quality data, I think you can believe what you get from 8 the tissue typing lab. 9 The other thing I would just say is that this 10 whole C1q thing to me is very problematic, it's become 11 sort of like religion, there are believers and non- 12 believers, and I think it's taking us off in kind of a 13 weird direction that is distracting, and it really 14 isn't, in my opinion, something that is going to change 15 the field in an important way. 16 DR. STEGALL: Can I? I agree with Bob. I 17 think that you didn't understand what I was proposing. 18 In the early posttransplant period, yeah, the antibody 19 levels are very helpful, there's no question, but what 20 I'm looking at about the biopsy is the de novo DSA 21 posttransplant 5 years out patient, and in that 22 situation, the levels aren't very high at all, and</p> | <p style="text-align: right;">Page 225</p> <p>1 actually less than 10 percent. And so when we lower 2 the MFI from, say, 7,000 to 5,500, I believe that, I 3 believe that we're on the way down. And when we see 4 progressive reductions, we're even more confident in 5 that. And so I agree with you. 6 In terms of Mark's point about early AMR, 7 absolutely. In terms of late AMR, we do have some data 8 that's starting to emerge that's indicating that if you 9 reduce the MFI in late AMR, it can impact graft 10 survival. That data is early. Clearly, other centers 11 are going to need to show that. 12 The one thing that we haven't done in our 13 program is we haven't given quite the attention to 14 dilutional analysis, like Anat recommends, in AMR, late 15 AMR, as we have in desensitization. In our prospective 16 trial, our iterative trial, of bortezomib-based 17 desensitization, we used the exact techniques that Anat 18 illuminated, and without that, we would not have had a 19 quantitative trial. It's not easy to do, and you have 20 to put a lot of time and effort into it. But I hope 21 that clarifies where we stand. 22 DR. VELIDEDEOGLU: Okay. In the interest of</p> |

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| <p style="text-align: right;">Page 226</p> <p>1 time, I plan on moving to the FDA questions, but I tend 2 to shorten them and revise them a little bit because we 3 won't have time to cover everything that we planned on 4 initially discussing.</p> <p>5 So actually, we got answers to most of our 6 questions during the presentations. Regarding the 7 first question, "Discuss the utility of surveillance 8 biopsies and single antigen beads and DSA, routine DSA, 9 monitoring," what we would like to hear from the 10 speakers and the other attendees is that we realize 11 that there are different practices among different 12 centers with regards to routine DSA monitoring and the 13 utilization of protocol biopsies.</p> <p>14 So if anybody wants to comment on -- and we 15 also realize that the landscape and the practices at 16 different centers are rapidly changing, especially with 17 regards to routine DSA monitoring. So if anybody has a 18 different point of view or wants to talk about their 19 center's practices in terms of DSA monitoring and 20 protocol biopsies, we would like to hear that.</p> <p>21 Dr. Nickerson?</p> <p>22 ATTENDEE: I think Mark wanted to.</p> | <p style="text-align: right;">Page 228</p> <p>1 transplant glomerulopathy and treat it, and also to 2 design therapies to whether you want to treat pure ABMR 3 or whether you need to give something to treat the T- 4 cell-mediated component as well.</p> <p>5 So I guess I would say that maybe later 6 protocol biopsies might be of more value than early 7 protocol biopsies, where you can usually tell what's 8 going on just from the DSA assays.</p> <p>9 DR. STEGALL: So I can say what -- so I'm the 10 protocol biopsy guy. We never did protocol biopsies 11 necessarily with the idea that we're going to manage 12 any individual patient. We started our protocol biopsy 13 study in '98 because we wanted to learn the natural 14 history of what happened to a kidney after we 15 transplanted it, and out of that, we thought we would 16 learn enough then to be able to design clinical trials 17 and improve the graft survival of the entire 18 population, and any one patient who participated 19 therefore would contribute to that knowledge.</p> <p>20 So I don't think you have to do protocol 21 biopsies to manage patients at all. I think that we've 22 outlined what we think. If you have DSA, we would call</p> |
| <p style="text-align: right;">Page 227</p> <p>1 DR. HAAS: Oh. I guess with regard to 2 protocol biopsies, maybe we're doing protocol biopsies 3 in the wrong patients. And we do protocol biopsies, a 4 lot of centers do protocol biopsies, at 3 months, 6 5 months. And I think Bob's point is very good. When 6 we're talking about the very early, sort of acute AMRs, 7 these are highly correlated with rebounds of DSA, and 8 it may be acceptable to, especially if a patient has a 9 rebound of DSA in a highly sensitized patient, to just 10 treat that patient to reduce that DSA.</p> <p>11 However, when we're talking about protocol 12 biopsies in 1 year farther out, the histologic lesions 13 look very different. These are rarely pure ABMRs. 14 They're frequently mixed rejections. The molecular 15 data tells us that there's a strong correlation between 16 the histology and whether these are a mixed rejection 17 versus a pure ABMR, depending on what the interstitial 18 inflammation looks like.</p> <p>19 And so in terms of guiding treatment, a year 20 or 2 years out, there still might not be a whole lot of 21 graft dysfunction going on, but it may pick up a 22 smoldering ABMR at a point before you have overt</p> | <p style="text-align: right;">Page 229</p> <p>1 that indication biopsy at that point.</p> <p>2 So I think the utility of protocol biopsies is 3 outlying the biology of the disease, and I think that 4 over the past 10 years we've actually started to do 5 that. And so don't misquote me to say that I think 6 everybody should do protocol biopsies. That's not the 7 case.</p> <p>8 DR. VELIDEDEOGLU: Please go ahead, Dr. Haas.</p> <p>9 DR. HAAS: Okay. Just to respond briefly to 10 that, so if you detect a DSA 1 year posttransplant, 11 you'll do an indication biopsy, and that indication 12 biopsy may show AMR, it may show mixed rejection, it 13 may show nothing. If that patient -- say the protocol 14 biopsy shows nothing or shows just T-cell-mediated 15 rejection, given that this patient has a DSA, would you 16 do a series or one or more protocol biopsies, say, at 2 17 years or at 3 years in that patient to see if there has 18 been a change in the histologic status?</p> <p>19 DR. STEGALL: We would not do any different 20 biopsy regimen than we currently do. So we do a 4- 21 month, a 12-month, a 24-month, and now we do 4, 7, and 22 10 years. That's what we would do, but we wouldn't --</p> |

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| <p style="text-align: right;">Page 230</p> <p>1 the idea is that if we are doing a clinical trial, then 2 we would actually have a better idea about -- you know, 3 we have a reason for doing -- I think there's a reason 4 to do a follow-up biopsy if you're doing treatment to 5 assess efficacy. 6 DR. VELIDEDEOGLU: Dr. Nickerson? 7 DR. NICKERSON: Yeah, so in our program, we do 8 a surveillance biopsy at 6 months, although we've 9 debated 6 versus 12, and I don't think it's really any 10 different. The reason we do it is to look for adequacy 11 of immunosuppression, mainly around cellular, and I 12 think there's a lot of data that comes out at 6 or 12 13 months that if you have ongoing cellular inflammation 14 in that graft, you actually have a high risk of 15 premature graft loss. So we look at it in that sense 16 for trying to define adequacy of immunosuppression. 17 And then we don't do any other surveillance biopsies. 18 We do, do single-antigen bead screening, and 19 we do that routinely starting at -- we do early, a few 20 months, but 6 months on, we're doing it semiannual to 21 then annual at 2 years on with the idea that if we find 22 an antibody, we're going to do a biopsy to look for</p> | <p style="text-align: right;">Page 232</p> <p>1 Number two, when we improve our ability to 2 measure the DSAs and get the most quantitative MFI and 3 remove as many variables as we can, the coefficient of 4 variation is actually low or lower than especially what 5 you're getting with our immunoassays for tacrolimus 6 these days. So I think that we're sending the wrong 7 message to the FDA in terms of what we maybe can or 8 cannot do with DSA in a clinical trial. 9 Now, I know that we're limited by the label of 10 the DSA and all of those different kinds of things, but 11 we are trying to use DSA and put more restrictions on 12 that than even we do on a tacrolimus assay today. So I 13 just think we need to compare and contrast when we're 14 thinking about those. 15 Right now, we don't know what the exact range 16 or level for tacrolimus is, but yet we use it every day 17 and we monitor it. We don't know what the exact number 18 of MFI is going to be, but we know that if we drop it, 19 we have an improvement. 20 DR. VELIDEDEOGLU: I'm sorry. I feel like I 21 should intervene at this point. We are into our lunch 22 hour, but I want to give the last word to Michael</p> |
| <p style="text-align: right;">Page 231</p> <p>1 whether there is any ABMR, because I also agree with 2 Mark, that you can have a de novo DSA, and there is no 3 pathology, I'm not going to go aggressively in that 4 patient per se. 5 If we are initiating treatment, we will do a 6 follow-on biopsy to see whether we've seen a change or 7 a progression. Ideally, that would be with a clinical 8 trial, but that's where we all want to have a clinical 9 trial. But the whole concern, and I think more and 10 more people are doing surveillance with single-antigen 11 bead measurements as a screening assay. The problem is 12 getting reimbursed for it and the cost of doing it, and 13 some programs have had real trouble getting that within 14 their programs. So we've managed it in our program, 15 but that's not necessarily true across all programs. 16 DR. ALLOWAY: Rita. I am afraid that 17 perfection is the enemy of good as we continue to talk 18 about DSA, and I think if you compare and contrast it 19 to what we do with tacrolimus assay monitoring, we do 20 not look at a single, or we should not look at a 21 single, tacrolimus level in isolation, we should look 22 at them as a continuum, just as we look at DSA.</p> | <p style="text-align: right;">Page 233</p> <p>1 Mittelman. He has been raising his hand. And some of 2 the issues that we have been discussing, the routine 3 DSA monitoring, also overlap, and there's another trial 4 design related question, which also falls under that 5 subject of the upcoming sessions, which could be 6 discussed further. So in the interest of time, I would 7 give the last word to Michael Mittelman. 8 MR. MITTELMAN: First, this is awesome. This 9 is a real privilege to kind of watch you guys debate 10 all of this. And you may get to this later, I'm trying 11 to figure out the agenda, but I would sort of urge you 12 guys to pursue other activities and research protocols 13 that do not involve biopsies. They are the worst. And 14 protocol biopsies give me nightmares. 15 I'm glad I'm not at a center and being treated 16 at a center that does protocol biopsies because, I'm 17 sorry, but I would walk away as a patient and go 18 somewhere else. So I just want to say that I urge you 19 guys to pursue other methods of detection because they 20 are terrible and horribly invasive. And that's all I 21 wanted to say. Thanks. 22 (Applause.)</p> |

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| <p style="text-align: right;">Page 234</p> <p>1 DR. VELIDEDEOGLU: Okay. We thank Michael for 2 his comment. And this concludes the discussion session 3 for Part II of Session 1. Now we have the lunch break 4 until 1:30, and we plan on reconvening and starting at 5 1:30. 6 (Lunch.) 7 Session 2: Factors Contributing to Antibodies 8 in the Pretransplant Period and Treatment Options 9 DR. CAVAILLÉ-COLL: Good afternoon, everyone. 10 I am Marc Cavaillé-Coll, from the FDA, and with my 11 colleague Milagros Samaniego-Picota, who will be 12 moderating this session. Session 2 is on factors 13 contributing to the antibodies in the pretransplant 14 period and what treatment options there are. 15 Our first speaker is Dr. Arjang Djamali, from 16 the University of Wisconsin, who will be talking about 17 the highly sensitized transplant candidate and give us 18 an overview. Thank you. 19 Highly Sensitized Transplant Candidate -- An 20 Overview 21 DR. DJAMALI: Thank you. And thank you to the 22 FDA for the invitation. It's a pleasure to be here and</p> | <p style="text-align: right;">Page 236</p> <p>1 number of patients approximately right now is around 2 14,000 on the wait list. And importantly, there has 3 been a modest improvement of transplant rates, overall 4 transplant rates, in highly sensitized patients despite 5 the Kidney Allocation System. 6 In fact, as you see here, while the very 7 highly sensitized are being transplanted at the higher 8 rates, those with a PRA between 80 and 98 percent are 9 declining in their transplant rates. So the problem 10 persists despite some successes. 11 And this is the problem. This is the 12 immunoglobulin, the IgG. And in our scenario, patients 13 get sensitized due to one of these three mechanisms: 14 blood transfusion, pregnancy, and/or previous organ 15 transplantation. 16 Some of the clinical studies that I'm going to 17 approach now are the most representative ones. I 18 apologize if I don't represent, I don't talk about all 19 of the clinical studies, but I selected the ones that I 20 thought were most important. 21 The first one and the only randomized clinical 22 trial in desensitization was published about 17 years</p> |
| <p style="text-align: right;">Page 235</p> <p>1 to give you the first talk after lunch. So please try 2 to keep your eyes open. We will talk about the highly 3 sensitized patient. That's the topic. 4 Would you please advance it for me? Just this 5 one. Okay. Thank you. 6 This is the disclosure. And I will be talking 7 about unapproved investigational use of products in 8 this presentation. 9 This is the outline of the talk. Background, 10 a few slides on that. The clinical studies that have 11 been conducted for the highly sensitized transplant 12 candidate, some of the outcomes related to those, the 13 limitations of those studies, and then future 14 directions. 15 So this is to set the problem. There is an 16 accumulation of the highly sensitized transplant 17 candidate on the wait list. You see here in the red 18 bar graph the definition of patients that are 19 sensitized with a PRA of higher than 80 percent to 98 20 percent from 2005 to 2015 based on the recent data from 21 2017, annual data report. And the very highly 22 sensitized have also increased so that the overall</p> | <p style="text-align: right;">Page 237</p> <p>1 ago by the Cedars-Sinai group, and the investigators 2 looked for the first time at the role of high-dose IVIG 3 in desensitization. This was a randomized controlled 4 trial. Patients received 2 g/kg of IVIG per month 5 times 4 compared to placebo. The first impact was to 6 see a decline in PRA. The second was that there was a 7 significantly higher transplant rate in those patients 8 that received IVIG. 9 A couple of additional observations are 10 important here. One is that the effect of IVIG was 11 temporary or transient by about 6 months. Second is 12 that the starting PRA was less than 80 percent, so 13 these were not highly sensitized. And third is that 14 the time at which this gap was closed was the time 15 approximately at which the two transplant curves 16 started to split. So maybe there's an impact of IVIG 17 later on, but at least it's important to note that the 18 desensitization effect on cPRA was relatively 19 transient. 20 You have seen this or another source of 21 figures on the role of IVIG in desensitization, but 22 from our perspective, the two important components are</p> |

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| <p style="text-align: right;">Page 238</p> <p>1 the properties, the immunomodulative properties of the 2 F(ab) segment and the FC segment. For desensitization, 3 the primary important part here is neutralization of 4 antibodies and cytokines. Then the other ones are 5 related to the Fc segment. 6 And more specifically, downregulation of 7 plasma cells, modulation of dendritic cells or 8 downregulation of their activity, inhibition of 9 activation of additional immune cells, upregulation of 10 Tregs, and for endothelial cells is saturating the Fc 11 receptor. 12 So this is an important role for IVIG that you 13 will see throughout either at the low dose or at high 14 dose has been utilized, and we can discuss that in more 15 detail later on. 16 The same group then added rituximab to IVIG. 17 Now, these are patients that got IVIG here and here, so 18 about 30 days apart, and in between they got rituximab 19 at 1 gram. Twenty patients were enrolled in this 20 study, and out of these 20, 16 got transplants, 10 of 21 them live donor and 6 of them deceased donor 22 transplants. Please note that their PRA declined also</p> | <p style="text-align: right;">Page 240</p> <p>1 least three other groups and published by three other 2 groups either at Montefiore in New York, this is in 3 Indiana University, and this is the Hopkins group. In 4 aggregate, these groups were unable, as we were at the 5 University of Wisconsin, Madison, to reduce any PRA in 6 patients that had a significant -- had a PRA of 80 7 percent or higher. So there is this limitation that is 8 important to note. 9 Now, what about live donor transplantation? 10 And this is the work of Bob Montgomery and his team at 11 Hopkins published sequentially in the New England 12 Journal, and in this category of patients, it is 13 feasible and the investigators have been successful to 14 reduce the PRA mean of 82 percent to the point to 15 transplant these patients through sequential plasma 16 exchange and low-dose IVIG therapy combined with 17 tacrolimus, mycophenolate, induction with Thymoglobulin 18 or IL-2 blockade, and then additional plasma exchange 19 sessions. 20 This has to do with the intensity of the MFI 21 or the intensity of the crossmatch, and the number of 22 sessions increased as the sensitization increased. But</p> |
| <p style="text-align: right;">Page 239</p> <p>1 significantly. Nevertheless, it was again less than 80 2 percent. And also the T-cell flow crossmatch declined 3 quite significantly, but the acceptance cutoff for the 4 T-cell crossmatch was at 250 at the time of transplant, 5 and at that time, already half of the patients were in 6 that acceptable range. So the combination of rituximab 7 and high-dose IVIG was effective to some extent. 8 The role of rituximab, I have summarized it 9 with this study, single study, from Hopkins. And I 10 think that it's important to remember that rituximab, 11 as you know, is an anti-CD20 agent that reduces B cells 12 in general, but not memory or plasma cells. So its 13 impact is primarily on rebound. 14 And the intensity of the HLA after receiving 15 rituximab is lower compared to the control group. And 16 these are graphs that are depicting the same impact, no 17 rituximab versus rituximab, whether it's a DSA HLA or 18 non-DSA HLA. 19 Having looked at the impact of rituximab and 20 high-dose IVIG in sensitized patients, but not very 21 highly sensitized patients, it's important to look at 22 the other negative studies that were conducted by at</p> | <p style="text-align: right;">Page 241</p> <p>1 obviously this is very cumbersome, and you need to have 2 a live donor available because you can't continuously 3 plasma exchange patients. 4 I'll come to another very interesting study 5 that was conducted in Cincinnati by Steve Woodle and 6 his team. This was a combination of proteasome 7 inhibition with B-cell inhibition and plasmapheresis. 8 They hypothesized that B-cell inhibition alone is not 9 enough and you need to combine that with plasma cell 10 inhibition. 11 So in an intent-to-treat iterative study, they 12 included 52 patients with a cPRA with an unacceptable 13 antigen MFI level of 1,500 of 91 percent. They 14 enrolled these patients in various combinations of 15 bortezomib, rituximab, and plasma exchange. Thirty 16 eight patients, or 73 percent, completed this study. 17 Nineteen of them were transplanted, which is a 18 reasonable rate of 37 percent. 19 Importantly to me is that they had about a 20 quarter of patients that responded by a decline in 21 their PRA defined as 1,500 MFI. And when you look at 22 PRA, you see that a good group of them had a PRA of 90</p> |

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| <p style="text-align: right;">Page 242</p> <p>1 percent or higher.</p> <p>2 Additional studies have been published over</p> <p>3 the past couple years looking at different elements of</p> <p>4 the B-cell development and maturation, specifically</p> <p>5 this one that was done at Indiana University looked at</p> <p>6 anti-BAFF therapy with tabalumab, and they looked at</p> <p>7 the impact on BAFF levels, that was positive, so they</p> <p>8 had an effect, but unfortunately the effect again on</p> <p>9 cPRA was quite minimal, and you see that a majority of</p> <p>10 the patients were very highly sensitized.</p> <p>11 Mark talked about this. This is a different</p> <p>12 representation of a study by the Mayo Clinic to inhibit</p> <p>13 C5 complements. And I will just summarize this again</p> <p>14 by showing that there was clear success in</p> <p>15 transplanting these patients with low clinical</p> <p>16 rejection rates, but at 2 years, there was not a</p> <p>17 significant difference in eculizumab versus control</p> <p>18 groups.</p> <p>19 Finally, another relatively recent study that</p> <p>20 was published from a Cedars-Sinai group using an IL-6</p> <p>21 receptor antagonist, tocilizumab, combined with high-</p> <p>22 dose IVIG in 10 patients who were unresponsive to IVIG</p> | <p style="text-align: right;">Page 244</p> <p>1 are successful in transplanting these patients, as you</p> <p>2 know, if we don't bring down their DSA or their</p> <p>3 antibody levels at the time of transplant to reasonable</p> <p>4 levels, then long-term graft and patient outcomes are</p> <p>5 not very good.</p> <p>6 So why are we having some of these</p> <p>7 limitations? One of the first things could be that we</p> <p>8 are missing some of the non-HLA antigens. And over the</p> <p>9 past 15 years, there have been a number of studies</p> <p>10 looking at this potential of AT1 receptor antibodies or</p> <p>11 other endothelial cell antigens that could be</p> <p>12 considered.</p> <p>13 Another option is -- or another explanation is</p> <p>14 that, as we discussed this morning, this B-cell</p> <p>15 response is not just purely a B-cell response. It</p> <p>16 starts with T cells. Even in the germinal center,</p> <p>17 there are T cells, and they continue to activate the B</p> <p>18 cells in the presence of antigen. We don't have the</p> <p>19 right treatment strategy to eliminate or inhibit plasma</p> <p>20 cells or memory B cells, and what we really need</p> <p>21 definitely is a multipronged approach or a combination</p> <p>22 therapy that would affect B cell maturation, B cell</p> |
| <p style="text-align: right;">Page 243</p> <p>1 and rituximab, and these patients received tocilizumab</p> <p>2 plus IVIG pre- and posttransplant if they got</p> <p>3 transplanted.</p> <p>4 It ended up that half of them got a kidney</p> <p>5 transplant, the other half didn't, and the overall</p> <p>6 complication rates, severe adverse effects, were 40</p> <p>7 percent. So some success at least in declining DSA in</p> <p>8 patients who were transplanted and in transplanting</p> <p>9 them, but the clinical safety was maybe not as great as</p> <p>10 we would like it to be.</p> <p>11 So in summary, all of these studies, I have</p> <p>12 depicted them for you here. This is the first author,</p> <p>13 these are the number of patients. This is the cPRA to</p> <p>14 start with. This is the regimen. This is the impact</p> <p>15 on PRA. What you see was kind of minimal overall. So</p> <p>16 the transplant rates, which are hard to determine</p> <p>17 whether this was an effect of the treatment or it was</p> <p>18 just a random effect of transplantation.</p> <p>19 And here I am also reporting the four trials</p> <p>20 that are in clinicaltrials.gov. One of them has</p> <p>21 stopped because the BAFF inhibition was not successful.</p> <p>22 So quite modest impact on therapy. And even when we</p> | <p style="text-align: right;">Page 245</p> <p>1 development, and plasma cell activation as well.</p> <p>2 I am going to spend just a few seconds on this</p> <p>3 slide because this is an important point from my</p> <p>4 perspective, and that is the targeting of bone marrow</p> <p>5 plasma cells and their survival niche.</p> <p>6 Plasma cells, once they are mature, they go</p> <p>7 primarily to the marrow. Some of them stay in the</p> <p>8 lymph nodes, but the marrow is their primary place to</p> <p>9 home. It's important to know why they home there and</p> <p>10 what is it that keeps them alive because they are long-</p> <p>11 lived, and nevertheless, as soon as you take them out</p> <p>12 of the bone marrow, what happens is that they die.</p> <p>13 And, finally, it's important to understand what</p> <p>14 signaling molecules are there to make this survival</p> <p>15 happen.</p> <p>16 So it turns out that there are a number of</p> <p>17 potential cells that could constitute this niche, but</p> <p>18 stromal cells as well as eosinophils are important</p> <p>19 components of this niche.</p> <p>20 And if you wanted to consider the whole</p> <p>21 process of desensitization, you may have to consider</p> <p>22 targeting upstream as well as downstream molecules or</p> |

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| Page 246 | Page 248 |
| <p>1 cells to B cells so that we can be effective, yet being 2 safe. 3 So the future directions I would say primarily 4 at this stage, we have the kidney paired donation as 5 the numbers are increasing. We have the combination of 6 desensitization and KPD, and a lot of institutions, 7 including us, are doing a lot of this. 8 And, finally, I think that we can conclude 9 that there is limited success, nevertheless, some 10 success, but also a transient impact on antibody and 11 PRAs. 12 We still don't know about the pathogenesis of 13 sensitization as well as we would like it. We don't 14 know why some patients don't get sensitized. We don't 15 know why some patients get highly sensitized, depending 16 on the genomics or cellular pathways behind it. 17 And, finally, defining the best combination 18 therapies that target the plasma cell niche as well 19 could be an important approach for desensitization. 20 And regarding the endpoints that we need to 21 target, what should be these endpoints? Should we 22 focus on cPRA and define the antibody strength for the</p> | <p>1 study was just remarkable, and one can see that there 2 was an overwhelming association of positive 3 crossmatches with what turned out to be hyperacute 4 graft rejection. It was the reason that HLA labs 5 become operational 24/7 365. Whenever Paul Terasaki 6 was in the audience, I would always look at him and 7 tell him that he's either blessed or cursed for making 8 that discovery in terms of keeping us busy 24/7. 9 Paul passed away last year. He spent his 10 entire career devoted to the humoral theory of 11 transplant rejection, and we wouldn't be here without 12 all of the contributions that he made. 13 So I already showed this slide this morning. 14 I won't spent any time on it other than to focus on the 15 fact that we're using these Luminex beads, a solid 16 phase assay, to detect HLA antibodies. And I showed 17 you a version of this slide earlier. And all the red 18 bars, no matter what lab you're in, there is a cutoff. 19 It doesn't matter what the number is, but there is a 20 cutoff above which those are considered unacceptable 21 antigens. And for deceased donors, if you put those 22 into the UNOS database, you are not going to get</p> |
| Page 247 | Page 249 |
| <p>1 unacceptable antigen? Should it be transplantation? 2 Should it be the immunodominant antibody? Should it be 3 non-HLA antibodies? Or a combination of all of these? 4 On this note, thank you very much for your 5 attention. 6 (Applause.) 7 DR. SAMANIEGO-PICOTA: The next speaker is Dr. 8 Howie Gebel, who this morning already spoke to us, 9 Emory University. "Recognized and Unrecognized 10 Sensitization: Assessment of the Pretransplant 11 Immunologic Memory and Its Importance." 12 Recognized and Unrecognized Sensitization: 13 Assessment of the Pretransplant Immunologic Memory and 14 Its Importance (with reference to the 2017 AST/ASHI 15 Antibodies in Transplantation Consensus Conference) 16 DR. GEBEL: Thank you. I already disclosed 17 this, that I have nothing to disclose. 18 Earlier this morning, I alluded to the data 19 that are shown in this slide. This was a paper that 20 was published by Paul Terasaki in 1969 that did 21 crossmatches between recipient sera and donor cells. 22 And without going through the data, the outcome of this</p> | <p>1 offered any donors that have any of the corresponding 2 antigens. 3 To the right of the red bars what you have are 4 a lot of blanks, you have nothing showing up, no red 5 bars. Those are antigens that did not react with your 6 patient's sera, so those are considered acceptable 7 antigens. 8 Over the past few hours, we've heard people 9 talking about sensitized patients, we've heard talking 10 about desensitization of these patients. I think it's 11 time to put some definitions to these terms. 12 So here is an antibody profile of three 13 potential candidates. And I'm having you look at Class 14 I and Class II. The first thing you should see is that 15 there are no red bars. So all three of these patients 16 have no Class I or no Class II antibodies, neither. 17 Now, the question I'm going to ask you is, are they 18 unsensitized? 19 At the beginning of my career, when I first 20 came into the lab, if a person presented with a zero 21 PRA, panel reactive antibody, activity, we were told 22 they were unsensitized. That's really not necessarily</p> |

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| <p style="text-align: right;">Page 250</p> <p>1 true, so let's get into the details, and as you all 2 know, that's where the devil is. 3 So the first patient in my study was a non- 4 transfused male. So this is one patient that you can 5 potentially consider unsensitized. I'll get to it in a 6 minute as to why even this person might not be 7 unsensitized. 8 The second candidate is a multiparous female. 9 She's got three children. Now, she clearly has been 10 exposed to the antigen, so there are mismatched 11 paternal antigens. But the question still remains, Is 12 she unsensitized or sensitized? And I like a term that 13 Steve Woodle came up with, which is "quasi-sensitized." 14 So we quasi know the answer to this. 15 The third patient is a previous allograft 16 recipient, and I don't think there is anybody in the 17 room who would deny that this person has been 18 sensitized, but there is still this question that they 19 all present with no antibodies. And that's the test 20 that we use. We use antibody detection as our 21 surrogate for whether somebody has been sensitized. 22 And I think what we need to remember is that</p> | <p style="text-align: right;">Page 252</p> <p>1 cells that are specific for different viruses -- 2 Epstein virus, CMV, or flu -- one can put them into a 3 gamma interferon production assay and stimulate them 4 with uninfected allogeneic cells, which I'm showing you 5 here. 6 And you can see that there was interferon 7 production in these cells after stimulation with just 8 A2. So somehow the A2 is being recognized by these 9 cells that are specific for a virus. So the virus 10 itself might be one of the factors involved in 11 generating what looks like alloimmunity. 12 And what you can see is, in this particular 13 slide, on the top, if you have, in an animal model, if 14 you have you low donor-reactive memory T cells, the 15 likelihood is that you're going to be able to induce 16 tolerance, but if you have a lot of these cells that 17 have donor-reactive memory, you wind up not being able 18 to tolerize this individual or these mice. 19 And in a human study and some work out of Rob 20 Fairchild's laboratory, one can take a look at again a 21 gamma interferon production assay. And what you're 22 looking at on the left side is rejection episodes in</p> |
| <p style="text-align: right;">Page 251</p> <p>1 indeed it's a surrogate. It's not the endpoint. The 2 antibodies are a surrogate for the cells that produce 3 them. And clearly it's plasma cells that produce them, 4 but plasma cells come from B cells, and B cells won't 5 make the antibody unless they've been helped by T 6 cells. 7 So it's time to move on because as far as I'm 8 concerned, we have one test, like the antibody 9 detection. Much like this horse hospital, if you take 10 a look, there is only one solution to every time that 11 patient presents. Let's do an antibody test. Well, I 12 think we can do better. We at least have to recognize 13 that we can do better. 14 For the next set of slides, I want to thank my 15 colleague Mandy Ford, who is an immunologist over at 16 Emory. She gave me these slides and then helped tutor 17 me through this so I could explain them correctly. 18 So alloreactive memory at the level of the T 19 cell doesn't just have to come from HLA antigen 20 exposure, it can come from pathogen exposure. This is 21 a paper that one of our HLA colleagues, Frans Claas 22 published several years ago, and taking clones of T</p> | <p style="text-align: right;">Page 253</p> <p>1 patients who made a lot, we'll say a lot of spots, 2 greater than 25 of the -- excuse me -- 50 percent of 3 the patients made more than 25 spots compared to four 4 out of 23 with less than 25 spots. The ones who had 5 lots of spots had more episodes of rejection, and the 6 ones with fewer spots had better GFR rates. 7 So all of this just goes on to show you that 8 we have the ability potentially to quantify our cells, 9 at least T cells, that are involved in alloimmunity. 10 But we look at peripheral blood. 11 And as you can see here, the T cells that are 12 involved in a number of different functions reside all 13 over the body. They reside in non-lymphoid tissues and 14 peripheral tissues like the lung and liver and spleen. 15 And what we're doing is focusing only on the peripheral 16 blood, and we have to recognize that cells that reside 17 elsewhere can contribute. If we don't look for them, 18 we're not going to be able to find them. 19 The same thing can be said for B-cell 20 differentiation pathways. We look for the production 21 of antibody, but just looking at this slide, one can 22 see that there are a number of other cells that either</p> |

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| <p style="text-align: right;">Page 254</p> <p>1 can make antibody themselves or become antibody- 2 producing cells. They don't all reside in the 3 peripheral blood. And it's another limitation of what 4 we can do with the information that we generate. 5 So we're not the first to come up with this 6 idea that we need to look for something better than 7 antibody. And, in fact, Sebastian Heidt and Frans 8 Claas came up with this notion recently, published it 9 in Transplantation, and we need more than serum 10 antibody screening. 11 And actually, I can go back to Bob Montgomery 12 and his colleagues at Hopkins when they first began 13 looking at circulating B cells that were specific for 14 antibody production to certain HLA antigens. They did 15 tetramer-specific testing to look at the circulating 16 number of cells that had the ability to produce an 17 anti-HLA antibody. 18 And they found what I think is a pretty 19 remarkably high number in some patients, up to 4 20 percent of the antibodies, in fact, in this slide, up 21 to 6 percent, of the circulating B cells had apparently 22 the ability to make a particular HLA antibody. And</p> | <p style="text-align: right;">Page 256</p> <p>1 appearing in the serum, but they were able to detect 2 them in this assay using gamma interferon binding or, 3 in this case, spots as a detection assay. 4 They continued along these lines. And the 5 purpose of this slide is to take a look among the 6 people -- let's look at the top two individuals -- who 7 were both immunized in the past with HLA-A2. And you 8 see that one of them had 99 spots compared to a second 9 one, who had zero spots. So one could take this to the 10 next level and at least imagine that the one with 99 11 spots had more likelihood to produce A2 antibody upon 12 reexposure to A2 compared to the second patient. 13 The question, of course, is, How many spots do 14 you need to see before that patient is recognized as 15 it's a risk factor for that patient to be transplanted 16 with an A2 donor a second or third time? I don't know 17 the answer to that, and that's not been identified yet. 18 So, again, here, this is more of the same, 19 looking at data in patients who have been exposed to 20 antigens in the past. The key element of this 21 particular slide, if you look at the third set of bars 22 on the left graph -- excuse me, the fourth set of bars</p> |
| <p style="text-align: right;">Page 255</p> <p>1 when they went into the next phase of the study to look 2 at B cells in patients who are about to be transplanted 3 or were transplanted, they looked at the frequency of 4 these cells, and found that somebody who had a previous 5 transplant had a stronger number, a higher number, of 6 these B cells that had the ability to make a particular 7 antibody. 8 So this is an assay that gives you a quick 9 peek at the ability of the cells that have the 10 potential to make antibodies. This doesn't prove that 11 they make antibodies. 12 And so Claas and his colleagues again went one 13 step further with these data and developed an assay, an 14 ELISPOT assay, to look for HLA-specific B cells where 15 they actually quantified the number of cells per 16 million that would make specific HLA antibodies. 17 And in this particular slide, you see that the 18 cells that they took from different patients, these two 19 patients had the ability to make antibodies to HLA-A2, 20 but they didn't make antibodies to HLA-A1 or HLA-A11. 21 But these were from cells that at the time the patients 22 were not necessarily making any antibodies there were</p> | <p style="text-align: right;">Page 257</p> <p>1 on the left graph, we see that in the serum, the 2 patient had no circulating antibody to DRB1*10. 3 However, in this culture of media that I'll be 4 getting to in a moment and how they did this, the cells 5 that were grown in the supernatant from this culture 6 media actually produced an antibody that was not seen 7 in the serum. That meant they had the capacity to do 8 it. It's giving you information of exposure to an 9 antigen that you would have relegated as not being an 10 antigen of concern. 11 So I didn't even get the chance to read this 12 paper. This is now in press, and it's an early view of 13 a paper that was just accepted as I sent my slides in 14 that Frans and his colleagues have got more data that 15 has published the ability of using this particular 16 assay, which involves culturing peripheral blood B 17 cells from your recipients in the context of C40 ligand 18 and cytokine supernatants and a number cells, cell 19 lines, that express certain HLA antigens. It's 20 tedious, but it is a reproducible assay in his hands. 21 But it's not as easy as it looks. All right? 22 As again you start with peripheral blood. You have to</p> |

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1 isolate the cells. You enrich the cells, deplete the T
 2 cells, culture the cells for 7 days. You can see where
 3 I'm going with this. It's not very easy to accommodate
 4 in a clinical laboratory. Once you've done that, you
 5 have to use those cells in number 4 as a stimulator,
 6 add IL-2, IL-10, IL-21, T-cell receptor ligand. And
 7 then you collect, freeze, and store all of these
 8 reagents and look at them for the production of spots
 9 or antibody testing.
 10 It's very labor intensive. It's going to
 11 demand extensive QC, proficiency testing of these
 12 particular components in order to know that you're
 13 doing the right thing. You have to maintain the cell
 14 cultures. This goes on and on. I don't see us doing
 15 this as a routine until we have the ability to do
 16 robotics, but I see this as an immediate need in the
 17 clinical setting.
 18 So one of the other factors that we also have
 19 to consider is once we take these B cells out and look
 20 at them in vitro, what have we now done to the system?
 21 Recently, there has been a great deal of attention on
 22 follicular helper T cells. And follicular helper T

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1 cells have the ability to regulate antibody production.
 2 The way they might do it is by acting on other T cells
 3 that help B cells become antibody producers, or the
 4 follicular regulatory cells work directly on B cells
 5 and prevent them from becoming antibody-producing
 6 cells. So the question becomes once you start to
 7 remove them from the physiological environment and put
 8 them into an artificial environment, what are you
 9 doing?
 10 So the summary from my point of view is that
 11 there is only one test right now that we have for all
 12 issues related to antibodies, and that is our solid
 13 phase multiplex assay. It's not truly quantifiable.
 14 It's not uniform. And it really is the tip of the
 15 iceberg. We have all of these different things to
 16 consider when dealing with the sensitized patient, and
 17 it's critical that we pay attention to these details.
 18 So to conclude, the current tools are better
 19 than anything we've had before, but they still remain
 20 rudimentary. The antibodies -- I said it once, I'm
 21 going to say it again -- they're surrogates for
 22 sensitization and memory. They tell you one part of

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1 the story, not the entire story.
 2 Risk assessment by antibody alone is, at its
 3 very best, incomplete, and at times it can actually be
 4 misleading.
 5 We need to transition to cellular assays for
 6 additional and perhaps better information to help us
 7 treat our patients. And the current testing for T and
 8 B cell memory is still very early in the stages of
 9 development. It's not quantifiable. It's labor
 10 intensive. The clinical applicability, barring my
 11 reading of that paper I showed you, is still
 12 speculative. And as far as I'm concerned, moving
 13 forward, it's definitely going to require some form of
 14 automation. We're going to have to vet all of these
 15 different assays to make sure that they meet our
 16 standards, and then we have to test for the clinical
 17 utility.
 18 Thank you.
 19 (Applause.)
 20 DR. CAVAILLÉ-COLL: Thank you, Dr. Gebel.
 21 Our next speaker is Dr. Robert Gaston, from
 22 the University of Alabama, who is going to address,

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1 "Prevention of Sensitization: Blood Transfusions,
 2 Nonadherence During the Previous Transplant, and the
 3 Management of the Failed Graft."
 4 Dr. Gaston.
 5 Prevention of Sensitization: Blood
 6 Transfusions, Nonadherence During the Previous
 7 Transplant, and the Management of the Failed Graft
 8 DR. GASTON: Again, thanks to the organizers
 9 for the opportunity to attend and participate in this
 10 outstanding meeting.
 11 Those are my disclosures. I apologize for
 12 changing the aesthetics to green. Maybe not.
 13 And I didn't have any conversation with Howie
 14 relative to the talk beforehand, but he really did a
 15 good job of setting the stage for what I want to say in
 16 this. And that is to go back to really our basic
 17 understanding of antibody responses, and they're
 18 basically an appropriate immunologic response to
 19 foreign antigen. They derive from basically four
 20 sources: heterologous immunity, which he presented,
 21 and I use that term very broadly, but the idea that
 22 sensitization can come from sources other than what we

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| <p style="text-align: right;">Page 262</p> <p>1 usually think, which is human antigen exposure. 2 For the patient undergoing initial 3 transplantation, the primary sources of sensitization 4 are pregnancy and blood transfusion. Those remain 5 important in the patient with a failing transplant, but 6 their importance is far superseded by exposure related 7 to a previous transplant, and that's going to be the 8 focus of what I talk about here. 9 The response can be directed at both MHC and 10 non-MHC antigens, but you've heard that addressed by 11 people far more competent than I. And so as we look at 12 this, we're basically talking about the specificity 13 related to exposure to MHC antigens Class I and 14 Class II. 15 This is a very nice study from Cambridge that 16 looks at the relationship between matching and 17 sensitization or DSA production. This is looking at 18 the serologic mismatching and presensitization. The 19 definition of sensitization is an MFI greater than 20 2,000. And this is 131 patients who had failed grafts. 21 What you see in the panel on the left is the 22 Class I antigens, Class II on the right. You can see</p> | <p style="text-align: right;">Page 264</p> <p>1 tacrolimus, even in patients who were pristine, 2 resulted in alloresponses that resulted in 3 discontinuation of the study. You can see this in 4 numerous other minimization studies. This is a CNI 5 minimization study in which patients randomized to be 6 treated with mTOR inhibitor everolimus were 7 substantially more likely to undergo development of DSA 8 than patients who remained on calcineurin inhibitor, 9 and as you can see, there were consequences of that in 10 terms of risk of AMR. 11 So not only do we see that in minimization 12 studies, but we see that in what I really think is 13 ultimate minimization, and that's related to adherence. 14 A lot of the specificity about adherence I will defer 15 to Rita Alloway's talk later in the day, but clearly 16 adherence plays a major role in this. 17 And you can see this work from Chris Wiebe and 18 the Winnipeg group, that on this axis this formation of 19 DSAs among the nonadherent patients, roughly 72 percent 20 by 12 years had developed DSA versus significantly less 21 DSA development in the patients who were adherent. 22 And there are consequences of the DSAs. These</p> |
| <p style="text-align: right;">Page 263</p> <p>1 that largely the patients are unsensitized 2 pretransplant. At the time the grafts fail, there is 3 greater sensitization, with the red being greater than 4 85 percent basically PRAs in this. And then during 5 their time on the list, after they've lost a graft, 6 there may be a time at which the antibody response has 7 become even greater. 8 And you can see here for really all 9 categories, both Class I and Class II, perhaps the 10 Class II response is a bit more intense, but it does 11 correlate with the degree of mismatching in the first 12 graft that was present. So that by the time at some 13 point in the time that the patient is on the waiting 14 list, the majority of the patients do show 15 sensitization or development of DSAs to the previous 16 donor that pose problems when thinking about 17 retransplantation. 18 So what we do know about all this? We know 19 that the development of DSAs is attenuated by 20 immunosuppression. That really comes from two sources, 21 as Dr. Nickerson has already showed, with CTOT-09, one 22 place this comes from, that basically withdrawal of</p> | <p style="text-align: right;">Page 265</p> <p>1 are the histologic consequences with both IFTA and 2 transplant glomerulopathy. You can see whether the 3 injury was subclinical on protocol biopsies or 4 clinical. The clinical expression was much more likely 5 in patients who were nonadherent than in patients that 6 were adherent, but, again, the risk of DSA associated 7 strongly with graft failure, particularly over years 8 and years, and you've already heard that time course 9 today. 10 So when you're thinking about the impact of 11 these events in retransplantation, as you've also heard 12 already, that not all DSA exerts adverse impact in 13 retransplantation. It's dependent on the 14 characteristics of DSA. It's very rudimentary, but 15 things are progressing in terms of defining in relation 16 to class and subclass and so on. It also depends very 17 much on just the gross specificities of the DSA. 18 One clinical impact is that it's hard for 19 these patients to receive another transplant. And 20 that's in this study from Toronto, as sort of 21 exemplified in this graph, and that is that patients 22 who were highly sensitized before the second</p> |

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| <p style="text-align: right;">Page 266</p> <p>1 transplant, basically in order to be transplanted, 2 required a very closely matched graft. So I stuck this 3 slide in basically to say that the first consequence of 4 sensitization in the patient with the failed transplant 5 on the waiting list is it's going to be really hard for 6 them to be retransplanted, and it will be from a very 7 limited well-matched pool for those patients. 8 The other characteristics that may play 9 significance, it appears that the antibodies that may 10 be most detrimental in retransplantation are Class II, 11 Class II rather than Class I. This comes from several 12 studies. 13 This is an analysis of USRDS data from the 14 Toronto group just recently published. What you see 15 here is all-cause graft failure, and then just death- 16 censored graft failure or immunologic graft loss here. 17 And so they fixed at no repeat mismatches as a risk of 18 1 patients who had only Class I mismatch, as it exerted 19 very little impact on outcome of the subsequent 20 transplant, but Class II exerted a much stronger impact 21 in terms of risk of both death-censored and all-cause 22 graft failure.</p> | <p style="text-align: right;">Page 268</p> <p>1 outcomes were most associated with Class II and/or both 2 Class I and Class II DSA. 3 Immunodominance, regardless of how meaningful 4 or meaningless these numbers are, they seem to come out 5 from time to time whether you looked at immunodominant 6 DSA or some of DSA, you see the same sort of effect. 7 They're more likely to be persistent and therefore 8 injurious, and then to be much more broadly reactive 9 associated with a persistent antibody. 10 They then used these data to look at 11 sensitivity and specificity. And actually there's an 12 error in this table because this should be sensitivity 13 and specificity across, and as they raise the MFI, the 14 1,500, 3,500, and 5,500, you see that it becomes much 15 less sensitive as a predictor of DSA -- excuse me -- of 16 persistence in retransplantation, but much more 17 specific with the higher MFI, so the correlation. And 18 then you see in the ROC curve whether you look at 19 immunodominant or some of DSAs, you see the predictive 20 value of changing this relative to the standard. 21 So beyond the characteristics of the DSA, I 22 think a great deal, as also Dr. Gebel said, depends on</p> |
| <p style="text-align: right;">Page 267</p> <p>1 You can see, though, that if you really then 2 tease it out by patients who are nonsensitized versus 3 patients who are sensitized, then the effect of Class 4 II really comes out much stronger in the patients who 5 are sensitized in terms of risk of all-cause and death- 6 censored graft failure with a second graft. So, again, 7 emphasizing the importance of Class II relative to 8 Class I in influencing outcome in the second 9 transplant. 10 You can see a little bit different approach in 11 this data from a French study, that it's a fairly small 12 number of patients, 34 patients, and they looked in 13 these patients -- they defined the patients most at 14 risk of adverse outcomes with the retransplant as those 15 who had persistent DSA that persisted after the 16 transplant, and then they contrasted that with patients 17 that had transient DSA. 18 You can see there is not a lot of difference 19 in terms of transfusion and pregnancy. The patients 20 who had persistent DSA were much more likely to have 21 been sensitized by the previous transplant or to have 22 had more than one sensitizing event. The adverse</p> | <p style="text-align: right;">Page 269</p> <p>1 the milieu that exists in the recipient in terms of 2 preexisting memory, and not to belabor this, this is a 3 20-year old article from Peter Heeger and the group, 4 and these are basically looking at preexisting T cell, 5 memory T cell, response in interferon gamma ELISPOT 6 testing, and these are for two different donor 7 recipient pairs who were equally matched, at least 8 matching as it was termed in those days, and you can 9 see that the T cell reactivity was very different, even 10 with the same degree of matching that was there. So 11 the degree of memory that's present in the patient is 12 very important in determining the relevance of the 13 antibody that's detected in the assays. 14 Another way of looking at this -- and this 15 group has been doing it for some time, as a marker of 16 underlying inflammatory or immunologic reactivity, is 17 looking at soluble CD30. And here where the patient 18 does not have this underlying evidence of immune 19 activation, if you will, you can see no real effect of 20 the DSA on subsequent outcome, whereas if they're 21 positive, if the inflammatory milieu is a bit more 22 aggressive, then DSA becomes a much more detrimental</p> |

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| <p style="text-align: right;">Page 270</p> <p>1 influence.</p> <p>2 So, finally, how do we manage the patient with</p> <p>3 a failed allograft? And the two questions are: Should</p> <p>4 they remain on immunosuppression or should they undergo</p> <p>5 transplant nephrectomy? And if you look at that, you</p> <p>6 have to first, in terms of the immunosuppression</p> <p>7 question, consider -- and this is in a very gross</p> <p>8 fashion, the drugs that we have available to maintain</p> <p>9 immunosuppression in these patients. And what you see</p> <p>10 here are drugs with basically fairly pure T cell</p> <p>11 reactivity. Obviously there is some broadness as you</p> <p>12 move across the spectrum, and this is as close as we</p> <p>13 come to purely B-cell reactive stuff.</p> <p>14 So that when you talk about maintenance of</p> <p>15 immunosuppression, you're basically talking about drugs</p> <p>16 over on this side of the equation that are</p> <p>17 predominantly T-cell focused drugs in terms of</p> <p>18 maintaining immunosuppression. But as has not been</p> <p>19 said here as eloquently as Kathryn Wood says most</p> <p>20 things, and this slide is borrowed from her, is that</p> <p>21 you don't have to have specific anti-B-cell therapy.</p> <p>22 Antihumoral therapy is not essential if the T cells are</p> | <p style="text-align: right;">Page 272</p> <p>1 specific sensitizing events.</p> <p>2 This is the raw reduction in mortality from 36</p> <p>3 to 32 percent, but when they adjusted for other</p> <p>4 variables, it was about a 30 percent risk reduction of</p> <p>5 mortality. And this basically has been used as strong</p> <p>6 evidence that transplant nephrectomy is beneficial in</p> <p>7 the patient with a failed graft.</p> <p>8 You have some other data. This is recently</p> <p>9 published data from Berlin. This looks at patients,</p> <p>10 Group A, or patients who underwent nephrectomy and</p> <p>11 withdrawal of immunosuppression at the same time.</p> <p>12 Group B, patients who underwent nephrectomy but</p> <p>13 remained on immunosuppression. Group C is patients who</p> <p>14 underwent withdrawal of immunosuppression, but retained</p> <p>15 their grafts in place. And you can see that all three</p> <p>16 approaches were associated with increased</p> <p>17 sensitization, perhaps a difference there with Class II</p> <p>18 and the patients who remained on immunosuppression but</p> <p>19 had the graft removed.</p> <p>20 If you go back to the Toronto series that was</p> <p>21 published as well, they looked at the effect on</p> <p>22 retransplantation of nephrectomy again, and again this</p> |
| <p style="text-align: right;">Page 271</p> <p>1 kept under control. The problem is that we don't keep</p> <p>2 the T cells under control.</p> <p>3 So this is a study again from Cambridge</p> <p>4 looking at patients, again this same cohort of 131</p> <p>5 patients with failed allografts who were sensitized.</p> <p>6 They look at the effect of maintaining the patient on</p> <p>7 no immunosuppression, fix that risk as 1, of developing</p> <p>8 significant DSA. Patients who were maintained on</p> <p>9 steroids alone, it had no benefit. Patients who</p> <p>10 remained on CNIs and steroids, there was a substantial</p> <p>11 reduction in univariate analysis here and risk of</p> <p>12 developing DSA. There was also a relationship to time</p> <p>13 since graft failure. And no statistical relationship</p> <p>14 at all of previous blood transfusions or pregnancy,</p> <p>15 again emphasizing the primacy of the transplant.</p> <p>16 The study that really has impacted</p> <p>17 significantly approach to transplant nephrectomy was</p> <p>18 this one published in 2010. The investigators were</p> <p>19 from the Brigham, but this was USRDS data. And it</p> <p>20 basically showed that undergoing transplant nephrectomy</p> <p>21 reduced overall mortality and enhanced the rate of</p> <p>22 retransplantation, and they really did not look at</p> | <p style="text-align: right;">Page 273</p> <p>1 is in the context of repeat mismatches, all-cause graft</p> <p>2 loss, and death-censored graft failure, and they showed</p> <p>3 that nephrectomy was actually associated, and this was</p> <p>4 not an endpoint in that previous study, they showed</p> <p>5 that nephrectomy was associated with an increased risk</p> <p>6 of all-cause graft failure and of death-censored graft</p> <p>7 failure versus patients with no nephrectomy. But,</p> <p>8 again, that seemed to be exacerbated, that risk was</p> <p>9 exacerbated in the patients who had Class II</p> <p>10 mismatches, again sort of emphasizing the primacy of</p> <p>11 Class II DSA in this scenario.</p> <p>12 So to summarize this, the development of DSA</p> <p>13 is attenuated by immunosuppression. Not all DSA exerts</p> <p>14 adverse impact in retransplantation. And in management</p> <p>15 of the patient with a failed allograft, I have no firm</p> <p>16 answers to this. I think in terms of continuing</p> <p>17 immunosuppression, our practice has become to continue</p> <p>18 it, particularly if the graft is in place and if the</p> <p>19 patient is a candidate for retransplantation. If the</p> <p>20 patient undergoes allograft nephrectomy and is a</p> <p>21 candidate for retransplantation, many times we'll</p> <p>22 continue immunosuppression as well.</p> |

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| <p style="text-align: right;">Page 274</p> <p>1 I think that nowadays we've really gravitated 2 to the approach to transplant nephrectomy, that only if 3 it's clinically indicated, there may be some benefit of 4 leaving the allograft in place, although it could, as I 5 think is hinted at in the study by Ayus, et al., that 6 the adverse effects associated with sort of a chronic 7 inflammation milieu may have some negative impact there 8 as well. 9 Thank you. 10 (Applause.) 11 DR. SAMANIEGO-PICOTA: The next speaker is Dr. 12 Robert Montgomery, Director of the Langone Transplant 13 Institute at NYU. 14 Welcome, Bob. 15 New Developments in Desensitization Protocols. 16 Is There a Standard of Care? 17 DR. MONTGOMERY: Thank you. And good 18 afternoon. 19 These are my disclosures. And specifically, I 20 am going to be mentioning quite a few off-label drugs 21 and focusing on the three that I listed here. 22 So it's pretty well established that patients</p> | <p style="text-align: right;">Page 276</p> <p>1 undergoing desensitization. 2 So this is a cohort of patients drawn from 22 3 transplant centers in the U.S. And at the time that 4 each of these patients were transplanted, they were 5 matched with five patients who were either on the 6 waiting list or on dialysis, and with sort of an 7 intent-to-treat type of methodology, we watched to see 8 what happened to the patients. 9 So when we first did our single-center study, 10 we looked at this group of patients -- so these are 11 patients who are on the transplant list who are 12 eligible for a transplant -- and looked to see what 13 happened to those patients, and you can see that there 14 was a significant improvement when the patients were 15 desensitized and transplanted versus staying on the 16 list waiting for a compatible organ. 17 But when we actually drilled down to look at 18 -- is that me or is that -- maybe it's the way the 19 pointer is. But when we actually looked at this group 20 of patients, only 16 percent of the patients received a 21 transplant during that period of time. So, in fact, 22 for 84 percent of your patients, the option wasn't</p> |
| <p style="text-align: right;">Page 275</p> <p>1 who have an antibody-mediated rejection do poorly in 2 comparison to control groups. And certainly when a 3 patient is sensitized and being desensitized, they are 4 at significantly higher risk of developing antibody- 5 mediated rejection than other transplant patients. And 6 so the results aren't as good for patients who have 7 been desensitized. 8 But I think it's important to mention that we 9 should be comparing apples to apples. So when we're 10 looking at the outcomes of desensitization protocols, 11 we need to compare those patients to options that are 12 actually available to them. Okay? So if you're a 13 patient who has a cPRA of 100 percent, receiving a 14 compatible kidney has not been a realistic option, and 15 that should not be our reference group. In other 16 words, we shouldn't be comparing unsensitized patients 17 to sensitized patients in terms of outcomes. 18 And this slide has already been shown, but 19 basically the point I want to make here is that when 20 you look at the other alternatives, which would either 21 be remaining on dialysis or staying on the transplant 22 list, there's a very significant survival benefit to</p> | <p style="text-align: right;">Page 277</p> <p>1 between waiting for a compatible organ versus 2 desensitization, it was staying on dialysis versus 3 desensitization and transplantation. And so that's 4 what this bottom line shows. And this has been 5 reproducible in our single center and in this cohort of 6 patients from 22 centers. There's about a doubling of 7 patient survival at 8 years for patients who undergo 8 desensitization. 9 Now, this slide shows the results of a study 10 that was done at our institution many years ago. And 11 what we did was patients who were desensitized, we 12 looked to see whether their immunodominant antibodies 13 were either eliminated or persisted after 14 desensitization a month after plasmapheresis was 15 stopped. 16 And what you can see is there is a difference 17 between Class I and Class II in terms of whether the 18 antibodies could be eliminated or persisted. So Class 19 I antibodies were eliminated at a much higher rate than 20 DQ antibodies and DR antibodies. And this may explain 21 why patients who have Class II antibodies do more 22 poorly because patients who are sensitized, after they</p> |

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| <p style="text-align: right;">Page 278</p> <p>1 undergo desensitization, are more likely to retain 2 Class II antibodies than Class I. 3 And what we do know -- and many centers have 4 demonstrated this now -- is that when you desensitize a 5 patient, the strength of immunodominant antibody, DSA, 6 going into the desensitization, determines to some 7 degree the fate of the patient after desensitization. 8 So patients who have higher level antibody, greater 9 strength, at a CDC cytotoxic level do more poorly than 10 patients who have antibody that's only detectable by 11 Luminex. 12 And this is probably part of the explanation 13 for why that is. So the way this is -- I'm afraid to 14 use the pointer now -- but the way this is set up is 15 that -- so these are patients who are desensitized who 16 had a negative flow crossmatch but had detectable 17 antibody by Luminex. These are patients who had a 18 positive flow in a negative CDC. And these are 19 patients who had a positive CDC. And this is roughly 20 correlated with MFIs down at the bottom. And what you 21 see is that the rate of rejection is about twice as 22 much for patients who have stronger antibody.</p> | <p style="text-align: right;">Page 280</p> <p>1 a negative CDC crossmatch, and one of them to a 2 positive crossmatch with a titer of 4, and then we 3 desensitized that patient to that paired donor. 4 Now, there has been kind of a game-changer 5 that's happened recently, and I think we should talk 6 about the impact that the new allocation system may 7 have on desensitization. 8 So this shows you the old system. The red 9 line demonstrates that at a cPRA of 80 percent, greater 10 than 80 percent, patients were given 4 points for their 11 priority scoring. Now it's a graduated scale, and as 12 you get closer to 100 percent, the curve gets 13 exponential. And for patients who are at the very high 14 end of that, they get a tremendous amount of benefit on 15 the allocation scoring. 16 And this is the effect that that new system 17 has had at 2 years. So for patients who have cPRAs of 18 99 to 100 percent, the total number of transplants that 19 were done during that period, if you look at this very 20 highly sensitized group of patients, they used to 21 contribute about 2 to 3 percent to the total. Right 22 after KAS was implemented, 17.7 percent of the</p> |
| <p style="text-align: right;">Page 279</p> <p>1 Now, one thing that we showed in our original 2 single-center paper is that even patients who have a 3 positive CDC crossmatch going into their 4 desensitization, we know they don't do as well, but 5 they still do better than the alternative, which is 6 either waiting for a compatible organ or undergoing 7 dialysis during that period. 8 So a number of years ago, we came up with this 9 concept. Again, we were trying to figure out a way to 10 have patients who showed up with a live donor better 11 served than to just desensitize them to their live 12 donor. And so this concept of combining paired 13 exchange and desensitization so that you have a pool of 14 potential donors for a patient, and you match that 15 patient to a donor that will give them the highest 16 likelihood of a good outcome, which is the lowest level 17 of DSA. 18 So in this three-way swap that we did a number 19 of years ago, you can see that pairs 1, 2, and 3 all 20 had CDC crossmatches with titers greater than 1024 to 21 their original donor, their loved one, but by swapping 22 the kidneys around, we were able to get two of them to</p> | <p style="text-align: right;">Page 281</p> <p>1 transplants that were done in the first few months were 2 in patients who had cPRAs of 99 to 100 percent. You 3 saw this bolus effect. Now it's settled down to about 4 10 percent. 5 And if you look at the data from our 6 institution, it's pretty interesting. So the current 7 waiting list at Hopkins has about 1,300 patients on it. 8 And there are about 164 patients who have cPRAs of 98 9 to 100 percent. Since the new KAS system, the number 10 of patients that were transplanted with deceased donor 11 organs that had a cPRA of greater than 98 percent were 12 66, and 64 out of the 66 had cPRAs of 100 percent. 13 So this new system is really only benefiting 14 patients who have cPRAs of 100 percent. And when an 15 organ with an unusual genotype comes out, you'll see a 16 whole bunch of 100 percent patients listed, and you 17 never get down to less than that. 18 And what we saw during the same period is the 19 number of patients that we desensitized with live 20 donors decreased. 21 Now, so let's talk about why this has really 22 changed things. If you consider let's say I have a</p> |

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| <p style="text-align: right;">Page 282</p> <p>1 cPRA of greater than 80 percent, and that's the blue 2 line, in this room, I could find somebody who I would 3 not have any antibody against. Okay? So then why -- 4 the red line on this graph is the likelihood of finding 5 a match in a paired donation pool. So the likelihood 6 for that same patient, me, of finding a match is less 7 than 10 percent, even if you show me 300 different 8 potential donors, right? 9 So why is there this big gap between the two? 10 The reason is that common antigens are common in the 11 population. Common antigens share epitopes with less 12 common antigens. And so all the highly sensitized 13 patients are looking for the same rare genotypes, and 14 it's the competition that makes the transplant rate so 15 low. But if you increase the pool, like we've done 16 with the KAS system, you can increase the number of 17 patients who find that rare genotype. 18 But the important thing to say is that that is 19 going to change because we're just going to shift the 20 patients. So there are patients with 100 percent cPRA 21 who are relatively easy to match compared to other 22 patients with 100 percent cPRA. So this is a spectrum.</p> | <p style="text-align: right;">Page 284</p> <p>1 rituximab? And this was mentioned earlier. Rituximab 2 does not seem to be effective to treat patients who 3 have antibody-mediated rejection -- and this was 4 recently shown in a French study -- but it does seem to 5 be fairly effective at preventing an anamnestic type of 6 response. 7 So Howie showed some of the data from two of 8 the papers, but this is another paper where we use the 9 tetramers to look at B-cell frequencies. So these were 10 patients who had donor-specific B cells but were not 11 making donor-specific antibody. Okay? So they had 12 these cells, memory cells, primarily, that were primed, 13 but weren't making antibody. 14 And then we looked at what happened in the two 15 groups, one that -- so on the left side of the screen, 16 yes and no, is whether they made donor-specific 17 antibody to those specificities after the transplant, 18 and then red is whether they had received rituximab or 19 not. So patients who did make antibody did not receive 20 rituximab, patients who did make antibody did. 21 So there may be some protective effect of 22 rituximab. And I think is shown well in the other</p> |
| <p style="text-align: right;">Page 283</p> <p>1 And then there are patients at the other end of the 2 spectrum that you'll never find a kidney for because 3 they require the rarest genotype. So we're going to 4 shift those down so eventually we will enrich our 5 population of highly sensitized patients for patients 6 who are unlikely to find a match, and that curve is 7 going to continue to come down. It won't come down to 8 3 percent, but it will come down. So the point is 9 there is going to be a need to desensitize some of 10 these patients. 11 So what's the standard of care? Well, there 12 are basically two, and these are accepted by KDOQI, 13 they're accepted by insurance companies, as being a 14 standard of care. There is plasmapheresis and low-dose 15 IVIG, which has been shown earlier, in which you 16 desensitize the patient by doing every other day 17 plasmapheresis, give 100 mg/kg of IVIG after each 18 treatment, get the patient to a reasonable level of 19 antibody, do the transplant, and then continue your 20 plasmapheresis afterwards until you get to a negative 21 flow crossmatch. 22 So the question has been, What is the role of</p> | <p style="text-align: right;">Page 285</p> <p>1 standard of care therapy, which is a combination of 2 IVIG and rituximab. 3 And as also mentioned earlier, this 4 combination seems to be a lot more effective than IVIG 5 alone. And this is data from Cedars showing that, 6 again, this special soup of IVIG and rituximab produces 7 better outcomes than IVIG alone. 8 Now, one kind of encouraging thing is that 9 there is a lot of interest now in therapeutics in this 10 space. And so I've listed here sort of the standard of 11 care therapies and then different drugs that are being 12 used, are being either used or tested, as add-ons to 13 standard of care. 14 So I'm going to focus really on one of these 15 because other ones have already been mentioned. So I'm 16 going to skip over the eculizumab and talk about this 17 new drug called IdeS. 18 So IdeS is an enzyme that's produced by Strep 19 pyogenes, and it's kind of an evil enzyme in that it 20 cleaves human IgG, and it's released in sort of a halo 21 around the bacterium and prevents binding of human IgG 22 antibody to the bacterium. And so it basically</p> |

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| <p style="text-align: right;">Page 286</p> <p>1 inhibits all the Fc-mediated activities. 2 It doesn't affect other antibody classes. 3 It's species-specific, just human and rabbit. Figure 4 that one out. And it cleaves and produces an F(ab')₂ 5 fragment and an Fc fragment, and this happens very 6 rapidly. And the important thing to say is it happens 7 across the entire space in the body. 8 So the way plasmapheresis works is that you 9 remove the IgG from the vascular space, and then it has 10 to reequilibrate because it doesn't do anything to the 11 IgG that's in the interstitium, and that's why it's a 12 very inefficient way to remove antibody, and that's why 13 you wait 2 days in between treatments, so that 14 reequilibration can happen. 15 This drugs knocks out all the IgG in the body, 16 and it does it within 4 hours. 17 So here's an example. This is a highly 18 sensitized patient. So in blue you see all the various 19 antibody specificities and the strength when the 20 patient was given a placebo, and then in red after they 21 received IdeS. The same thing Class II antibody. So 22 very dramatic effect.</p> | <p style="text-align: right;">Page 288</p> <p>1 And the other thing to mention, too, is that 2 it doesn't only cleave IgG, but also B-cell receptors. 3 So the B-cell receptors are all removed from the 4 surface of the B cells. We use Campath after it's safe 5 to do that in terms of the drug. And then we 6 immunomodulate with IVIG and anti-CD20. 7 So I'm just going to give you an example of 8 one patient that we did last week. And this was a 45- 9 year-old who was on dialysis for 20 years and had a 10 cPRA of 100 percent. So what we did is we eliminated 11 all the unacceptable HLA antibodies with an MFI less 12 than 20 percent from her profile. She still had a cPRA 13 of 100 percent, so that's how sensitized she was. 14 We received an offer, 100 percent PRA offer, 15 and this is the flow crossmatch both at the time the 16 patient came in and then 2 hours after IdeS, so it had 17 reduced the crossmatch significantly, but not 18 eliminated, it was still a positive crossmatch. And 19 the CDC crossmatch was positive at a titer of 8, so a 20 very strong antibody. 21 And you can see here that this is the pre- 22 IdeS, and these are the MFIs. So there was a A2</p> |
| <p style="text-align: right;">Page 287</p> <p>1 However, there is trouble in paradise, and the 2 trouble is that the IgG rebounds, and it rebounds 3 within about 14 days. And you can't give more than two 4 doses because humans will make an anti-IdeS antibody, 5 and the immune system reacts very strongly to this 6 enzyme for evolutionary reasons. 7 So the study that we're currently doing is 8 we're taking patients who are very unlikely to receive 9 a transplant, and the FDA was very clear that if we 10 were going to do this study without a control group, 11 the patients had to be unlikely to receive a transplant 12 and otherwise could not receive that organ because of a 13 positive crossmatch. 14 So what we do is bring a patient in who has a 15 positive cytotoxic or flow crossmatch. We give them a 16 dose of IdeS. Two hours later, we recheck the 17 crossmatch. If it's turned negative, we move to 18 transplant. If it's still positive, we give a second 19 dose of IdeS. We do the transplant. We give Solu- 20 Medrol for 4 days because the half-life of the drug is 21 about 4 or 5 days, and remember that it will cleave all 22 of the induction drugs except for Atgam.</p> | <p style="text-align: right;">Page 289</p> <p>1 antibody -- sorry, an A1 antibody at a titer of 24,000, 2 and several Class I antibodies at very high titer. And 3 then this is 2 hours after IdeS. So 24,000, went down 4 to 10,000, and you can see the other antibodies. And 5 then 48 hours, further decrease. 6 And this is 5 days pretty much down to a 7 negative result. So she just got her Campath 8 yesterday. We're starting her high-dose IVIG today. 9 But, again, this is a pretty remarkable response to 10 this new drug. 11 I can't tell you whether this is going to be 12 effective or not, but what I can say is that 13 reproducibly it's lowering the donor-specific antibody 14 very dramatically after the patients receive the drug. 15 So there are lots of people who are involved 16 in this work, and they're listed here. 17 Thank you for your attention. 18 (Applause.) 19 DR. CAVAILLÉ-COLL: Thank you, Dr. Montgomery. 20 Public Comment and Discussion 21 DR. CAVAILLÉ-COLL: We are now going to 22 proceed into our public comment and discussion session.</p> |

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| <p style="text-align: right;">Page 290</p> <p>1 Before we go to the questions from the FDA, I would 2 like to first go around and see if there are questions 3 or clarifying questions for our speakers right now. 4 Dr. Knoll? 5 DR. KNOLL: I have a question for Howie. Is 6 he still over there? Yeah. I just want to go back to 7 that example of the male, unsensitized male, never 8 transfused or transplanted with an antibody that's 9 presumably from a pathogen, as we've been discussing. 10 So are those antibodies, do they have the same 11 pathogenic potential as the same antibody with the same 12 MFI, for example, from a previous transplant? 13 DR. GEBEL: That's a great question that I ask 14 myself every day. And I don't know the answer to that. 15 We treat them as if they do, but the way that they were 16 generated is clearly different, and our readout is the 17 fact that it has the same binding ability, but that 18 doesn't mean that they're going to have the same 19 pathogenic potential, but I don't know how to go about 20 proving that it would or wouldn't. 21 DR. KNOLL: So there is no series of, for 22 example, transplants that have occurred across</p> | <p style="text-align: right;">Page 292</p> <p>1 to get amputated at the end, but by then, they have 2 very bad rejection and are also losing their allograft. 3 So I do believe they are equally, or not all the cases, 4 but at least in my experience they are. 5 DR. CAVAILLÉ-COLL: Okay. Could I have the 6 questions for the Session 2, the public discussion, 7 please? Very well. Okay. 8 The first question we have is sort of a 9 rhetorical one, but we'll see what the strength of the 10 evidence is. How important is it to identify 11 transplant candidates who have donor HLA-specific 12 quiescent memory B cells, but do not have DSA? And 13 should their induction or immunosuppression regimens be 14 different? 15 Anybody want to attack that question? 16 DR. WOODLE: So, Marc, I think what we need is 17 we actually need clinical correlation for these memory 18 B-cell assays that if the assay is positive, what is 19 the actual degree of risk that you have? 20 So even if you identify a patient that has 21 increased risk, then the question is, What are you 22 going to do posttransplant? And I can tell you what</p> |
| <p style="text-align: right;">Page 291</p> <p>1 antibodies that were presumed to be formed in this way 2 where there was in fact a documented bad outcome? 3 DR. GEBEL: Not to my knowledge. 4 DR. SAMANIEGO-PICOTA: Just as an anecdote or 5 as an experience, in a sensitized patient you have 6 desensitized and have recurring urinary tract 7 infections, develop osteomyelitis, those patients all 8 experience a spike in their DSA. Many of them, it's 9 not uncommon to see the patient who's compliant, had a 10 bad infection 2 or 3 weeks before, presents with 11 antibody-mediated rejection. 12 So in particular, patients with osteomyelitis 13 are particularly difficult to treat because we know 14 that infection in the bone, osteomyelitis, is a B cell 15 mitogen. That's why all those patients used to develop 16 amyloidosis in the good old days, stimulates the plasma 17 cell. 18 So we're actually aggressive on those 19 patients. If we don't think they're going to get 20 better, we try to amputate those patients as soon as 21 possible because at the end, it's going to be like the 22 deli, right? The little salami stick. They're going</p> | <p style="text-align: right;">Page 293</p> <p>1 we're doing now in the absence of those. 2 We monitor intensively patients who are at 3 high risk for memory responses, that is, a marked DSA 4 response within the first 7 to 10 days posttransplant. 5 And when we see -- and if their antibodies are 6 negative, we will see epitope clustering and marching 7 of those antibodies towards the 1,500 MFI cutoff, and 8 we can often see that for 2 or 3 days before the 9 antibodies ever exceed 1,500. We will treat those 10 responses before they hit 4,000 MFI. And in the 18 11 months that we've been doing this, we have not seen a 12 clinically overt AMR. We prevent any elevation in 13 creatinine, and we intervene very early. 14 So our answer in our program is the intensive 15 monitoring for epitope clustering in patients that are 16 antibody-negative that you don't need a predictive 17 marker, you're going to intervene anyway. I'd be 18 interested to hear what Howie Gebel and others think 19 about that approach. 20 DR. GEBEL: I think we just need more data, 21 Steve. I mean, it's a good start. And the question 22 becomes there has to be an initiation point. You're</p> |

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| <p style="text-align: right;">Page 294</p> <p>1 doing it.</p> <p>2 DR. WOODLE: Yeah. So we think the answer is</p> <p>3 actually intervention and intensive monitoring. And so</p> <p>4 we presented this data the year before last at the ATC,</p> <p>5 and we'll be submitting the manuscript very soon.</p> <p>6 DR. ROITBERG-TAMBUR: So I can speak for</p> <p>7 Northwestern a little bit. And when we are crossing</p> <p>8 historic antibodies, we usually add Rituxan just for</p> <p>9 good measure as we're doing this, but we definitely</p> <p>10 intensely monitor those patients, and the minute we see</p> <p>11 a spike in the antibodies, then treat it.</p> <p>12 Those respond very well to treatment, and the</p> <p>13 antibody usually is gone, and you continue monitoring</p> <p>14 those patients, and it's not coming back. If you don't</p> <p>15 treat them right away -- and you've shown this in</p> <p>16 several publications -- the horses are out of the barn,</p> <p>17 it's very difficult to then stop the response.</p> <p>18 DR. WOODLE: Yeah, that's exactly what we</p> <p>19 think. We think actually the earlier you catch an</p> <p>20 anamnestic memory response, the better it responds to</p> <p>21 therapy.</p> <p>22 DR. CAVAILLÉ-COLL: Thank you. I think you're</p> | <p style="text-align: right;">Page 296</p> <p>1 that you have a B cell that might have the ability to</p> <p>2 produce those antibodies. If you don't get a positive</p> <p>3 response, it doesn't mean that you don't have those</p> <p>4 cells. And I think that's going to be problematic with</p> <p>5 all the cell-based assays, not to mention those that</p> <p>6 are at different niches, et cetera, et cetera. But I</p> <p>7 think there will be tools that at least can give you a</p> <p>8 positive predictive value, not a negative predictive</p> <p>9 value.</p> <p>10 DR. MONTGOMERY: One approach that we've</p> <p>11 adopted with our desensitization is that patients who</p> <p>12 have repeat mismatches, we just treat those patients</p> <p>13 with rituximab in addition to plasmapheresis and IVIG.</p> <p>14 DR. SAMANIEGO-PICOTA: Yeah, obviously,</p> <p>15 rituximab will be the drug that will be more effective,</p> <p>16 at least what we have right now, in elimination of</p> <p>17 memory B cells. However, something that I learned</p> <p>18 recently coming from the Pittsburgh group is that many</p> <p>19 of the transitional B cells, although a very small</p> <p>20 population in peripheral blood, have a high expression</p> <p>21 of C20. And transitional B cells are essential for the</p> <p>22 development of B-cell tolerance at the level of the</p> |
| <p style="text-align: right;">Page 295</p> <p>1 talking about interventions after transplantation. Is</p> <p>2 there anybody who wants to speak about any testing or</p> <p>3 any results before the transplant that could be used to</p> <p>4 identify these patients who may have quiescent memory B</p> <p>5 cells?</p> <p>6 DR. MONTGOMERY: Well, the tetramers are very</p> <p>7 effective. The problem is that there is a very limited</p> <p>8 number of specificities that we have tetramers to. So</p> <p>9 that's the downside of that.</p> <p>10 Anat?</p> <p>11 DR. ROITBERG-TAMBUR: Javeed Ansari,</p> <p>12 transplant nephrologist from Northwestern, is actually</p> <p>13 using the One Lambda single-antigen beads in a B-cell</p> <p>14 assay, I think it's 12, 13, whatever number of colors</p> <p>15 on a flow cytometry, so it can actually qualify at what</p> <p>16 stage of development those B cells are. And he has</p> <p>17 some interesting data, and I'm part of those studies,</p> <p>18 but I do see significant limitation of those studies.</p> <p>19 What you can see is the whatever, 40 cc's, 100</p> <p>20 cc's of blood that you're testing, and you don't really</p> <p>21 know what else is going to be there, those are rare</p> <p>22 events. So if you get a positive response, you know</p> | <p style="text-align: right;">Page 297</p> <p>1 spleen.</p> <p>2 So the question would be we can still use the</p> <p>3 rituximab as an induction or as a -- we used to do in</p> <p>4 Hopkins a week or two before the transplant, because in</p> <p>5 that case, by the time the transitional cells are</p> <p>6 moving from the bone marrow to the periphery to the</p> <p>7 spleen, anti-CD20 hopefully will be out of the way, and</p> <p>8 that subset will not be depleted.</p> <p>9 The question with rituximab continues to be,</p> <p>10 When is the right timing to give the drug? At what</p> <p>11 period of the transplantation history is the best time?</p> <p>12 And only by doing these peripheral studies and using</p> <p>13 different combination of drugs, we're going to be able</p> <p>14 to learn what is really happening in these patients.</p> <p>15 DR. GEBEL: So, Millie, also in regards to</p> <p>16 when is the right time to give Rituxan, I think an</p> <p>17 alternative question is, When might be the wrong time</p> <p>18 to give it? I went to a CIAT (ph) meeting recently,</p> <p>19 and I think it was somebody from Anil Chandraker's</p> <p>20 group who tried to use Rituxan in patients to prevent</p> <p>21 AMR and compared it to placebo, and actually the</p> <p>22 patients with the placebo had less rejection, as if you</p> |

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| <p>1 were getting rid of a regulatory B cell.</p> <p>2 DR. SAMANIEGO-PICOTA: Yeah. These products</p> <p>3 of rituximab is very well known. Clatworthy described</p> <p>4 it in the New England Journal several years ago. Those</p> <p>5 patients treated with rituximab actually had more T-</p> <p>6 cell-mediated rejection. But then the Scandinavians</p> <p>7 and the Japanese that may give it at a different</p> <p>8 timing, those patients have less incidence of cellular</p> <p>9 rejection even when they do not have a major impact in</p> <p>10 incidence or lack thereof antibody-mediated rejection.</p> <p>11 So we really do not know the right timing.</p> <p>12 And there is a very old paper now from Francis</p> <p>13 Larned (ph) about the use of rituximab and what has</p> <p>14 been learned with rituximab from the lupus and the</p> <p>15 autoimmune diseases trials in which many of these</p> <p>16 patients actually did better, not because of any effect</p> <p>17 that rituximab would have in antibody production, but</p> <p>18 in modification of T-cell responses. The timing is</p> <p>19 when we're going to have it. When we have the B</p> <p>20 regulatory cells or the B effector cells, I can leave</p> <p>21 that to Anita Chong to talk a little bit more in detail</p> <p>22 tomorrow, but the timing of giving the drug seems to be</p> | <p>1 algorithm. Basically what we do is we decide what</p> <p>2 level of antibody we're willing to desensitize to, and</p> <p>3 then we drop out all the unacceptables that have</p> <p>4 antibody at that strength and below.</p> <p>5 So I think your point is very good. That</p> <p>6 probably should be part of the decision-making process.</p> <p>7 DR. SAMANIEGO-PICOTA: Bob, I have a question</p> <p>8 for you about your IdeS protocol. Why Campath and why</p> <p>9 CD2?</p> <p>10 DR. MONTGOMERY: Why?</p> <p>11 DR. SAMANIEGO-PICOTA: Campath.</p> <p>12 DR. MONTGOMERY: And what was the second one?</p> <p>13 DR. SAMANIEGO-PICOTA: In the CD2.</p> <p>14 DR. MONTGOMERY: Oh, right, right. Okay.</p> <p>15 Well, you know, it was primarily driven by, you know,</p> <p>16 when you're doing a study, a multicenter trial, you</p> <p>17 have to compromise. And Stan's group was very</p> <p>18 committed to alemtuzumab, and the other alternative</p> <p>19 would have been to start Atgam earlier because Atgam is</p> <p>20 not cleaved. But, anyway, we compromised, and we</p> <p>21 decided on this.</p> <p>22 I think the important thing about the protocol</p> |
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| <p>1 important.</p> <p>2 DR. CAVAILLÉ-COLL: Dr. Haas?</p> <p>3 DR. HAAS: Yeah, I actually had a question for</p> <p>4 Bob, and this actually is not one of these two, but</p> <p>5 concerns sort of the combining of paired exchange and</p> <p>6 desensitization.</p> <p>7 Do you specifically pair exchange away from DR</p> <p>8 mismatches or Class II sensitivity, Class II DSAs, even</p> <p>9 at low titer? So if you were faced with a patient who</p> <p>10 had a low titer anti-Class II against their donor</p> <p>11 versus a high titer, even a positive cytotoxic anti-</p> <p>12 Class I, would you pair exchange away from those and go</p> <p>13 ahead and try and desensitize against the high-titer</p> <p>14 Class I given that the Class II is more likely to</p> <p>15 persist and cause TG?</p> <p>16 DR. MONTGOMERY: That's a great question. I</p> <p>17 would say that our selection of a donor is based</p> <p>18 primarily on the strength of the antibody rather than</p> <p>19 the class of the antibody, but it is noted when we're</p> <p>20 reviewing whether this is a good candidate for that</p> <p>21 patient, whether it's all Class II antibody, and we try</p> <p>22 to avoid that, but it's not formalized in our</p> | <p>1 is that you're immunomodulating the patient's immune</p> <p>2 system in a quiescent state. So when we do these</p> <p>3 transplants where there is significant amount of donor-</p> <p>4 specific antibody, you get the innate response from the</p> <p>5 transplant itself, from transplant injury. And then</p> <p>6 you get antibody injury, you get a tremendous amount of</p> <p>7 endothelial disruption, and then this thing sort of</p> <p>8 spirals out of control.</p> <p>9 When we go in with no antibody and we're able</p> <p>10 to maintain that for a period of days to weeks, I think</p> <p>11 that this approach, at least philosophically, seems to</p> <p>12 make more sense.</p> <p>13 Stan and I, both of our fathers were World</p> <p>14 War II pilots, and Stan's dad used to always say it's</p> <p>15 easier to repair an airplane on the ground.</p> <p>16 (Laughter.)</p> <p>17 DR. MONTGOMERY: And so I think to some extent</p> <p>18 that's what we're doing with this protocol, we're</p> <p>19 intervening at a time when there's not a tremendous</p> <p>20 amount of inflammation, and we'll see what happens.</p> <p>21 But this is the most exciting drug, this is the most</p> <p>22 exciting thing I've seen in this field in the last 15</p> |

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| <p>1 years. So we're hopeful.</p> <p>2 Bob?</p> <p>3 DR. COLVIN: Bob, what happens to the</p> <p>4 F(ab')₂s? Do they stay in the circulation? They might</p> <p>5 be very good blocking reagents for that very same</p> <p>6 patient later on.</p> <p>7 DR. MONTGOMERY: Yeah. I mean, it's -- so</p> <p>8 there's that thought, and then there's also the idea</p> <p>9 that you still will get binding of the fragment of</p> <p>10 antibody to the endothelium, it can't activate</p> <p>11 complement, but it may be able to induce endothelial</p> <p>12 apoptosis or injury -- a la Elaine Reed's work -- and</p> <p>13 so it may not completely eliminate inflammation, but</p> <p>14 your thought is an interesting one as well, yeah.</p> <p>15 DR. SAMANIEGO-PICOTA: Steve Woodle?</p> <p>16 DR. WOODLE: So, Bob, we're following that</p> <p>17 work kind of closely. And there are a couple of things</p> <p>18 that came to mind when we first looked at it. One is,</p> <p>19 as you mentioned, the lattice formation that a F(ab')₂</p> <p>20 can form with a Class I or Class II complexes on the</p> <p>21 endothelium.</p> <p>22 The other one is when you look in the papers</p> | <p>1 if you look at the westerns that I've seen anyway, you</p> <p>2 just see two bands. You see F(ab')₂ and an Fc, but you</p> <p>3 may have seen data that I haven't seen.</p> <p>4 So the FDA was very worried about this as</p> <p>5 well, and so we're doing 24-hour creatinine clearance</p> <p>6 with protein measurements for the first 9 days after</p> <p>7 the transplant, which it's not as bad as a biopsy, but</p> <p>8 it's still very difficult to accomplish. But that's</p> <p>9 what we're doing.</p> <p>10 DR. CAVAILLÉ-COLL: Dr. Haas?</p> <p>11 DR. WOODLE: Yeah, one other question, Bob.</p> <p>12 How long do you think the IdeS molecule is</p> <p>13 enzymatically active after single-dose administration?</p> <p>14 DR. MONTGOMERY: So it's about 3 to 4 days.</p> <p>15 DR. WOODLE: And that's why you delay</p> <p>16 administration of any IVIG or any monoclonal or</p> <p>17 polyclonal antibody, therapeutic antibody, for that</p> <p>18 many days.</p> <p>19 DR. MONTGOMERY: Yes. Right.</p> <p>20 DR. CAVAILLÉ-COLL: Okay. Dr. Haas, please.</p> <p>21 DR. HAAS: Steve, in answer to your question,</p> <p>22 I have looked at some biopsies of patients who have</p> |
| Page 303 | Page 305 |
| <p>1 that have been published, and you look at the western</p> <p>2 blots representing the degraded protein fragments, it</p> <p>3 looks as if there are actually fragments that are</p> <p>4 smaller than light chains, suggesting that maybe the</p> <p>5 enzyme doesn't just stop cleaving at the points that</p> <p>6 you pointed out, but that it can further cleave the</p> <p>7 light chains and heavy chains.</p> <p>8 And I wonder, if you cleave several grams of</p> <p>9 protein suddenly in a patient, will you not create a</p> <p>10 situation similar to that seen in myeloma nephropathy,</p> <p>11 where you have tremendous amounts of protein that hit</p> <p>12 the kidney that cannot be cleared at once? Indeed,</p> <p>13 there is some literature suggesting that you get a</p> <p>14 significant proteinuria within hours after</p> <p>15 administration of IdeS. So the question I have is, How</p> <p>16 are you looking at that and what does your protocol</p> <p>17 include as far vis-à-vis the FDA in terms of looking at</p> <p>18 injury to graft resulting from this massive protein</p> <p>19 degradation?</p> <p>20 DR. MONTGOMERY: So I haven't seen those data</p> <p>21 that suggest that there is ongoing cleavage because</p> <p>22 this enzyme is very specific for the hinge region. And</p> | <p>1 received the IdeS, and I haven't noticed anything that</p> <p>2 resembles like a myeloma cast nephropathy. I haven't</p> <p>3 specifically looked at protein reabsorption droplets in</p> <p>4 the tubules, but the light chains, you know, they</p> <p>5 specifically combine with the Tamm-Horsfall protein,</p> <p>6 and certain pHs and interactions of the light chains</p> <p>7 with the Tamm-Horsfall proteins are important. And</p> <p>8 there are certain light chains that are tubulopathic</p> <p>9 and there are certain light chains that are not</p> <p>10 tubulopathic, and it has to do with the property of the</p> <p>11 light chain.</p> <p>12 So just having a lot of proteinuria per se due</p> <p>13 to cleavage of the immunoglobulin wouldn't necessarily</p> <p>14 in itself produce a cast nephropathy, although you</p> <p>15 would have to have sort of a tubulopathic light chain</p> <p>16 to really do it. And maybe it's important to first</p> <p>17 study the light chains of the DSAs that you're trying</p> <p>18 to cleave to make sure that they wouldn't qualify as a</p> <p>19 tubulopathic light chain. But I haven't seen it in any</p> <p>20 of the biopsies.</p> <p>21 DR. WOODLE: Yeah, I just wanted to correct</p> <p>22 what I had said about the westerns. The actual data is</p> |

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| <p style="text-align: right;">Page 306</p> <p>1 from IdeS cleavage of IgG in human blood from one of 2 the IdeS articles. And there is actually further 3 degradation of the heavy chain, but not the light 4 chain. I misspoke. 5 Mark, I think that's reassuring data, but I 6 think that -- do you think urinary pH plays a role? 7 DR. HAAS: Yeah, I do. Certainly it does in 8 cast nephropathy, that patients whose urinary pH plays 9 a role, concentration plays a role, dehydration 10 certainly plays a role. We see cast nephropathy very 11 often in people who are dehydrated. So maintaining 12 strong hydration during IdeS therapy would, if there's 13 any kind of a risk, would decrease that risk. 14 DR. WOODLE: Are we getting too far off the 15 path and going on for too long? Because there are 16 other questions we could go on with. 17 DR. SAMANIEGO-PICOTA: Any other questions? 18 DR. WOODLE: So you could alkalize the urine 19 is another thing you could do? 20 DR. HAAS: I don't know. I would have to 21 actually look that up. But hydration and urine pH -- 22 DR. WOODLE: Renata, I just wanted to bring up</p> | <p style="text-align: right;">Page 308</p> <p>1 of them are clustered near 99.5 percent, which is about 2 a 1-in-200 chance of actually finding a match, but 3 there are others that extend out to 1 in 1 million. 4 So within that population of a cPRA of 100 5 percent are patients who are very transplantable under 6 the old allocation, very much more transplantable under 7 the new KAS, but there is still a population, very 8 importantly, who are virtually untransplantable. 9 And so what he then did was took a number 10 called "number of patients required to match." We have 11 been applying that number for the past couple of years 12 in the context of our IND-approved carfilzomib protocol 13 as an endpoint for desensitization. We actually think 14 it is the endpoint that the agency should view now as 15 potentially the preferred endpoint for desensitization, 16 that is, the reduction in the number of donors required 17 to match with desensitization. It is sensitive, it is 18 powerful, and it far exceeds the old cPRA data. 19 ATTENDEE: Hear, hear. 20 DR. ALBRECHT: So just to follow up, has that 21 been corroborated by others or do you -- 22 DR. WOODLE: So this is really new.</p> |
| <p style="text-align: right;">Page 307</p> <p>1 one additional point, and Bob got to this, but there 2 has actually been what I think is an important advance 3 in looking at the transplantability of patients with a 4 cPRA of 100. And this is a paper by Marcelo Pando 5 Rigal. It's been published in Human Immunology just 6 within the last months. It may actually be in press. 7 It's actually early, early view. 8 But what he did was he calculated -- so at 9 UNOS, with a calculated PRA, once you hit 99.5 percent, 10 you're automatically rounded up to 100. And what he 11 has done is taken what he calls a decimal PRA 12 calculator where he actually calculates the PRA up to 13 six digits rather than the traditional two, with cPRA, 14 but actually four that's available with the UNOS CPR 15 calculator on the Internet. And so what it can do is 16 it can calculate chances of being transplanted up to 1 17 in 1 million. 18 And if you look within the 100 percent -- so 19 one of the things he did in the paper is he looked 20 within the cPRA 100 percent population in UNOS and 21 looked at -- I can't remember exactly how many patients 22 it was, I think it was between 1,000 and 2,000. Most</p> | <p style="text-align: right;">Page 309</p> <p>1 DR. ALBRECHT: Right. 2 DR. WOODLE: It's really new -- 3 DR. GEBEL: It's not that new, Steve. Last 4 year I published a paper with the SRTR where we modeled 5 2010 data, and basically out of the 5,000 people who 6 were in the 100 percent category, if you allocated all 7 the organs that were transplanted to that group 8 starting 100 percent and then it went down to 99, 98, 9 what you found -- and you would allow every organ to be 10 offered to every patient. 11 So as a group, it turned out that the 100 12 percenters had an average of three offers per 13 individual. However, if you broke those down, there 14 were 3,700 people out of the 5,000 who were actually 15 able to get a median of six offers, an average of 17, 16 but there were about 1,300 patients who didn't get a 17 single offer. And if we look at those patients, those 18 patients were all over 99.9. And more recent data from 19 Nicole Turgeon and UNOS, the Kidney Committee, has 20 shown that it's 99.95 which is the cutoff. 21 So I believe Marcelo's data, no question about 22 it, but it's not unexpected.</p> |

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| Page 310 | Page 312 |
| <p>1 DR. WOODLE: Yeah, so 99.95 is 1 in 2,000, 2 which when you look at the number of donors that are 3 out there per year in the United States, and break it 4 down by blood group, that's an offer per patient, 5 actually one offer or less per patient. And so -- 6 DR. GEBEL: It's 99.95, not 99.5. 7 DR. WOODLE: Oh, I'm sorry, I'm sorry. 8 DR. GEBEL: 99.95. 9 DR. WOODLE: So it's 5 in 10,000. 10 DR. GEBEL: Yeah. 11 DR. WOODLE: Okay. So, but the point is that 12 these are actually -- not only that, but these are 13 kidneys that are shipped, and they usually have several 14 hours of cold time, and you don't know about the 15 quality of them. And so if you really need a high- 16 quality kidney with short cold time, these patients are 17 still at desperate risk to find a matchable donor. 18 I mean, the point is, is that there are better 19 ways than cPRA that are out there. They're emerging. 20 They aren't currently existent. But calculating the 21 change in the number of donors required to match before 22 you desensitize and after you desensitize is actually</p> | <p>1 tomorrow, of course, although it is the last talk of 2 the day tomorrow, so -- 3 (Laughter.) 4 DR. KNECHTLE: We've just shown 5 mechanistically in a non-human primate model that 6 proteasome inhibitors actually activate the lymph node 7 germinal center. So BAFF levels are increased, IL-6 8 goes up, and so we are proposing that dual targeting is 9 a better strategy if you want to have a durable effect 10 of reducing DSA with proteasome inhibitors or any other 11 means of targeting of plasma cells. So that's turned 12 out to be a useful model. 13 Thanks, Steve. 14 DR. MONTGOMERY: I would say the anti-IL-6 15 receptor blocking antibodies are interesting. The C1 16 INH, the C1q inhibitor, because it's blocking the 17 pathway to a much more proximal level before the 18 anaphylatoxins are being produced, which are not blocked 19 by C5 inhibitors. And there's a lot of work going on 20 there right now. 21 And I think probably what we're going to end 22 up with at the end of the day is some combination of</p> |
| Page 311 | Page 313 |
| <p>1 the direction which we think the primary endpoint of 2 desensitization is going to move. It's not there yet, 3 but it's moving. 4 DR. ALBRECHT: Thank you. So we look forward 5 to hearing more on that topic. 6 DR. SAMANIEGO-PICOTA: So, Bob and Steve, if 7 there is anything new in desensitization treatments, 8 would you say, in addition to IdeS? 9 DR. WOODLE: I think Bob's data with IdeS is 10 great. I mean, he and Stan are really forging a 11 pathway to that agent, and I think that it's something 12 we've really got to watch. 13 I would mention that in the proteasome 14 inhibitor work, that there's a lot going on. I'm going 15 to talk a little bit about it tomorrow. I specifically 16 wanted to mention Stuart Knechtle's recent primate work 17 published in JASN that indicates that there's a strong 18 proliferative response that's associated with 19 proteasome inhibitors that may explain the rebound. 20 I don't know, Stuart, if you want to talk a 21 little bit about that. 22 DR. KNECHTLE: Sure. I'll be talking about it</p> | <p>1 the standard of care therapy with these add-on 2 therapies that will produce better results. 3 And I think also trying to identify the 4 patients that are going to most benefit from 5 desensitization versus those who are likely to be 6 matched with the KAS system is going to be a really 7 important contribution. 8 So I think -- I mean, I have to say I'm more 9 optimistic that we're getting a better handle on this 10 now than I was 5 years ago, where we just seemed to be 11 doing the same thing over and over again. And there 12 were some centers, referral centers, that had a lot of 13 experience, that that experience was difficult to 14 translate and to proliferate to other centers, and a 15 lot of it was kind of anecdotal, but those centers had 16 pretty good results. 17 I think now we're starting to develop some 18 tools that are going to be able to be used by a wider 19 audience because they're more effective. 20 DR. SAMANIEGO-PICOTA: Dr. Djamali? 21 DR. DJAMALI: I have a question for you guys. 22 How do you handle a slight decline in PRA from 99</p> |

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| Page 314 | <p>1 percent to, let's say, 97 or 96, and then losing their</p> <p>2 priority with the Kidney Allocation System?</p> <p>3 ATTENDEE: Don't let them lose priority.</p> <p>4 ATTENDEE: Right.</p> <p>5 DR. MONTGOMERY: You can always find some low-</p> <p>6 level antibodies that you might otherwise have</p> <p>7 eliminated. And there are groups, I think Emory, you</p> <p>8 know -- certainly I know UCSF, they list all the</p> <p>9 unacceptables regardless of the strength, and they're</p> <p>10 still getting a lot of organs, so that it depends on</p> <p>11 your comfort level at your institution. If you want to</p> <p>12 list all of the unacceptables, you're less likely to</p> <p>13 have your patients match, but you're probably more</p> <p>14 likely to have a better outcome. And the places that</p> <p>15 are really comfortable with desensitization would</p> <p>16 probably be a little more supporting and allow flow-</p> <p>17 level antibodies, and we'll see how that turns out.</p> <p>18 But clearly what we know is that if your</p> <p>19 patient is not at 100 percent, they are very, very</p> <p>20 unlikely to get an offer. Now, that may shift as we --</p> <p>21 the bolus effect, you know, if you think about it,</p> <p>22 we're going to transplant all those 100 percenters who</p> | Page 316 | <p>1 system when you -- you want your patient at 99.5,</p> <p>2 transplantable at 99.5 percent, because that gives them</p> <p>3 national priority, a cPRA of 100, and gives them a 1-</p> <p>4 in-200 chance of finding a donor. Okay?</p> <p>5 So ideally, even if you remove an antigen, you</p> <p>6 can declare it nonacceptable and still have it count</p> <p>7 towards the PRA. So if you overshoot with</p> <p>8 desensitization, you take somebody that's got a decimal</p> <p>9 PRA that gives them a chance of 1 in 10,000, let's say</p> <p>10 you overshoot and they get to 98 percent, I would have</p> <p>11 unacceptables in there where that patient would be at</p> <p>12 99.5, and that's what's going to get them transplanted.</p> <p>13 And that's gaming the system to some degree,</p> <p>14 but it's actually improving their chances of being</p> <p>15 transplanted, and at the same time, keeping national</p> <p>16 priority.</p> <p>17 DR. MONTGOMERY: It's really -- you know, it's</p> <p>18 establishing your threshold for positivity, and there</p> <p>19 are no regulations about that right now.</p> <p>20 DR. WOODLE: Exactly.</p> <p>21 DR. MONTGOMERY: So when I came to NYU there</p> <p>22 were like 10 patients with cPRAs over 90 percent, and</p> |
| Page 315 | <p>1 are easier to transplant, and then we're going to be</p> <p>2 left with this group of patients that are 1,000 percent</p> <p>3 cPRA. And we probably will start to shift down then to</p> <p>4 patients who are at the 99, 98, 97 percent, because</p> <p>5 this is competition. That's all it is. You run the</p> <p>6 100 percent list on a rare genotype that everybody is</p> <p>7 looking for, and you get like 70, 100 percenters who</p> <p>8 match, and they're listed by wait time and everything</p> <p>9 else.</p> <p>10 It's never going to get down to that 99</p> <p>11 percent patient. But that's going to thin out those --</p> <p>12 those 100 percent patients are going to thin out, and</p> <p>13 so then I think it's going to be less important. But</p> <p>14 right now, having your patient at 100 percent by</p> <p>15 changing the MFIs that you count as unacceptables is</p> <p>16 the key.</p> <p>17 DR. WOODLE: Yeah. So if you have no living</p> <p>18 donor, you game the system. Okay? And the idea is to</p> <p>19 get the patient --</p> <p>20 DR. MONTGOMERY: I don't think that's gaming</p> <p>21 the system.</p> <p>22 DR. WOODLE: Well, I think it's gaming the</p> | Page 317 | <p>1 our list was like 350 patients. I was like, how is</p> <p>2 this possible? This is crazy. And so then I</p> <p>3 discovered that they had put their benchmark, their</p> <p>4 threshold, at an MFI of 10,000, right? So, you know,</p> <p>5 we dropped it down. I don't see that that's gaming the</p> <p>6 system, that's just smart -- you know, that's just</p> <p>7 understanding -- and, again, it's also understanding</p> <p>8 the system, but also your capabilities and what you're</p> <p>9 able to do and how likely are you able to rescue a</p> <p>10 patient, be able to rescue a patient who gets into</p> <p>11 trouble after one of these transplants?</p> <p>12 What I'm really looking forward to are the</p> <p>13 data on outcomes. Now, the 2-year data, which I've</p> <p>14 just looked at, actually looks pretty darn good for</p> <p>15 these 100 percent PRA'ers in terms of graft loss.</p> <p>16 But it's going to be interesting as time goes</p> <p>17 on to see how suddenly you've got all these patient who</p> <p>18 have, like this patient, been waiting 20 years, and</p> <p>19 they have all sorts of comorbid conditions. They</p> <p>20 haven't been seen by a doctor in years, right? And</p> <p>21 suddenly they're getting offers. It's frightening</p> <p>22 actually some of the stuff you see. And I can't</p> |

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| <p style="text-align: right;">Page 318</p> <p>1 believe that it's not going to have an impact on 2 outcomes. 3 DR. CAVAILLÉ-COLL: Thank you. I think Stuart 4 Knechtle has something to say. 5 DR. KNECHTLE: I just wanted to ask the panel 6 for -- I think it was Mark Stegall who basically 7 discussed this notion of clinical trial design with 8 ongoing modification, and it's basically to try to get 9 at this tough problem. We're not about to do 10 controlled clinical trials of no therapy versus therapy 11 in this area. This is a very difficult area. Here we 12 are with the FDA and this is a good time, I think, to 13 discuss, "How do you take novel agents?" 14 Bob, you told us about IdeS. We've got some 15 promising results in the non-human primate that we 16 would like to move into human clinical trials. The 17 typical way is you do a couple of patients. You showed 18 us a case report. How do we move beyond one to five 19 patients into a rational design of a novel and high- 20 risk therapy? 21 DR. WOODLE: So I'll take a stab at it because 22 this was part of the talk that I had yesterday. So my</p> | <p style="text-align: right;">Page 320</p> <p>1 AMR in the controls such that when it reached 2 enrollment, the treatment difference didn't meet the 3 predefined expectations, and it didn't match up to the 4 power calculation. 5 That trial, had it been conducted under an 6 adaptive trial design where the number of patients 7 enrolled could have changed, would have led to an FDA 8 recommendation for approval of that drug. Instead, now 9 the drug is dead in transplant -- okay? -- in the U.S. 10 right now, at least for that indication. The company, 11 I think, my impression is that it's been abandoned. 12 I would love to see that trial resurrected 13 under an adaptive trial design, allowed to extend 14 enrollment, and then possibly lead to an indication. 15 I can tell you right now in my hospital, if I 16 have atypical HUS and I have a kidney that's shutting 17 down, the biopsy looks like it may be TMA or something 18 like that, I can get eculizumab no problem because 19 there is no concern about payers paying for it. But if 20 I've got a kidney that's threatened to either rupture, 21 it's oliguric ATN, it's a threatened rupture, the 22 patient is going to lose the graft, the head of the</p> |
| <p style="text-align: right;">Page 319</p> <p>1 talk was on progress in AMR. And in particular, I 2 found the eculizumab trial in the U.S. an outstanding 3 example of how old traditional methods can fail a good 4 drug that's effective. And I know this will be 5 repeating some things, but I think it's important for 6 industry to hear how I think some of us think about 7 that trial. 8 That trial was designed based on Mark's 9 incidences, historical, based on a flow crossmatch of 10 300 or greater, with control, basically IVIG 11 desensitization,, to give you an AMR rate of about 40 12 percent. The estimated effect of the drug was to 13 reduce it to 10 percent. An old tired traditional 14 power calculation was done, and the number of patients 15 was established. 16 The trial was conducted. Enrollment was slow, 17 very typical for an AMR type of study, and the expanded 18 center is still low. I think there was internal 19 pressure. I'm very careful about what I want to say 20 here. But the inclusion criteria were altered, and 21 they were lowered so that patients with lower barriers 22 of antibody were let in, and that lowered the rate of</p> | <p style="text-align: right;">Page 321</p> <p>1 Pharmacy and Therapeutics Committee has to approve it, 2 and I have to beg, borrow, and steal, and then he calls 3 my chairman and says, "Woodle wants to order this 4 expensive drug that's going to cost the health system 5 \$400,000. Do you approve it?" And I can only get it 6 maybe for one patient a year or two. 7 That's the reality we live in. And it's 8 because -- and I think that FDA bears some 9 responsibility for the field being in that position 10 with eculizumab because we need adaptive trial designs 11 and we need more innovative ways. But I think -- and I 12 would be interested in what my colleagues have to think 13 about it, but that's the personal way that I view what 14 happened with that drug in that trial. 15 DR. MONTGOMERY: Well, Steve, you explained 16 that perfectly. I think that, you know, the -- so the 17 acute AMR rate was the same at the Mayo Clinic as it 18 was in the Phase 2/Phase 3 trial, but it was the 19 control group that was different. And I think the 20 problem with eculizumab is it got a two-punch effect, 21 and that's that it's the TG data from the Mayo Clinic. 22 Now, the thing about the protocol -- and I</p> |

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| <p style="text-align: right;">Page 322</p> <p>1 argued with Alexion forever about this -- is that they 2 didn't have -- so the patient would get desensitized, 3 then they would get the drug, and then they would just 4 get observed, and most of the patients went into the 5 transplant with significant amounts of antibody. 6 And the problem is if you allow large amount 7 of antibodies to circulate over a very long period of 8 time, even if you have a complement inhibitor on board 9 -- and remember most of these patients it was stopped 10 after the first month or two -- you are going to get 11 TG, right? So I think a much more rational approach 12 would have been to make sure that the antibody was 13 lowered to some threshold after the transplant while 14 the patient was on eculizumab. 15 The problem with that is you have to redose 16 the drug after each plasmapheresis treatment. Nobody 17 likes to do that. It's an expensive drug. Nobody 18 likes to pull it off afterward. But that, at least in 19 our experience, if you can lower that antibody and sort 20 of protect the endothelium during that period, you get 21 a good outcome and you don't get TG. 22 So it's going to be hard to resuscitate</p> | <p style="text-align: right;">Page 324</p> <p>1 where the field is going and new opportunities and some 2 of the great new biologics that are being developed in 3 other areas, can you speak to whether you are finding 4 any obstacles or lost opportunities because of the 5 complexities of trying to get drugs developed for one 6 particular area and trying to then apply it to this 7 particular relatively high-risk area that precludes you 8 from designing trials with some of these really 9 incredible new agents? 10 DR. MONTGOMERY: I would say actually there is 11 a tremendous amount of openness right now on the part 12 of PhRMA to address this unmet need. And the 13 difficulty is the studies, and the difficulty with the 14 studies is enrollment. And, again, I think if this 15 group can talk in more detail about how to overcome the 16 fact that we're dealing with a relatively speaking rare 17 event at any transplant center, and how to really 18 design an effective study when that's the case, PhRMA 19 is really open to advancing these drugs. So I think 20 that's the problem. 21 DR. KAUFMAN: Is that kind of a universal 22 experience by some of the other investigators? Steve,</p> |
| <p style="text-align: right;">Page 323</p> <p>1 eculizumab because there are two reasons not to -- 2 there are three reasons not to like it. 3 DR. ALBRECHT: So could Dr. Bill Irish and 4 then the gentleman at the mic, and then Dr. Colvin. 5 DR. IRISH: Yeah, so I'm going to talk about 6 unique design strategies tomorrow in a little bit of 7 detail, but the adaptive design, that's been well 8 vetted statistically for a while now, but those designs 9 are complicated. They're complicated analytically, and 10 they're subject to a certain level of operational bias. 11 So flow of information has to be protected when you're 12 doing an adaptive design. 13 So the operational components of that are much 14 more complicated. But there is certainly a viable 15 strategy, especially for studies in which you have a 16 rare condition. 17 DR. SAMANIEGO-PICOTA: Gentleman, Dr. Dixon 18 Kaufman. 19 DR. KAUFMAN: Thank you. Dixon Kaufman, from 20 the University of Wisconsin. We're hearing about some 21 really innovative new therapies. And I have a question 22 for the investigators. And as you are thinking about</p> | <p style="text-align: right;">Page 325</p> <p>1 Arji or others that are -- 2 DR. WOODLE: So one of the problems we've 3 encountered is that -- and this one is certainly 4 understandable -- is that when a drug gets FDA 5 approval, for example, for cancer in an expedited 6 pathway, and it's a nonrandomized trial, you can forget 7 it until the randomized trial is completed. Okay? 8 They really -- the companies are very, very worried 9 that we will see a toxicity that will jeopardize them 10 before they meet the requirements for full approval. 11 And if there is some way that that level of 12 toxicity can -- that companies can be reassured that if 13 toxicity is seen in another population, it won't count 14 against the population they're really interested in, 15 that might help us. But when I sit back and look at 16 the number of drugs being developed in oncology, and we 17 look at the number of drugs that are being developed in 18 autoimmune disease -- RA has had 10 drugs approved in 19 the last decade or so, we've got 1, every one of them 20 was looked at -- almost every one of them was looked at 21 transplant -- what you're seeing and what you're 22 hearing here, most of what you've heard today, except</p> |

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1 for IdeS, is a drug that's being taken from another
 2 area, another franchise area, and moved into
 3 transplant.
 4 We're begging, borrowing, stealing, going to
 5 PhRMA on our knees begging to get a small pilot to look
 6 and show feasibility in a small pilot trial. If I can
 7 get \$250,000 to do a small pilot, I feel lucky. But
 8 that's where most of what you're hearing today and the
 9 excitement is, is drugs being brought over.
 10 And young people that don't have track records
 11 and don't have street cred that some of these guys
 12 have, have no chance of getting drug from those
 13 companies. If you walked in and you've got a CV and
 14 you've shown you've been doing this for 20 years, you
 15 might can do it.
 16 And so where it really hurts is young
 17 investigators, much more than it hurts the senior
 18 investigators. And as we get old and retire, I don't
 19 know what's going to happen.
 20 DR. SAMANIEGO-PICOTA: Dr. Colvin?
 21 DR. COLVIN: Thank you. I want to get back to
 22 the eculizumab trial. And a lesson that I think we can

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1 learn from that trial, and it has to do with
 2 personalized medicine, at the Banff conference we heard
 3 a postdoc analysis of their studies with eculizumab
 4 that indicated that two things predicted the response
 5 to eculizumab: C1q fixation by the antibody in vitro
 6 and a five gene set from the renal transplant biopsy.
 7 And the lesson I think that makes is that we
 8 need to incorporate exploratory phenotyping, if you
 9 will, of our patients into these trials so we can
 10 identify subsets that may respond to these very, very
 11 specific agents.
 12 DR. SAMANIEGO-PICOTA: Dr. Knechtle?
 13 DR. KNECHTLE: I just wanted to follow up on
 14 Dixon Kaufman's question because there's an obvious
 15 example of what he's talking about and that I'm faced
 16 now. So one of the agents I'm looking at is an anti-
 17 CD40 monoclonal antibody that's currently in Phase 2 as
 18 well as Phase 3 trials, and to put that into a novel
 19 indication right now despite very promising preliminary
 20 data is unacceptable to the company that owns it
 21 because that would potentially result in data that has
 22 to be disclosed and might be negative. So as far as

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1 the company is concerned, no go until they're past
 2 their Phase 2/3 clinical trials. I think most people
 3 in this room probably are aware of that challenge. But
 4 that's a reality. You don't --
 5 DR. SAMANIEGO-PICOTA: Dr. --
 6 DR. KNECHTLE: -- a drug in a novel
 7 indication.
 8 DR. SAMANIEGO-PICOTA: Sorry.
 9 Dr. Djamali.
 10 DR. DJAMALI: I would like to echo what Steve
 11 was saying. It is extraordinarily complex to combine
 12 therapies involving PhRMA with different drugs. It
 13 makes mechanistic sense, and you all agree that we need
 14 more than two or three agents to handle these kind of
 15 complex patients. But try to get three, two, companies
 16 collaborate, and sometimes with the NIH, to get the
 17 paperwork done, it's just incredible. That's why when
 18 you see the studies that we propose or we demonstrated
 19 here, to have 10 patients for the vast majority of
 20 time, and that's the sad part.
 21 So I think it's going to be tough, but we need
 22 support from you guys and PhRMA, if they are here, to

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1 conduct good, strong mechanistic studies.
 2 DR. SAMANIEGO-PICOTA: I just have a question
 3 for the group, and this will be the last Marc tells me.
 4 It's time to go on a break. What about the creation of
 5 consortia specifically focusing at the combined
 6 academic-pharma enterprise looking into this?
 7 I worked with consortia now for about 15
 8 years, and although it takes time, at least with
 9 CTOT-09 and CTOT-19, the group of investigators
 10 developed the protocol, everybody was on the same line.
 11 Although recruitment could be a little painful,
 12 recruitment is actually going. So I do not know if you
 13 guys think that it's probably time to get a couple of
 14 consortia groups prepared and put together for that.
 15 DR. ALBRECHT: I would like Inish O'Doherty to
 16 answer that one.
 17 DR. O'DOHERTY: Hi. Inish O'Doherty, from the
 18 Critical Path Institute. And in answer to your
 19 consortia question, so we've started the Transplant
 20 Therapeutics Consortium, between is between the AST and
 21 ASTS, and we have eight industry members already. We
 22 have our first face-to-face coming up in May. We're

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| <p style="text-align: right;">Page 330</p> <p>1 selecting working group topics to work on. Obviously, 2 there is plenty in the field that can be put forward as 3 a topic, but we're trying to limit our scope to things 4 we can achieve and hope to have success in the first 5 couple of years. I'm happy to share more information 6 as we progress in that.</p> <p>7 DR. ALBRECHT: And just on behalf of FDA, as 8 you know, as Dr. Mannon summarized, we've been holding 9 a number of open public workshops trying very much to 10 sort of talk about these areas of unmet need. And the 11 role we have is, again, we are the regulators, and we 12 meet with individual investigators, with companies, 13 under IND meetings, provide advice, help talk about 14 protocols.</p> <p>15 I think Dr. Woodle identified a problem that 16 is not new to us, that we see that very good protocols 17 are designed, and then for whatever reasons, they get 18 modified, and sometimes they succeed, and sometimes 19 they don't. And so we're very aware of these 20 challenges and continue to try to provide both public 21 venues as well as through the IND route to discuss 22 these topics. Thank you.</p> | <p style="text-align: right;">Page 332</p> <p>1 DR. SAMANIEGO-PICOTA: Thank you. I want to 2 thank everyone and the FDA for the invitation to this 3 symposium.</p> <p>4 These are my disclosures. I don't have any 5 conflicts, but I will be talking about many drugs used 6 off-label. The whole talk is about off-label use.</p> <p>7 About 5 years ago, there was a meta-analysis 8 published in Transplantation by Roberts and colleagues 9 using the grade system to assess the quality of the 10 different papers published on the topic. And the goal 11 of the meta-analysis was to analyze all the drugs that 12 had been published as effective drugs in the treatment 13 of antibody-mediated rejection, and these are listed 14 here on this column.</p> <p>15 And if you look based on the grade system, the 16 evidence supporting the treatment, only plasmapheresis, 17 plasma exchange, and immunoabsorption, according their 18 methods, had enough scientific background to be used as 19 therapies.</p> <p>20 Unfortunately, we know that although this is 21 certain, many of these drugs also have an effect, some 22 in a greater extent than others, but all of them had</p> |
| <p style="text-align: right;">Page 331</p> <p>1 DR. CAVAILLÉ-COLL: Well, thank you. With 2 that, let's break for 15 minutes and come back here at 3 5 before 4:00. Thank you.</p> <p>4 (Break.)</p> <p>5 Session 3: Factors Contributing to Antibodies 6 in the Post-Transplant Period</p> <p>7 DR. BELEN: Hello, everyone. This is our 8 third and final session. I'm going to moderate this 9 session along with Dr. Anat Tambur. And my name is 10 Ozlem Belen, and I'm from the FDA.</p> <p>11 The name of this session is "Factors 12 Contributing to Antibodies in the Post-Transplant 13 Period."</p> <p>14 And our first presenter is Dr. Millie 15 Samaniego, from the University of Michigan. She is 16 going to present, "The Choice of Induction and 17 Maintenance Immunosuppression and their Impact on 18 Preexisting and De Novo Antibodies."</p> <p>19 Okay. Dr. Millie Samaniego.</p> <p>20 The Choice of Induction/Maintenance 21 Immunosuppression and their Impact on Preexisting and 22 De Novo Antibodies</p> | <p style="text-align: right;">Page 333</p> <p>1 been published at having some kind of beneficial 2 results in patients with antibody-mediated rejection.</p> <p>3 This meta-analysis was also interesting 4 because it shows how it has changed the interest in 5 drugs treating antibody-mediated rejection throughout 6 the years. And what is more interesting is that you 7 see that tacrolimus, that you cannot see here very well 8 because of the way the slide projects, one of the drugs 9 that although we know today have a major role in 10 preventing the development of de novo antibodies, was 11 considered to be in the bottom of the pile.</p> <p>12 Now, if one goes to a pharmacology class, a 13 transplant pharmacology class, all of the drugs that we 14 use today in the management of antibody-mediated 15 rejection, early or late acute antibody-mediated 16 rejection, have an effect at least theoretically and 17 should have some benefit theoretically in the outcomes 18 of these patients, yet in real life, in practice, that 19 does not happen all the time.</p> <p>20 For the purposes of this lecture, I am going 21 to include primarily induction agents, belatacept, 22 alemtuzumab, ATG, and talk primarily about mTOR</p> |

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| <p style="text-align: right;">Page 334</p> <p>1 inhibitors and CNIs, will talk briefly about rituximab, 2 and I have left bortezomib to the expert speakers 3 tomorrow so they will have more time to present their 4 data, and hopefully it won't happen what happened to me 5 where all my slides have been shown already this 6 morning.</p> <p>7 So primarily the induction agents are being 8 used in antibody-mediated rejection with the goal of 9 suppressing T-cell responses. From that standpoint, we 10 have the depletional and the non-depletional agents, 11 agents that can be used in the treatment of antibody- 12 mediated rejection as well as the prevention of it, and 13 we also have agents that use primarily as depleters of 14 antibody-producing cells, or their precursors.</p> <p>15 Thymoglobulin. Thymoglobulin is an 16 interesting drug used off-label, FDA approved for the 17 treatment of rejection, not approved for the -- that we 18 use as an induction agent. However, it's the most 19 commonly used induction agent in the United States.</p> <p>20 This is a study that my friend Arjang Djamali 21 published now 3 years ago in Transplantation. This is 22 a single-center retrospective study in patients that</p> | <p style="text-align: right;">Page 336</p> <p>1 that received the interleukin 2 receptor antagonist for 2 induction, suggesting that these patients not only have 3 an early beneficial effect in modulating the immune 4 response, but also may have a later modulating event 5 that at least can be detected up to 24 months after the 6 transplant event and the induction therapy.</p> <p>7 Now, this has been replicated in this very 8 interesting paper by Peter Reese's group that just got 9 published in the electronic format at JASN last month 10 where he shows patients registered in UNOS who have 11 also had a Medicare charge for transplantation, they 12 matched multiple pairs of patients that had either been 13 induced with Thymo and alemtuzumab or induced with 14 Thymo and basiliximab. And he goes to show that there 15 is a very mild but yet statistically significant 16 benefit in the survival of patients treated with 17 Thymoglobulin compared to those treated with 18 basiliximab. There was no statistical significance in 19 the survival without sepsis, neither it was in the 20 survival on allograft, without allograft failure, or 21 lymphoma or melanoma, which is not included here.</p> <p>22 So Dr. Djamali and his group concluded that</p> |
| <p style="text-align: right;">Page 335</p> <p>1 were transplanted between 2009 and 2011 with a presence 2 of donor-specific antibody with MFIs within this range. 3 Their flow crossmatch prior to transplant was negative. 4 And patients were either treated with rabbit ATG or 5 basiliximab on the basis of the surgeon that was in 6 charge of the patient at the time of admission.</p> <p>7 All patients received TAC, MPA, and 8 prednisone-based immunosuppression. And the goal of 9 the study was to look at the difference in these two 10 groups in cellular rejection, antibody-mediated 11 rejection, and development of donor-specific 12 antibodies.</p> <p>13 The two figures that we're going to see right 14 now are logram (ph) analysis of the incidence of 15 antibody-mediated rejection in these two groups, and 16 it's clearly evident here that patients treated with 17 ATG had a much lower incidence of acute antibody- 18 mediated rejection than those treated with the 19 interleukin 2 receptor antagonist.</p> <p>20 Interesting as well, we see that the 21 development of donor-specific antibodies in the ATG- 22 treated patients is lower than what we see in patients</p> | <p style="text-align: right;">Page 337</p> <p>1 Thymoglobulin was associated with a reduction in the 2 incidence of donor-specific antibody and antibody- 3 mediated rejection without significant infections, side 4 effects, that can be attainable to this drug, and that 5 he suggested as well that randomized clinical trials 6 were necessary to address this issue.</p> <p>7 As far as I know, there is only one randomized 8 trial that was done comparing interleukin 2 receptor 9 antagonist and Thymoglobulin, was done by Bob 10 Montgomery and his group at Hopkins.</p> <p>11 And, Bob, if you want to comment about that 12 trial later, please be my guest.</p> <p>13 The next one is alemtuzumab. And I have to 14 say that I have bias or my experience with alemtuzumab 15 is colored by the years I spent at the University of 16 Wisconsin. And I don't pretend to be an expert, there 17 are experts in this group, about Campath.</p> <p>18 As you know, it's a humanized monoclonal 19 antibody against CD52, which is a pan T-cell marker. 20 It's also expressed by B cells, monocyte, macrophage, 21 and natural killer cell lineage.</p> <p>22 Now, it was introduced as an induction agent</p> |

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| <p style="text-align: right;">Page 338</p> <p>1 in desensitization protocols in this study that you 2 have heard quite a bit today, was the 2008 paper of the 3 results of the rituximab and IVIG regimen at Cedars- 4 Sinai. 5 What I never understood about the use of 6 Campath was the predisposition and the reports that 7 induction with alemtuzumab could be associated with the 8 generation of antibodies. Many people in this room had 9 published case reports about the development of 10 autoantibodies in patients being treated with 11 alemtuzumab for other types of autoimmune diseases. 12 It's known to know that they may develop 13 thrombocytopenic purpura, they may develop thyroid 14 disease, so on and so forth. 15 Jun Cai, after working in Wisconsin with 16 Stuart, went to the Terasaki Foundation, and they 17 looked at some of the patients that Stuart had 18 recruited in the alemtuzumab induction trial. This was 19 a calcineurin-avoidance protocol. And 42 percent of 20 the patients enrolled in this study went on to develop 21 Class I and Class II anti-HLA antibodies that were 60 22 percent donor-specific and 40 percent non-donor-</p> | <p style="text-align: right;">Page 340</p> <p>1 alemtuzumab? This trial, an initial trial, is the 2 INTAC study group trial that, as we all know, showed no 3 difference between ATG and alemtuzumab in high-risk 4 patients. There was no significant difference in terms 5 of the antibody cellular-proven rejection, biopsy- 6 proven acute rejection. There was no difference in 7 patient or graft survival. There was a benefit of 8 alemtuzumab in the development of early infections 9 compared to Thymoglobulin. 10 Now we move to the study of Peter Reeves. In 11 this study, he compares all the outcomes of patients 12 that receive antibody induction in kidney 13 transplantation. It's a very well-designed and 14 statistically balanced paper. 15 At the end, after the exclusion criteria, he 16 ends up with approximately 36,000 patients, about over 17 5,000 induced with alemtuzumab, close to 10,000 induced 18 with basiliximab, and over or close to 22,000 induced 19 with rabbit ATG, and he matches patients with 20 alemtuzumab and ATG that can be matched on specific 21 criteria that are mentioned in the paper, and as well 22 matches that he makes between basiliximab and ATG.</p> |
| <p style="text-align: right;">Page 339</p> <p>1 specific. And of these patients that developed 2 antibodies, 40 percent, 4, have gone on to develop 3 clinical and histological antibody-mediated rejection 4 during the period of follow-up. 5 Those who critiqued this study mentioned that 6 the reason why these patients were at a risk to develop 7 antibodies is because this was a CNI-free protocol. 8 The only study that I really found was published in 9 Transplant Procedures, and the University of Michigan 10 seems to be a little bit snobby, and we couldn't have 11 access to the paper, so this is data from the abstract. 12 These were patients published from a single center in 13 Pennsylvania transplanted between 2009 and 2011, all of 14 whom received tacrolimus and MMF immunosuppression with 15 steroid with avoidance. 16 They go on to show in this small study that 17 the incidence of antibody-mediated rejection was 18 significantly higher in patients that receive 19 alemtuzumab induction compared to those who receive 20 rabbit ATG, whereas the incidence of acute cellular 21 rejection was comparable. 22 So what do we know from the literature about</p> | <p style="text-align: right;">Page 341</p> <p>1 The data between ATG and basiliximab you 2 already saw. The data between alemtuzumab, in the 3 solid line, and ATG, in the hashed line, is shown here. 4 There was a benefit in the probability of survival in 5 those patients that were treated with ATG compared to 6 those treated with alemtuzumab. There was also a trend 7 for patients treated with ATG to have a lower -- or a 8 higher survival without -- a lower survival without 9 sepsis, but this did not reach statistical 10 significance. But when we get the survival without 11 allograft failure, obviously the patients treated with 12 Thymoglobulin fare much better than patients treated 13 with alemtuzumab. There was no difference, although a 14 little trend towards the end of the comparison 15 benefiting Thymo versus alemtuzumab in patient survival 16 without lymphoma. 17 Now, regardless of the induction agent that 18 one decides to use for depletion purpose of the 19 T-cell compartment, we know from the studies from Allan 20 Kirk and Pearl, at the NIH, that neither ATG or 21 alemtuzumab has a great effect in controlling 22 immunological response, memory response. No effect in</p> |

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| <p style="text-align: right;">Page 342</p> <p>1 central memory, very little effect in CD45RA memory in 2 the peripheral tissues. And no effect on the effector 3 memory. 4 Now, we move again coming from the depletion 5 agents in T-cell responses to depletion agents that 6 may have effect in T-cell biology, but are primarily 7 directed to depletion of antibody cells, either 8 precursors or in the plasmablast stage. 9 Now, we have discussed, and some of you have 10 seen the presentation of this trial. It was the final 11 trial in which the Cedars-Sinai group compared in a 12 randomized fashion IVIG alone versus rituximab and IVIG 13 for desensitization of patients between 2011 and 2012. 14 The goal of enrollment was 90 patients, but this study 15 was stopped early because of the incidence of antibody- 16 mediated rejection compared in the IVIG alone arm of 17 the study compared to antibody-mediated rejection in 18 the rituximab and IVIG arm. 19 Important aspects of this study, in addition 20 of the higher incidence of antibody-mediated rejection 21 in the IVIG alone, was that in first place there was a 22 rebound of antibody 6 months after treatment and</p> | <p style="text-align: right;">Page 344</p> <p>1 different treatments? This is a study that Mark 2 Stegall published 10 years ago in which he reviewed all 3 the patients at Mayo Clinic that had been desensitized 4 with different protocols: high-dose IVIG; a 5 combination of rituximab, IVIG, and plasma exchange; a 6 combination of plasmapheresis, IVIG, monitoring; and a 7 group of patients that receive all treatments combined. 8 And what is obvious is that as one adds more 9 synergistic agents, the incidence of antibody-mediated 10 rejection decreases substantially, but the group that 11 fares the best is the group that is treated with 12 synergistic agents, but also managed with 13 posttransplant DSA monitoring. 14 We move now to belatacept. Belatacept, as you 15 know, has been linked to higher incidence of T-cell- 16 mediated rejection, not only in frequency, but also in 17 the severity of the rejection and the need for 18 antilymphocytic therapy. However, even when this is a 19 very well-documented fact, patients that are treated 20 for induction with belatacept tend to develop lower 21 levels of donor-specific antibodies in spite of the 22 higher incidence of rejection compared to the control</p> |
| <p style="text-align: right;">Page 343</p> <p>1 transplant in the IVIG placebo group that was not 2 observed in the group that was treated with IVIG and 3 rituximab. None of the patients with IVIG and 4 rituximab had antibody-mediated rejection in protocol 5 biopsies. 6 And this is what I think the value of 7 rituximab should be nowadays, is in the prevention or 8 control of rebound. You have seen these already today. 9 This is the study of Annette Jackson at Johns Hopkins, 10 where you can see the rebound of antibodies in patients 11 that receive rituximab and in patients that did not 12 receive rituximab. 13 You can also see that there is a significant 14 change in the MFI in those patients that were induced 15 with rituximab compared to those who did not receive 16 the induction. And although it is true that there was 17 no statistical significance between graft or patient 18 survival, rituximab for patients with high levels of 19 antibody facilitates the management of those patients 20 and reduces the number of plasma exchange treatments 21 that they usually require. 22 So what happens when we combine all the</p> | <p style="text-align: right;">Page 345</p> <p>1 arms. 2 Move to the complement inhibitors. And you 3 heard from Mark Stegall this morning about these 4 patients, and what he's seen in the early outcomes is 5 that there is a lower incidence of antibody-mediated 6 rejection, that these patients require less 7 plasmapheresis, less splenectomy; in other words, can 8 be rescued in an easier way than patients that only 9 receive plasmapheresis and IVIG. The initial benefits 10 seen with eculizumab stems from protection of the 11 endothelium by inhibition of the distal formation of 12 the MAC complex. 13 Now in long-term outcomes, there was no 14 difference between outcomes and the initial benefit, as 15 you heard today about that eculizumab had on transplant 16 glomerulopathy disappears. And the reason why it 17 disappears, you also heard from Mark today, is because 18 these patients have continuous microcirculatory 19 inflammation, and the reason of the maintenance of the 20 inflammation is that none of these patients that 21 require eculizumab for a long time had a reduction in 22 antibody levels.</p> |

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| <p>1 C1q inhibitor has only been utilized in this</p> <p>2 day and age for desensitization. This is the protocol</p> <p>3 that was utilized. No difference was observed between</p> <p>4 one group or the other, but the important message is</p> <p>5 that although C1q inhibitor seems to work fairly well</p> <p>6 in reducing titers of antibodies, when the titers are</p> <p>7 low, there is very little effective of C1q inhibition</p> <p>8 in reducing donor-specific antibody levels.</p> <p>9 Finally, we have tocilizumab. And tocilizumab</p> <p>10 has been used right now for the treatment of chronic</p> <p>11 antibody-mediated rejection. The greatest benefit that</p> <p>12 we can encounter in this group of treated patients is</p> <p>13 the effectiveness that tocilizumab has in resolving the</p> <p>14 microcirculatory injury and inflammation that</p> <p>15 eculizumab and other complement inhibitors have not</p> <p>16 been able to achieve.</p> <p>17 Finally, we see that the best drugs in</p> <p>18 inhibiting CD4 memory cells continue to be the</p> <p>19 calcineurin inhibitors. You have seen this slide</p> <p>20 several times today of the CTOT-09 trial where</p> <p>21 obviously patients that were continued on calcineurin</p> <p>22 inhibitors develop less donor-specific antibody than</p> | <p>1 nonadherence.</p> <p>2 Thank you.</p> <p>3 (Applause.)</p> <p>4 DR. BELEN: Thank you. Next we have Dr.</p> <p>5 Arthur Matas, from the University of Minnesota, and he</p> <p>6 is going to present, "Calcineurin Inhibitor and</p> <p>7 Corticosteroid Minimization and Avoidance Protocols and</p> <p>8 HLA Antibodies."</p> <p>9 Calcineurin Inhibitor (CNI) and Corticosteroid</p> <p>10 Minimization/Avoidance Protocols and HLA Antibodies</p> <p>11 DR. MATAS: Thank you. Thank you for the</p> <p>12 opportunity to be here. The nice thing is I got to</p> <p>13 hear everyone else's talks as well. And it's been a</p> <p>14 terrific day.</p> <p>15 I'm going to try and talk quickly because a</p> <p>16 lot of what I am going to present has been shown by a</p> <p>17 number of speakers.</p> <p>18 I've got no disclosures related to this</p> <p>19 presentation, but we do have grant funding from a</p> <p>20 number of companies to continue our DeKAF study. And I</p> <p>21 won't discuss any off-label drugs.</p> <p>22 When one talks about calcineurin and</p> |
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| <p>1 those that were withdrawn and kept on MMF and</p> <p>2 prednisone.</p> <p>3 DR. ALBRECHT: Dr. Samaniego, could you wrap</p> <p>4 up, please?</p> <p>5 DR. SAMANIEGO-PICOTA: Something similar</p> <p>6 happens when we withdraw patients or maintain patients</p> <p>7 on calcineurin inhibitors. This is a cohort you saw</p> <p>8 this morning as well showing patients that had an</p> <p>9 increase in incidence of DSA when they were withdrawn</p> <p>10 from cyclosporine and treated alone with MMF and</p> <p>11 everolimus, something similar occurs in the incidence</p> <p>12 of antibody-mediated rejection.</p> <p>13 So in conclusion, I would say that we do have</p> <p>14 effective immunosuppression that has been available</p> <p>15 since the 20th century. In my opinion, CNI-based</p> <p>16 regimens should be the first choice for patients at</p> <p>17 risk to develop antibody-mediated rejection. Rituximab</p> <p>18 should be considered in patients with rebound. And</p> <p>19 there are much more important issues that still have to</p> <p>20 be -- need to be addressed, as the number of</p> <p>21 mismatches, the association of BKV infection, with de</p> <p>22 novo antibody production, DSA monitoring, and</p> | <p>1 corticosteroid minimization, it's important to</p> <p>2 recognize that the steroid sparing studies were done</p> <p>3 before anyone really tested donor-specific antibody,</p> <p>4 and so the endpoints of those trials were really acute</p> <p>5 rejection and graft loss, whereas more recently with</p> <p>6 calcineurin minimization, we had antibody testing to</p> <p>7 use as an endpoint. And so as I present this steroid</p> <p>8 data, really there is long-term follow-up, but very</p> <p>9 little DSA data.</p> <p>10 The goals of prednisone minimization trials</p> <p>11 were really to avoid prednisone side effects. And we</p> <p>12 certainly heard from our patients this morning the</p> <p>13 plethora of prednisone side effects that we've been</p> <p>14 trying to avoid in our patient population. The hope</p> <p>15 was to do that without an increase in acute rejection</p> <p>16 and no change in chronic graft loss.</p> <p>17 And these trials started in the prednisone-</p> <p>18 Imuran era with calcineurins and cyclosporine, and</p> <p>19 there were a number of trials with cyclosporine-</p> <p>20 prednisone or cyclosporine-Imuran-prednisone with</p> <p>21 prednisone withdrawal, and essentially with selected,</p> <p>22 clinically well low-risk patients, these trials</p> |

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| Page 350 | <p>1 resulted in increased acute rejection and increased</p> <p>2 graft loss, and that was shown in a meta-analysis by</p> <p>3 Bert Kasiske.</p> <p>4 When CellCept was brought in, there were two</p> <p>5 major trials, one in Europe and one in the United</p> <p>6 States, in which prednisone withdrawal was tried late</p> <p>7 posttransplant on a background of cyclosporine and</p> <p>8 CellCept, and both of those trials showed an increased</p> <p>9 incidence of acute rejection after steroid withdrawal.</p> <p>10 And, in fact, with late steroid withdrawal there are</p> <p>11 meta-analysis showing significant increases in acute</p> <p>12 rejection.</p> <p>13 And this led to trials of what I would call</p> <p>14 rapid discontinuation of prednisone, and Steve Woodle</p> <p>15 calls early corticosteroid withdrawal, in which</p> <p>16 prednisone is stopped in less than 2 weeks, and usually</p> <p>17 within 1 week posttransplant, and essentially there</p> <p>18 have been numerous single-center studies, randomized</p> <p>19 and non-randomized, but as well, meta-analyses and</p> <p>20 registries reports on these early prednisone-stopping</p> <p>21 studies, all showing an increased incidence in acute</p> <p>22 rejection rates, or the majority at least showing that,</p> | Page 352 | <p>1 Dr. Woodle's study was the only prospective,</p> <p>2 randomized, double-blind study early on. In that</p> <p>3 study, there was antibody induction with TAC and MMF</p> <p>4 and prednisone for 7 days versus a taper to 5 mg by 6</p> <p>5 months. And the major findings at 5 years were there</p> <p>6 was increased biopsy-proven rejection in the steroid</p> <p>7 withdrawal group, albeit in a subanalysis less with</p> <p>8 Thymo than with IL-2R.</p> <p>9 There was no difference in the primary</p> <p>10 endpoint, which is a composite of death, graft loss, or</p> <p>11 moderate to severe acute rejection, no difference in</p> <p>12 the rate of antibody-mediated rejection, no difference</p> <p>13 in renal function, and the steroid withdrawal group had</p> <p>14 improvements in cardiac risk factors.</p> <p>15 The only study looking at antibody development</p> <p>16 in steroid withdrawal was one published by Cantarovich</p> <p>17 in AJT in 2014. In that study, there was anti-</p> <p>18 thymocyte globulin induction with cyclosporine and</p> <p>19 CellCept and zero prednisone versus a steroid taper for</p> <p>20 at least 6 months. The major findings at 5 years,</p> <p>21 increased biopsy-proven acute rejection in the zero</p> <p>22 prednisone group again, but no difference in death,</p> |
| Page 351 | <p>1 albeit some of them are early and mild and easy to</p> <p>2 treat.</p> <p>3 There has been no increase in steroid-</p> <p>4 resistant rejection, no impact on patient and graft</p> <p>5 survival, and a number of reports showing that rapid</p> <p>6 steroid withdrawal is associated with significantly</p> <p>7 lower rates of new onset diabetes, cardiovascular risk</p> <p>8 factors, avascular necrosis, and fractures.</p> <p>9 In one report by Pascual and Cochrane</p> <p>10 analysis, noted there was a significant increase in</p> <p>11 acute reject with rapid discontinuation of prednisone</p> <p>12 only when cyclosporine was used, and that was not true</p> <p>13 when tacrolimus was used. But in reverse, when the</p> <p>14 decrease in new onset diabetes was only seen when</p> <p>15 cyclosporine was used, not when tacrolimus was used.</p> <p>16 It was a very interesting analysis because it</p> <p>17 said there were a few studies of the benefits of rapid</p> <p>18 discontinuation of prednisone, and I think those of us</p> <p>19 that started these trials never thought to try and</p> <p>20 measure things like skin changes and appearance</p> <p>21 changes, it was just sort of intuitively obvious that</p> <p>22 if you didn't use the drugs, you would not have those.</p> | Page 353 | <p>1 graft loss, or renal function.</p> <p>2 Determination of DSA was actually not planned</p> <p>3 in that study, but they had the information in 151 out</p> <p>4 of the 197 patients, and they reported that in each</p> <p>5 group, about 11 percent developed donor-specific</p> <p>6 antibody, obviously no difference between groups. And</p> <p>7 interestingly, their steroid protocol was noted to have</p> <p>8 increased diabetes, dyslipidemias, and in this</p> <p>9 particular study, malignancies.</p> <p>10 One of the concerns about rapid</p> <p>11 discontinuation of prednisone has been that late</p> <p>12 posttransplant graft survival might be worse. And this</p> <p>13 is our data. And our study is not randomized; it's</p> <p>14 looking at steroid-free versus historical controls.</p> <p>15 We now have 15-year data, and we decided we</p> <p>16 would look at those that survived 5 years with graft</p> <p>17 function. So we got rid of all the early noise. And</p> <p>18 you can see on the left, living donor; on the right,</p> <p>19 deceased donor; on the top, patient survival; on the</p> <p>20 bottom, graft survival. In 5-year survivors, there is</p> <p>21 no difference in long-term outcome whether you are on</p> <p>22 or off steroids. So early steroid withdrawal and being</p> |

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| <p style="text-align: right;">Page 354</p> <p>1 steroid-free up to 5 years and after that does not hurt 2 your long-term outcome. 3 Turning now to DSA and minimization trials, 4 CNI minimization, where there is more data, certainly 5 the early studies, as shown on this slide, did not have 6 DSA, but the study by Ekberg, et al.; the Caesar Study; 7 the Abramowicz study; the study by Smak Gregoor; all 8 looking at CNI minimization; reported increased acute 9 rejection in CNI withdrawal or minimization. And you 10 can see the data for each of these on this slide. 11 This slide has been shown before. It's the 12 randomization of patients on cyclosporine, to continue 13 on cyclosporine versus being converted to everolimus. 14 And has been reported before, those converted to 15 everolimus had more donor-specific antibody, more 16 antibody-mediated rejection. 17 A similar study, the first one being 18 cyclosporine-based, this study now tacrolimus-based, 19 with de Sandes-Freitas, et al., looking at subclinical 20 lesions and donor-specific antibody in patients on TAC, 21 CellCept and prednisone randomized to continue 22 tacrolimus versus conversion to sirolimus. They had a</p> | <p style="text-align: right;">Page 356</p> <p>1 again you can see a host of exclusion criteria, so 2 these were low-risk patients who were randomized, and 3 they were randomized to a 50 percent reduction, so not 4 withdrawal, but a 50 percent reduction in their 5 tacrolimus dose -- you can see the targeted trough 6 level there -- versus continuation. 7 And you can see the results on this slide. 8 There were 188 patients randomized. And in the 50 9 percent reduction group, there was significantly more 10 biopsy-proven acute rejection, more donor-specific 11 antibodies, and in protocol biopsies at 1 year 12 posttransplant, there was significantly more patients 13 who had a Banff "i" score greater than zero, and the 14 conclusion from this study was TAC levels should be 15 maintained at least during the first year. 16 Well, this particular study by Dugast, et al., 17 looks at late TAC withdrawal and entitled, "Failure of 18 Calcineurin Inhibitor Weaning." This study was a 19 prospective, randomized trial, multicenter, that looked 20 at patients 4 or more years after transplant who had 21 normal histology, stable graft function, and no anti- 22 HLA immunization. And only 10 patients were randomized</p> |
| <p style="text-align: right;">Page 355</p> <p>1 whole host of exclusion criteria, so these are low-risk 2 patients that were randomized. 3 And at the bottom of the slide, you can see at 4 24 months, there was increased biopsy-proven acute 5 rejection, increased Banff "i" greater than zero 6 scores, and increased donor-specific antibodies in 7 those who were randomized to the sirolimus group. 8 Don Hricik's CTOT study has been mentioned 9 before. So I think the important part of this study 10 was these were absolutely pristine patients. They had 11 no donor-specific antibody, they had a low PRA, from 12 zero to 6 months, had no rejection, no donor-specific 13 antibody, and at 6 months had a totally clean biopsy, 14 and the goal was TAC withdrawal, and as you've heard 15 already today, the group randomized to TAC withdrawal 16 had significantly more immune events, including donor- 17 specific antibody, and the study was stopped by the 18 DSMB. 19 In a similar study, not TAC withdrawal, but 20 TAC weaning, by Gatault, et al., using extended-release 21 tacrolimus, patients with no DSA and no acute rejection 22 at 3 months were then randomized at 4 months. And</p> | <p style="text-align: right;">Page 357</p> <p>1 because in the placebo group, they had three acute 2 rejections, two patients developed anti-HLA antibodies, 3 of which one was a donor-specific antibody, and all 4 five patients were started back on tacrolimus, and even 5 at 4 years in clinically well patients, tacrolimus 6 withdrawal failed. 7 There are other lists, and I think Ros Mannon 8 mentioned them earlier this morning, and they're shown 9 on this slide, of other studies in which there has been 10 minimization, and in each of these studies, the 11 minimization group had increased donor-specific 12 antibody. 13 And then, finally, the real calcineurin-free 14 study, which has been mentioned before, is the BENEFIT 15 study, which was a prospective, randomized study with 16 100 centers and over 650 patients. There were three 17 groups: more intensive belatacept, less intensive, and 18 cyclosporine. 19 And the important point I think is that early 20 on there was no difference in patient or graft 21 survival. There was certainly more acute rejection in 22 the belatacept group, as you've heard already, and more</p> |

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| Page 358 | Page 360 |
| <p>1 severe rejection in the belatacept group. But when you</p> <p>2 looked at 7 years at the percent of patients that</p> <p>3 developed donor-specific antibody, as shown on this</p> <p>4 slide, the cyclosporine group, in the pink, had had</p> <p>5 significantly more development of donor-specific</p> <p>6 antibody.</p> <p>7 We all know from the series of studies that</p> <p>8 the GFR was always better in the belatacept group as</p> <p>9 compared to the calcineurin group, but this had not</p> <p>10 translated into better graft survival or patient</p> <p>11 survival until the 7-year data. So it's certainly in</p> <p>12 concert with the better GFR and the reduction in donor-</p> <p>13 specific antibody. The 7-year data with belatacept</p> <p>14 shows a 43 percent reduction in the risk of death or</p> <p>15 graft loss as compared to the cyclosporine group.</p> <p>16 So to summarize, steroid minimization was done</p> <p>17 before donor-specific antibody testing. It showed an</p> <p>18 increased early acute rejection but no change in graft</p> <p>19 survival. This was mostly limited to low-risk groups,</p> <p>20 although we certainly in our center apply this protocol</p> <p>21 to essentially all first or second transplants. And</p> <p>22 we've looked at a variety of higher risk groups, and</p> | <p>1 Prevention/Management</p> <p>2 DR. ALLOWAY: Thank you very much. I would</p> <p>3 like to thank the organizers for allowing this topic to</p> <p>4 be discussed here today. While we refer to</p> <p>5 nonadherence quite frequently, I compel you to actually</p> <p>6 define, monitor for it, and attempt to develop a</p> <p>7 strategy that prevents it, or we're able to maintain a</p> <p>8 good solid adherence plan for our patients.</p> <p>9 These are the following disclosures.</p> <p>10 The objectives of the talk today are to</p> <p>11 differentiate medication nonadherence and compliance,</p> <p>12 describe measures to quantitate medication</p> <p>13 nonadherence, and discuss efforts towards prevention</p> <p>14 and management of nonadherence.</p> <p>15 So nonadherence is not new to us. I think</p> <p>16 that basically Hippocrates in 500 B.C. said, "Keep</p> <p>17 watch also on the fault of patients which makes them</p> <p>18 lie about taking things as prescribed."</p> <p>19 Also, C. Everett Koop quoted as saying, "Drugs</p> <p>20 don't work if people don't take them."</p> <p>21 Now, I think that by the show of hands</p> <p>22 earlier, we've shown that none of us are very compliant</p> |
| Page 359 | Page 361 |
| <p>1 they seem to be comparable results, the same results,</p> <p>2 for that same high-risk group that you would get if you</p> <p>3 continued prednisone.</p> <p>4 The CNI minimization studies, both</p> <p>5 cyclosporine and tacrolimus, there have been studies of</p> <p>6 minimization or conversion all the way out to 4 years</p> <p>7 in low-risk or pristine patients, and there has been</p> <p>8 increased acute rejection, increased donor-specific</p> <p>9 antibody, increased Banff "i" scores, and in one study,</p> <p>10 increased graft loss.</p> <p>11 And then, finally, in belatacept versus</p> <p>12 cyclosporine, although there was increased acute</p> <p>13 rejection in belatacept, there was less donor-specific</p> <p>14 antibody, and right now that's been shown in better</p> <p>15 graft survival. So perhaps with this particular drug</p> <p>16 we're changing the paradigm.</p> <p>17 Thank you.</p> <p>18 (Applause.)</p> <p>19 DR. BELEN: Thank you. Next we have Dr. Rita</p> <p>20 Alloway, and she is going to present, "Nonadherence --</p> <p>21 Definitions, Monitoring, Prevention and Management."</p> <p>22 Nonadherence -- Definitions, Monitoring,</p> | <p>1 or very adherent. However, I think we need to</p> <p>2 especially look for strategies to intervene in this</p> <p>3 regard.</p> <p>4 While there has been a lot of talk today about</p> <p>5 nonadherence and the development of new therapeutics,</p> <p>6 adherence rarely has been incorporated into the</p> <p>7 therapeutic drug development process. And I maintain</p> <p>8 to you that transplantation can no longer accept the</p> <p>9 status quo of the level of nonadherence that we have</p> <p>10 become to accept.</p> <p>11 I think, as been described here today, the</p> <p>12 first shot that we have at transplant is our best shot</p> <p>13 for transplant long-term success, and managing and</p> <p>14 keeping the patient on an adherent regimen at this time</p> <p>15 is very appropriate.</p> <p>16 The other thing is despite millions of</p> <p>17 investment, the "magic" drug or procedure to render</p> <p>18 adherence irrelevant is not on the horizon. So it's a</p> <p>19 thing that's going to continue to be something that's</p> <p>20 very important for us to discuss.</p> <p>21 And hopefully federal mandates are not</p> <p>22 necessary for us within our centers to properly</p> |

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| <p style="text-align: right;">Page 362</p> <p>1 resource adherence initiatives if adherence continues 2 to be neglected primarily as it is today. 3 So when you talk about medication adherence, 4 and talk to the experts, there is a difference in terms 5 of which they like to use. The two terms that are most 6 commonly used are medication "adherence" and 7 "compliance." "Adherence" is the preferable term. It 8 refers to the extent to which patients take the 9 medications as prescribed by the health care providers. 10 "Compliance" is more referred to as a passive act of 11 which the patient follows the provider's orders. And I 12 think that because this tends to show obedience or 13 passive following of the patient, people have wanted to 14 promote the idea of adherence to improve the knowledge 15 that the patient has to adhere to their medication. 16 So medication adherence must be recognized as 17 a behavioral process that is influenced by many 18 factors. It assumes that the patient has the 19 knowledge, the motivation, the skills, and the 20 resources to follow what the health care provider's 21 prescription actually is. 22 When we look at medication nonadherence, we</p> | <p style="text-align: right;">Page 364</p> <p>1 assessment, you look at which of these factors are 2 modifiable. And I think if you look at the health 3 system factors and the therapeutic-related factors, 4 you'll see that there are actually some ways to improve 5 this area, and there are some factors here which we can 6 modify. 7 So when we begin to talk about measuring 8 medication adherence, there are objective measures and 9 subjective measures. Objective measures tend to be 10 direct measures that provide the evidence that the 11 medication has been consumed or taken. Luckily, within 12 transplantation, we actually now have a drug, 13 belatacept, where if the patients come and get their 14 infusions, we have direct observation of them actually 15 receiving their drug. 16 There are also indirect measures that we can 17 look at that can be made objective as well, such as 18 providing evidence suggesting that the medication has 19 been consumed or taken. Pill counts are frequently 20 used. Tacrolimus drug levels we use quite frequently. 21 Pharmacy refill records and medication possession 22 ratios.</p> |
| <p style="text-align: right;">Page 363</p> <p>1 all know that there may be intentional medication 2 nonadherence or unintentional. Intentional medication 3 nonadherence is actually defined as an active process 4 whereby the patient chooses to deviate from a treatment 5 regimen; while unintentional medication nonadherence, 6 which I think represents most of the cases, is a very 7 passive process which the patients may be careless or 8 forget about adhering to their treatment regimen. 9 So the World Health Organization identified 10 five dimensions of adherence for all medications 11 focusing on health system factors, socioeconomic 12 factors, therapeutic-related factors, patient-related 13 factors, and condition- or disease-related factors. 14 And this has been very well studied in the transplant 15 population. 16 And as you can see by the complexity of 17 components of each of these factors' spectrum, that an 18 adherence or a development of a strategy to provide 19 optimal adherence is going to be complex, it's not 20 going to be the same for everybody, and we will have to 21 intervene and have the patient involved in this. 22 But I think anytime you do a risk factor</p> | <p style="text-align: right;">Page 365</p> <p>1 But there are actually subjective measures as 2 well where patients provide testimonials that the 3 medication has or has not been taken, and this can be a 4 self-report or assessment by others. 5 So, again, the direct observation options in 6 transplantation, the advantages are that they are 7 objective, they're highly specific, and they're non- 8 invasive. The disadvantages are the feasibility issues 9 that occur along with it. They are labor-intensive, 10 and in many cases, they're not practical. They may be 11 expensive. And as you know, they're not an option for 12 all transplant recipients. 13 Now, fortunately, in transplantation, drug 14 concentration monitoring has been available for our 15 primary immunosuppressants for the CNIs, and it is 16 incorporated as standard of care. The advantages of 17 that are it's objective, it may be part of standard of 18 care, and it is a direct assessment of whether the 19 patient is taking their medicine, at least in the close 20 proximity of when the level is drawn. 21 However, there are disadvantages. All of our 22 medications do not have a routine drug concentration</p> |

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| <p style="text-align: right;">Page 366</p> <p>1 monitoring plan that has been associated with long-term 2 outcomes that we use routinely. The disadvantage, too, 3 as I said, it is just a snapshot of the behavior that 4 occurs prior to the drug being taken. It's affected by 5 many factors other than medication adherence, as well 6 all well know: metabolism, drug-drug/drug-food 7 interactions, poor absorption. While we have become 8 willing to accept the costs that are associated with 9 it, there is a high cost associated of monitoring 10 therapy, and it is invasive. 11 So recently there has been a lot of work 12 looking at tacrolimus interpatient variability and its 13 impact on long-term graft outcomes. Now, when you look 14 at all of these studies, they basically imply that the 15 interpatient variability that occurs is not only 16 related to nonadherence, but they tend to say that they 17 think that nonadherence is a large predictor in this. 18 However, I just want to point out that we know 19 that that's not the only factor. But there are a lot 20 of studies out there, I'm just going to talk about 21 three of those real quickly. 22 This study basically had 310 renal transplant</p> | <p style="text-align: right;">Page 368</p> <p>1 you look at the development of de novo DSA, again you 2 can see that the patients with the lower IPV had an 3 improvement or had a lower incidence of the development 4 of de novo DSA in the study. 5 Another study that looked at this focused more 6 on the late outcomes with the composite endpoint of 7 graft failure, late biopsy-proven acute rejection, 8 transplant glomerulopathy, and doubling of serum 9 creatinine censored for death. 10 And the reason that I want to point this out 11 is this was a study in over 200 transplant patients 12 where they analyzed the tacrolimus levels between 6 and 13 12 months posttransplant, and basically if you look at 14 the hazard ratio, the TAC IPV was the highest predictor 15 of this composite endpoint, where you saw 1.4 percent 16 increase in every unit of IPV that was noted in the 17 patients. So as you can see, with the increasing IPV, 18 the composite endpoint was met. 19 But what is even more significant is when they 20 looked at this and they compared it with the target 21 tacrolimus levels that the patients were on and 22 receiving, you can see that at the lower tacrolimus</p> |
| <p style="text-align: right;">Page 367</p> <p>1 patients who had their tacrolimus levels analyzed for 4 2 to 12 months posttransplant, and their interpatient 3 variability of the trough levels were calculated. They 4 had an arbitrary break of less than or greater than 30 5 percent IPV. 6 Roughly, as you can see -- and this is what 7 it's turned out in a lot of studies -- roughly a third 8 of the patients were considered to have a high 9 interpatient variability, and roughly two-thirds had 10 what has been defined as acceptable. DSA was performed 11 at 1, 3, and 5 years. And in this cohort of patients, 12 17 percent lost their graft, and 12 percent or 13 13 percent developed a de novo DSA. 14 Now, when you and you apply the interpatient 15 variability calculations to their primary outcomes of 16 death-censored graft survival here, you can see that 17 the patients had an interpatient variability of greater 18 than 30 percent, had a lower cumulative death-censored 19 graft survival than compared with those that had a 20 lower IPV. 21 Although the legend is different on the 22 subsequent slide that they have in their paper, when</p> | <p style="text-align: right;">Page 369</p> <p>1 levels, that really we currently target anywhere from 4 2 to 6 or maybe 6 to 8 posttransplant, the impact of 3 interpatient variability is actually higher when we're 4 targeting these lower tacrolimus levels, as we are in a 5 lot of our regimens today. 6 This is another study that looked at 7 interpatient variability in 220 renal transplant 8 patients, and essentially they again analyzed their 9 levels between 6 and 12 months posttransplant and 10 divided them into three tertiles with the lowest IPV 11 being approximately 10 percent, the mid mean was 18 12 percent, and again the highest tertile was 31 percent. 13 And in this study, in this center that 14 conducted protocol biopsies in 3 months and 2 years, 15 they used this to calculate the change in chronicity 16 score during this time. And basically the recipients 17 with the highest IPV had an increased risk in the 18 moderate to severe fibrosis and tubular atrophy at 2 19 years compared to those with a low IPV. And, again, 20 this was the single most important predictor of long- 21 term graft survival in these groups. 22 Now, tacrolimus interpatient variability is</p> |

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| <p style="text-align: right;">Page 370</p> <p>1 something that you can implement within your clinics 2 today if you cooperate really well with your IT 3 department. It's difficult, but they can do it. And 4 we're attempting to utilize that on a day-to-day basis 5 in our center. 6 Now, electronic monitoring is available. The 7 advantages of this are it is objective. It can 8 indicate the actual time and date of the bottle 9 opening. So what this allows us to do is detect poor 10 adherence with a dosing schedule. You can see if 11 someone is taking a medication twice a day, if they 12 miss the dose more frequently in the morning or if they 13 miss the dose more frequently at night. It also can 14 detect pill dumping. And it's noninvasive. 15 The disadvantages of it are the cost, it's not 16 effective with liquid medications, it can malfunction 17 and lose the data. Sometimes the device is bulky, as 18 you see here, with the MEMS Cap strategies, that 19 basically the patients don't want to carry these 20 around. And it also assumes that the medication that 21 was actually removed from the bottle or the box is 22 actually taken.</p> | <p style="text-align: right;">Page 372</p> <p>1 there has been a variety of doses changed. 2 I offer to you -- and maybe I shouldn't be so 3 specific -- but I think it's almost impossible to use 4 pharmacy refill records when you're evaluating a drug 5 like tacrolimus or sirolimus or any of these others 6 where you change the dose frequently and it doesn't 7 elicit a new prescription. So that is one of the 8 things that limits the usefulness of this type of 9 information. 10 This type of information is actually used to 11 calculate a medication possession ratio, or essentially 12 proportions of days covered. And these are the two 13 most common formulas that used to estimate patients' 14 adherence to chronic medication. Both formulas use 15 prescription data and calculate the days of which the 16 patient has the medication on hand. 17 This type of analysis has been incorporated 18 into a lot of the chronic disease trials of diabetes 19 and cardiovascular disease, but what is interesting is 20 we don't know in transplantation what the optimal 21 medication possession ratio for any immunosuppressant 22 is. We obviously tell the patient, "You need to be 100</p> |
| <p style="text-align: right;">Page 371</p> <p>1 Now, there was a study in Minneapolis in 2 Minnesota that basically looked at the nonadherence 3 utilizing the MEMS Cap with antiproliferative agents -- 4 MMF, sirolimus, and azathioprine -- in 195 kidney 5 transplant recipients. And what was very interesting I 6 thought was that adherence between months 1 and 2 7 actually predicted adherence at 6 and 12 months. And I 8 think that that's an important concept for us to 9 understand and see. 10 Nonadherent patients in this study had more 11 frequent and earlier acute rejection and death-censored 12 graft survival. And during the 1 to 3 months, 13 adherence with 4-times-daily drugs, as we know, is 84 14 percent, 91 percent with twice-daily drugs, and 94 15 percent with once-daily drugs. And you can refer to 16 this paper for more information. 17 There's another way to assess adherence, with 18 pharmacy refill records. Again, they're objective, 19 they're standardized, they identify patients who fail 20 to refill their medications, they're noninvasive, and 21 they're not expensive. But there's a big problem with 22 misinterpreting the usage of this information when</p> | <p style="text-align: right;">Page 373</p> <p>1 percent adherent. Take every dose, every time, on 2 time." But we really don't know what the optimal 3 medication possession ratio is. 4 There are self-reports. The advantages of 5 these are quick, simple, inexpensive. The 6 disadvantages primarily are that they overestimate 7 adherence. And they're burdensome. And basically 8 patients, when you ask them at the clinic visit, they 9 tend to remember what they've done the last 3 or 4 10 days, but not necessarily what they've done 3 months or 11 even 6 months since their last visit. 12 The last thing is in clinician reports, again 13 the advantages are simple, quick, and inexpensive. And 14 to be honest, in a lot of these reports that are in the 15 literature right now, these are clinician reports to 16 nonadherence. 17 But unfortunately for you guys, you tend to 18 underestimate nonadherence. So if we're talking right 19 now that we have a problem with DSA development and 20 nonadherence based upon clinician information, it's 21 underestimated for nonadherence. 22 So I know my time is over, but let me just</p> |

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| <p style="text-align: right;">Page 374</p> <p>1 briefly take you through this last concept. We need to 2 develop interventions which promote adherence. We need 3 to think about when we intervene, where we intervene, 4 and how. 5 And I'm not going to spend the time going 6 through the status posttransplant, but it's optimal to 7 find an intervention time that promotes adherence, and 8 it's going to be different from every patient. 9 Luckily, we have a lot of new interventions to 10 promote adherence with the smartphone apps and the 11 computers, and we have a lot of different types of 12 interventions that I want to point out. It needs to be 13 multidisciplinary, and when we've seen the most 14 success, they have been in multicomponent 15 interventions. 16 Right now, there have been more randomized, 17 controlled trials that actually look at adherence, but 18 the scientific rigor there has increased, but it's not 19 as it should be. The types of interventions that are 20 tested are heterogeneous. Multicomponent interventions 21 appear to be the most effective. 22 Intervention effectiveness appears to be</p> | <p style="text-align: right;">Page 376</p> <p>1 management this is, and the emotional management 2 related to chronic conditions. 3 So this is references on this slide, but 4 essentially we need to focus on things that strengthen 5 the patients' ability to learn how to self-manage their 6 conditions and diminish the interventions that make the 7 self-management harder. 8 And what is interesting is the transplant 9 patients basically say that the reason why they try to 10 be adherent and what scares them the most is their 11 prevailing fear of the consequences. And I think that 12 that is something that we have to understand. 13 When you look at immunosuppression and taking 14 immunosuppressants, basically when this shows you how 15 many domains that taking immunosuppressants impacts, it 16 shows you that it's going to be a complex solution. So 17 just as we're talking about a precision medicine in 18 transplantation, I think that we need a transplant- 19 specific precision prescription for adherence for each 20 individual patient. And this includes putting the 21 patient first, hearing what they have to say, and 22 knowing that this is adaptive over time.</p> |
| <p style="text-align: right;">Page 375</p> <p>1 increased when you actually tailor it to what the 2 patient says they need, and it needs to be dynamic 3 based upon the patient's response. 4 The degree of the intervention impact is 5 variable. And often trials don't evaluate clinical 6 outcomes, especially when it comes to long-term 7 outcomes. 8 So I just want to leave you with a new 9 paradigm as you think about nonadherence, focusing on 10 the qualitative measurements. This is really where the 11 field is going. And basically the qualitative 12 measurements provide insight into patients' values, 13 knowledge, beliefs, that influence behaviors and 14 choices in transplantation self-management. And the 15 focus now begins on self-management of the patient. 16 And when you do this, self-management begins 17 to explore the task that individuals must undertake to 18 live with this chronic condition that we've given them 19 now. They may not have end-stage renal disease, but 20 they have the disease of immunosuppression. They need 21 to have confidence to deal with the medical management 22 of this. They need to know what their role in</p> | <p style="text-align: right;">Page 377</p> <p>1 So with that I would like to thank you for 2 this lecture. Thanks. 3 (Applause.) 4 DR. BELEN: Thank you, Dr. Alloway. 5 Next we have Dr. Robert Gaston, who is going 6 to present, "The Role of Acute Cellular Rejection 7 Episodes in the Development of HLA Antibodies." 8 The Role of Acute Cellular Rejection Episodes 9 in the Development of HLA Antibodies 10 DR. GASTON: Thank you again. I think if I 11 were putting this talk together at 5:00 this afternoon, 12 it would be different than the talk I've put together, 13 having heard everything there because I sort of 14 interpreted the mandate as, Is there still a role for 15 acute cellular rejection in the development of HLA 16 antibodies? And so you'll I think tell that from the 17 tone of the talk to follow. 18 So I can't but thinking, how did we get to 19 having this talk at 5:00 at the end of this symposium 20 on antibody-mediated rejection? I have a book, it was 21 given to me years ago, Amburjay's (ph) book from 1972, 22 and I use it as an easy reference on what people</p> |

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| <p style="text-align: right;">Page 378</p> <p>1 thought 50 years ago, and these are several quotes from 2 that book. "There is no doubt that the cell-mediated 3 immune response is a predominant factor in rejection." 4 "These nonthymus-dependent lymphocytes can become 5 actively sensitized against antigens, but in cell- 6 mediated immunity, they participate, if at all, only in 7 effector mechanisms, only in association with thymus- 8 dependent cells." And they did recognize a bit of the 9 future, that, "Circulating antibody against donor 10 cells...have been detected by the use of specially 11 sensitive techniques, while the transplant organ was 12 still in place," because they couldn't find them with 13 usual techniques, "and there seems to be a definitive 14 correlation between this finding and the appearance of 15 progressive lesions in the graft, especially vascular 16 lesions." So lots of looking forward there. 17 But if you look at the more recent literature, 18 a half century later, this is what you see. And these 19 are three very elegant papers, Professor Loupy's paper, 20 "...lack of association of subclinical TCMR with graft 21 survival thus challenges the historical conclusion that 22 T-cell-mediated rejection increases the risk of future</p> | <p style="text-align: right;">Page 380</p> <p>1 individuals are genetically identical, grafts exchanged 2 between them are equal, but not the same. On the other 3 hand, if they're genetically different, their grafts 4 are the same, but not equal. It is here that 5 transplantese ceases to be homologous with English or 6 indeed with common sense." 7 And I think the discussion about the role of 8 T-cell- versus antibody-mediated rejection falls a bit 9 into this category of transplantese, and hopefully in 10 the next few minutes I can bring some resolution to at 11 least some of it. 12 So how did we get there? I really think we 13 got there in the '90s when we for the first time had 14 specific effective immunosuppression and started to see 15 data like these -- this is from Minnesota -- and the 16 concept that there was a subset of acute rejection that 17 did not associate itself with long-term graft failure. 18 And in this study, it was the rejections that 19 occurred within the first 3 months. There was really 20 no association with late chronic rejection. 21 Conversely, later rejection episodes, 3 to 6, 6 to 12, 22 12 to 24, and beyond 24, as you can see on the right</p> |
| <p style="text-align: right;">Page 379</p> <p>1 graft loss, confirms the findings of recent clinical 2 trials, showing that indolent T-cell-mediated rejection 3 can be adequately treated as not associated per se with 4 graft loss...." 5 Phil Halloran's paper, "We conclude the main 6 cause of kidney transplant failure is ABMR, which can 7 present even decades after transplantation. In 8 contrast, T-cell-mediated rejection disappears by 10 9 years posttransplant...." 10 And then from Cleveland Clinic, "However, B 11 cell depletion inhibited alloantibody generation and 12 significantly extended graft survival, indicating that 13 donor-specific alloantibodies (not T cells) were the 14 critical effector mechanisms of renal allograft 15 rejection induced by memory CD4 T cells." 16 How did we get from '72 to 2016? And why am I 17 giving this talk? And in the research, I came across a 18 very interesting paper from 1960 from the father of 19 antibodies, Peter Gorer, or one of the fathers, and it 20 was about terminology. And I think a lot of what's 21 been said here today is about terminology. In the 22 Greek "iso" means equal, "homo" means the same. If two</p> | <p style="text-align: right;">Page 381</p> <p>1 there -- maybe I can resurrect some of this -- were 2 highly associated with risk of rejection or risk of 3 late graft failure. 4 I think it was perpetuated with these data, as 5 we had availability of tacrolimus, mycophenolate, and 6 so on. And prior to this, this is the risk of acute 7 rejection, these were largely T-cell-mediated 8 rejections in those days, and you can see with the new 9 drugs, the risk of rejection in the early period, 6 to 10 12 months, 12 to 24 months, declined, but yet there was 11 no impact at all of reducing rejection on long-term 12 graft survival. T-cell-mediated rejection must not be 13 as significant as we thought it was. 14 We contributed to this with the DeKAF study, 15 and I've updated the data from what's usually used from 16 that, and that is these are late biopsies in the mean 17 of 7 years posttransplant in people who previously had 18 stable function. Basically, what this study seemed to 19 say is that if you didn't have C4d, if you didn't have 20 DSA, you did pretty well. If you had one, either or 21 both of those, you did quite poorly. And this is again 22 starting at day times zero, 7 years, out to there.</p> |

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| <p style="text-align: right;">Page 382</p> <p>1 What is not often quoted is that there was 2 really a high degree of cell-mediated rejection in all 3 of these categories as well, and that's not accounted 4 for in this analysis. But nonetheless, the concept 5 that only antibody-mediated rejection was important. 6 You've seen that in the work from Chris Wiebe and Peter 7 Nickerson, again, that in this protocol biopsy study, 8 the patients who developed DSA did very poorly, the 9 patients who did well, and then nonadherence was a risk 10 factor, and we'll come back to that again in a minute. 11 Okay. Well, you've seen this a dozen times 12 already, so I'm really disappointed this didn't come 13 through in the transition. But basically the survival 14 -- maybe I can bring it down. No. 15 This is in protocol biopsies in patients who 16 had subclinical T-cell-mediated rejection. They did 17 just as well as the patients -- this is a French series 18 from Loupy -- they did just as well as the patients who 19 had no rejection on protocol biopsy long term. 20 Conversely, it was those with subclinical ABMR that had 21 the poor outcomes. 22 The next slide did come through from that, and</p> | <p style="text-align: right;">Page 384</p> <p>1 cell-mediated rejection, by histology, had the same 2 outcomes long term as those patients with relatively 3 normal biopsy. Pure ABMR had the worst outcomes. And 4 these are for-cause biopsies, by the way. And then the 5 mixed was intermediate. 6 When they then added the molecular qualifier 7 to it, the mixed group basically segregated with the 8 antibody-mediated rejection, but again you see the pure 9 T-cell-mediated rejection group did not look any 10 different long term. 11 And it's real easy from all of this then to 12 come to the conclusion that T-cell rejection doesn't 13 play much of a role in all this, but looking at the 14 molecular transcripts over time, what you can see is 15 the T-cell-mediated transcripts are highly present, 16 early posttransplant, late posttransplant. They 17 diminish and are replaced instead by markers of 18 antibody-mediated injury in the grafts. 19 And the title of the article was, 20 "Disappearance of T Cell-Mediated Rejection Despite 21 Continued Antibody-Mediated Rejection in Late Kidney 22 Transplant Recipients."</p> |
| <p style="text-align: right;">Page 383</p> <p>1 this is basically looking at the patients who -- the 2 incidence of or the probability of developing 3 transplant glomerulopathy in the patients with no 4 rejection, subclinical TCMR, and subclinical ABMR. And 5 what you can see is that the patients who had 6 subclinical T-cell-mediated rejection look very little 7 different from the patients who had no rejection, but 8 you can see that very quickly the subclinical ABMR 9 group developed transplant glomerulopathy. 10 What is interesting, though, is that in this 11 group, the T-cell-mediated group, the development of 12 transplant glomerulopathy was pre-staged by sort of a 13 transition at some point, and development of de novo 14 DSA over time. 15 This then, sort of in my mind at least, 16 culminated in a paper by Phil Halloran and the group 17 there in which they looked at both histology and then 18 molecular diagnosis. 19 Basically if you look here, there is some 20 mixed diagnosis, mixed T-cell, mixed antibody-mediated 21 rejection, normal biopsies in green. This is looking 22 at graft survival. And you can see that the pure T-</p> | <p style="text-align: right;">Page 385</p> <p>1 So why are things more complicated than that? 2 What is the relevance of T-cell-mediated rejection? 3 And I think I'm going to go into hopefully just a few 4 slides, and build a case that is still very important, 5 and it's really a continuum. And back to the 6 transplantese, we need to really think about alloimmune 7 activation as a continuum across the board. 8 This is a study from the Barcelona group in 9 which they looked at patients who had a protocol biopsy 10 at 6 months, and then subsequently over time required a 11 for-cause biopsy, the patients who had chronic humoral 12 rejection, the patients who had isolated IFTA. And 13 then you see the other characteristics on the biopsy, a 14 total N of 86 only, but some very interesting findings 15 in this over time. 16 And what they found, they were looking at what 17 on the 6-month biopsy predicted chronic antibody- 18 mediated rejection. And what they found was on the 6- 19 month biopsy were markers of cell-mediated injury, that 20 is, interstitial infiltrate, tubulitis, and arteriolar 21 hyalinosis against vascular disease as well. But the 22 suggestion was that the findings most predictive on the</p> |

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| <p style="text-align: right;">Page 386</p> <p>1 6-month protocol biopsy of long-term injury were 2 related to cell-mediated mechanisms within the graft. 3 This is a bit more elegant, again from the 4 same group in Barcelona, looking at T-cell reactivity, 5 as documented by ELISPOT testing, posttransplant 6 ELISPOT testing, at 3 and 6 months, with a 6-month 7 protocol biopsy in it. And basically, even though it's 8 very beautiful, it's a bit complicated, that over here 9 are the patients who had a negative ELISPOT test at 3 10 months and at 6 months, and over here, the patients who 11 had a positive ELISPOT test at 3 and 6 months. 12 And what you can see is the patients who had 13 ELISPOT again as a proxy for T-cell activation, that 14 those patients who were positive subsequently went on 15 to have subclinical cell-mediated rejection at 6 16 months, and the predominance of de novo DSA within the 17 entire group was in the group who had positive ELISPOT 18 testing, evidence of T-cell activation, early in the 19 posttransplant course, translated into a higher risk 20 for de novo DSA at 24 months. Conversely, in the 21 absence of T-cell activation, only these two patients 22 demonstrated evidence of de novo DSA at 24 months. So</p> | <p style="text-align: right;">Page 388</p> <p>1 antibody and antibody-mediated, presumably B-cell- 2 mediated, effector mechanisms. 3 We then go back to the nonadherence. We've 4 seen this over and over again. And what's interesting 5 -- I don't want to explain this too much -- if the 6 injury was found that they had subclinical with de novo 7 DSA versus clinical, both had adverse impacts on graft 8 survival with a quicker course in the patients who had 9 clinical DSA, and the endpoints being transplant 10 glomerulopathy and interstitial fibrosis. 11 What's interesting in this study -- and this 12 is further data from the study -- they broke the 13 patients at the time of biopsy into those who had no 14 DSA, no graft dysfunction, that was the majority of 15 patients; no DSA, but graft dysfunction; DSA, 16 subclinical, so no evidence of graft dysfunction at the 17 time of the biopsy; and then clinical. What you can 18 see is that the nonadherence increases across with the 19 highest degree of nonadherence in those with clinical 20 rejection. 21 But what you can see is that, as in the 22 antibody, those patients were significantly more likely</p> |
| <p style="text-align: right;">Page 387</p> <p>1 a link between cell-mediated immunity and de novo DSA. 2 This is a very elegant study, has been 3 referred to a couple of times, in JASN from Anna 4 Volushka (ph) at Cleveland Clinic, and this is a study 5 in mice. And basically they sensitized the mice to 6 donor antigens, and basically you can see the donor 7 responsiveness here. They then treated them with an 8 anti-CD8 antibody or a polyclonal, essentially 9 eliminated that responsiveness, that antibody 10 responsiveness, but it had no impact at all on graft 11 survival when they eliminated the cells that were 12 present via mouse, if you will, Thymoglobulin. 13 Contrary, on the other hand, you can see the 14 same sort of response, a sensitized memory in the 15 model, donor-specific, that were then treated with 16 Rituxan either at day 7 -- or excuse me, were tested 17 again at day 7 and day 30 after Rituxan, and by 18 eliminating the B-cell responsiveness, the antibody 19 responsiveness, in this model, they then were able to 20 prolong allograft survival the same as in the 21 nonsensitized people, again emphasizing the link 22 between T cell sensitization and the importance of</p> | <p style="text-align: right;">Page 389</p> <p>1 to have experienced T-cell-mediated rejection early in 2 the posttransplant course that ultimately resulted in 3 -- or ultimately in those patients -- I don't want to 4 say evolved into, I want to say the same patients over 5 time developed donor-specific DSA ultimately with 6 consequence on graft function. 7 And then, finally, I can't do this without 8 referring to at least somewhat to the DeKAF study. And 9 this is the prospective cohort, and now after this many 10 years, we're just now completing the database in the 11 prospective cohort. But approximately 4,000 patients 12 at the time of this analysis, 3,300 patients with 13 functioning grafts at least 90 days. We were not 14 interested in early graft loss, we were interested in 15 late graft loss. The baseline status for these 16 patients was established at 90 days. 17 At the time of this, we had a mean follow-up 18 of 32 months. We termed the index biopsy, the first 19 for-cause biopsy, after establishing this. It was 20 standardized across seven centers as a 25 percent 21 increase in the serum creatinine or new onset 22 proteinuria. Obviously an increase in creatinine</p> |

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| <p style="text-align: right;">Page 390</p> <p>1 accounted for most of these.</p> <p>2 What was interesting in the patients who met</p> <p>3 those criteria, the incidence of death was the same.</p> <p>4 We were not selecting for people who had increased risk</p> <p>5 of mortality. But ultimately the subsequent risk of</p> <p>6 death-censored graft failure, 20 percent of those</p> <p>7 patients who had index biopsy went on to that versus</p> <p>8 very few, if any, that did, and the people who did not</p> <p>9 have an index biopsy.</p> <p>10 If we looked at then what were the risk</p> <p>11 factors for the biopsy, basically what these data say</p> <p>12 is that at 90 days, the patients look the same. There</p> <p>13 was a significant difference in age between 50 and 46.</p> <p>14 But I guarantee you I can't look at anyone in this room</p> <p>15 and tell whether you're 50 or 46. Gender was not</p> <p>16 significantly different. Race was slight</p> <p>17 overrepresented, but not largely. PRA was no</p> <p>18 difference in the patients. Serum creatinine at 90</p> <p>19 days was no difference in the patients. There had been</p> <p>20 a slight increase in evidence of delayed graft function</p> <p>21 early on. And then very early acute rejection in the</p> <p>22 patients.</p> | <p style="text-align: right;">Page 392</p> <p>1 then result in T-cell-mediated rejection. There's that</p> <p>2 word, transplantese, about smoldering.</p> <p>3 But ultimately the key link in the pathway is</p> <p>4 under-immunosuppression, and that certainly this mixed</p> <p>5 phenotype of cell-mediated rejection in combination</p> <p>6 with antibody to me is a phenotype of under-</p> <p>7 immunosuppression in the patient. Unfortunately, it</p> <p>8 can be physician guided. Many times it's patient</p> <p>9 guided in terms of nonadherence.</p> <p>10 Ultimately, then what may begin as T-cell-</p> <p>11 mediated rejection then in the same patients then</p> <p>12 evolves into a picture, the picture we've been</p> <p>13 describing today, and ultimately unfortunately in graft</p> <p>14 failure.</p> <p>15 So the impact of T-cell-mediated rejection is</p> <p>16 less than we probably thought it was many years. It's</p> <p>17 declined in frequency, and if recognized early, is</p> <p>18 relatively responsive to treatment. It clearly pales</p> <p>19 in comparison to subclinical antibody-mediated</p> <p>20 rejection as a predictor of graft dysfunction and</p> <p>21 failure. It remains a strong risk factor for de novo</p> <p>22 donor-specific antibody, particularly in the setting of</p> |
| <p style="text-align: right;">Page 391</p> <p>1 And what you can see then if you look at risk</p> <p>2 of death-censored graft survival in the patients, that</p> <p>3 those early rejections did not seem to have a</p> <p>4 significant impact on risk of subsequent graft failure.</p> <p>5 Delayed graft function didn't have a significant</p> <p>6 impact. What did was something happening to the</p> <p>7 patient beyond day 90, in this case, that triggered an</p> <p>8 index biopsy, that is, new onset of some event, and in</p> <p>9 a larger number of those patients than we would have</p> <p>10 ever predicted, it was cell-mediated rejection or mixed</p> <p>11 rejection in those patients.</p> <p>12 So the last slide is basically this one, and</p> <p>13 this is to reiterate the algorithm developed by Chris</p> <p>14 and Peter Nickerson that sort of pulls this together,</p> <p>15 that there are some minor pathways that ultimately</p> <p>16 graft loss is a consequence, late graft loss is a</p> <p>17 consequence of IFTA, but perhaps even more so of</p> <p>18 transplant glomerulopathy.</p> <p>19 Pathways that contribute are certainly these</p> <p>20 things that we've spent a lot of time and effort</p> <p>21 talking about: CNI toxicity, age, ischemia,</p> <p>22 reperfusion injury, and so on. Many of these things</p> | <p style="text-align: right;">Page 393</p> <p>1 inadequate immunosuppression, whether it be</p> <p>2 minimization or nonadherence.</p> <p>3 And then the question that I would raise at</p> <p>4 the end in thinking about this is, given the role of</p> <p>5 the T cell in promoting B cell responses, can there be</p> <p>6 effective prevention control of DSA without effective</p> <p>7 T-cell therapy? I think the basis of what we do -- and</p> <p>8 I was pleased to hear some of the discussion today --</p> <p>9 to talk about looking at B-cell therapies in the</p> <p>10 context of what we do and what we know works well in</p> <p>11 suppressing T-cell responses.</p> <p>12 Thanks very much.</p> <p>13 (Applause.)</p> <p>14 DR. BELEN: Thank you, Dr. Gaston.</p> <p>15 Public Comment and Discussion</p> <p>16 DR. BELEN: Perhaps we'll take some clarifying</p> <p>17 questions for the presenters before we go on with</p> <p>18 public comment and discussion.</p> <p>19 (No response.)</p> <p>20 DR. BELEN: If you don't have any questions,</p> <p>21 we're going to go ahead and discuss the discussion</p> <p>22 questions.</p> |

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| <p style="text-align: right;">Page 394</p> <p>1 I'll go ahead and start with the second one</p> <p>2 since Dr. Gaston already touched upon it a little bit.</p> <p>3 Is T-cell-mediated rejection early a risk</p> <p>4 factor for de novo DSA formation? Does anyone want to</p> <p>5 start discussing with this point?</p> <p>6 Yes, Dr. Haas.</p> <p>7 DR. HAAS: Just a point of concern is I think</p> <p>8 to group all T-cell-mediated rejection together may</p> <p>9 have some of the same drawbacks as grouping all</p> <p>10 antibody-mediated rejection together.</p> <p>11 I noticed on one of the slides in Dr. Gaston's</p> <p>12 talk, for example, that while tubulitis seemed to be a</p> <p>13 potential risk factor for de novo DSA formation,</p> <p>14 endarteritis was not, yet both might be classified as</p> <p>15 T-cell-mediated rejection. And it was also not clear</p> <p>16 if you're referring to very early clearly steroid-</p> <p>17 sensitive episodes of T-cell-mediated rejection with</p> <p>18 lots of edema and tubulitis and very little</p> <p>19 interstitial fibrosis versus more of a smoldering TCMR</p> <p>20 in which, in addition to tubulitis, there is, for</p> <p>21 example, i-IFTA.</p> <p>22 So I think before we definitively try to</p> | <p style="text-align: right;">Page 396</p> <p>1 So I would make that comment.</p> <p>2 I agree with you, there may be features of the</p> <p>3 TCMR that we need to learn about that are putting the</p> <p>4 patients at risk within the context of the graph.</p> <p>5 The other comment that I would make, though,</p> <p>6 is that the TCMR might be a correlate because it's</p> <p>7 causal in the pathway of DSA formation through</p> <p>8 inflammation in the graft, but it also may be a flag of</p> <p>9 allorecognition occurring in the regional lymph node</p> <p>10 system. That is where we're seeing T follicular helper</p> <p>11 cells interacting with B cells. And so it may just be</p> <p>12 that the TCMR itself is a flag of allorecognition</p> <p>13 activity going on, and that the sentinel event is</p> <p>14 actually occurring outside the graft in the regional</p> <p>15 lymphoid system that is leading to B-cell</p> <p>16 sensitization, and it's flagging that there's a problem</p> <p>17 here.</p> <p>18 DR. HAAS: Yeah, the other, on the same point,</p> <p>19 is that with regard to TCMR is actually in itself the</p> <p>20 risk factor, is that your data suggests that TCMR is</p> <p>21 kind of a flag for under-immunosuppression, and that</p> <p>22 maybe TCMR is just sort of signaling that the patient</p> |
| <p style="text-align: right;">Page 395</p> <p>1 answer that question, I think we need to consider that</p> <p>2 T-cell-mediated rejection is not a homogeneous set of</p> <p>3 lesions.</p> <p>4 DR. NICKERSON: I might just add to that</p> <p>5 comment. And we were talking a little bit earlier.</p> <p>6 When we did publish our original paper talking about</p> <p>7 the link of TCMR as a correlate with subsequent de novo</p> <p>8 DSA formation, one of the things that Chris had</p> <p>9 observed was in the first 6 months, and, in particular,</p> <p>10 in the biopsies that we did as surveillance, a lot of</p> <p>11 these patients who had TCMR who went on to develop DSA,</p> <p>12 one of the features of their TCMR that was strongly</p> <p>13 correlated with DSA formation was that they had</p> <p>14 peritubular capillaritis as a feature of their TCMR.</p> <p>15 And so their severity of that score was double</p> <p>16 that of those that didn't form de novo DSA, and we had</p> <p>17 the hypothesis in that construct that the inflammation</p> <p>18 in the microcirculation may be through interferon</p> <p>19 gamma-mediated pathways upregulating MHC, especially</p> <p>20 Class II, which we know is interferon gamma-responsive,</p> <p>21 and that increased expression may be part of why</p> <p>22 there's an increased association with DSA formation.</p> | <p style="text-align: right;">Page 397</p> <p>1 is under-immunosuppressed, and because he or she is</p> <p>2 under-immunosuppressed, is at risk for thus developing</p> <p>3 donor-specific antibodies. And so treating the TCMR</p> <p>4 per se may not necessarily -- just as an acute event</p> <p>5 may not necessarily prevent the subsequent development</p> <p>6 of de novo DSA, but a complete sort of reassessment of</p> <p>7 the immunosuppression may really be what's necessary.</p> <p>8 DR. BELEN: Dr. Mannon, yes.</p> <p>9 DR. MANNON: So I think the one dissociation</p> <p>10 of -- the only case I can think of right now clearly is</p> <p>11 belatacept. So the high risk of rejection early.</p> <p>12 However, the reversibility of those episodes has been</p> <p>13 dissociated from the development of DSA. And that's</p> <p>14 probably one of the few studies that I've seen that I</p> <p>15 can recall where you see that dissociation.</p> <p>16 Or in the olden days when we would have these</p> <p>17 very early rejections and they went away very quickly</p> <p>18 with steroids, and you didn't have to go to other</p> <p>19 agents, my recollection of those -- and there has been</p> <p>20 data to show that those patients can actually do quite</p> <p>21 well.</p> <p>22 But the belatacept is a good example where</p> |

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| <p style="text-align: right;">Page 398</p> <p>1 there is clearly a significantly higher rate of 2 rejection and a dissociation from DSA. And that's the 3 only exception. I mean, otherwise I think it actually 4 -- it's either chicken or egg, but it's involved. 5 DR. BELEN: Dr. Nickerson. 6 DR. NICKERSON: One more comment. I think I 7 want to just build on your last comment, Mark, which is 8 that the TCMR may represent under-immunosuppression. 9 Agreed. That's one possibility. It also may represent 10 dominant HLA genetics that are driving an immune 11 response despite us giving what we think is adequate 12 immunosuppression by whatever definition we give. In 13 other words, there are still probably antigens that 14 will drive an immune response that will break through 15 what we would consider is adequate immunosuppression by 16 the drug levels or combination therapies that we 17 currently use. And so I think that we also must be 18 mindful that even with adequacy and full adherence of 19 our patients, there may be mismatches that are really 20 quite dominant in driving a response. 21 DR. GASTON: I agree with all of this. I 22 think it all sort of fits together actually and in a</p> | <p style="text-align: right;">Page 400</p> <p>1 and the patients remain on bela, they're adherent to 2 their medication most of the time, and we know. And if 3 that is now adequate immunosuppression, we know that 4 they're receiving it, and therefore we're continuing to 5 see the positive outcomes long term. 6 DR. MANNON: Fair enough, but I don't know why 7 people reject on bela, and it's shocking. And I agree 8 with you. I mean, I think histologically, there's a 9 swing towards higher vascular inflammation that's 10 dramatic and the graft dysfunction is dramatic. But it 11 also has impressed me that they've resolved very 12 quickly. 13 Now, Minnie Sarwal apparently had data with 14 the Immucor or whatever her transcript said, saying, 15 oh, it's very different. That hasn't been 16 substantiated, and there is some information in the 17 literature. I mean, we looked in the CTOT study and 18 unpublished data and we couldn't -- now, we didn't have 19 a lot of control rejecters on standard of care, but we 20 didn't see these upper -- and we did low-density rates, 21 so we weren't doing big chip, and so we didn't really 22 see anything different.</p> |
| <p style="text-align: right;">Page 399</p> <p>1 sense that I think the reason why bela is different is 2 because bela provides -- again, back to this term -- 3 adequacy of immunosuppression and how you define it. 4 It provides at one level or another immunosuppression 5 adequate beyond the acute rejection episode to cut down 6 the immune -- or to keep the immune system in check. 7 So I think it is a flag for what's there, and 8 I can't help but think that you said twice what we 9 think is adequate immunosuppression, and what you said. 10 And I think that's the fallacy, is that we don't really 11 have a good way to determine what that is until we see 12 the adverse consequences. And it may well be a flag, 13 it may well be something else that's going on. 14 DR. BELEN: Dr. Alloway. 15 DR. ALLOWAY: I think that when we talk about 16 the rejections that are occurring in belatacept, we 17 don't really know yet if biologically they're the same 18 as the rejections that we're used to seeing under 19 calcineurin-inhibitor therapy, and Dr. Woodle may want 20 to discuss more about that. 21 But I want to bring up that even when the 22 acute rejection has occurred and it's fully treated,</p> | <p style="text-align: right;">Page 401</p> <p>1 I think the biological behavior is different, 2 though, because you're not expecting a 2B to go away 3 very easily, and they do with bela for some reason. 4 And then you put them back on it and you treat them, 5 and then they're okay, which is odd, because, again, I 6 don't think -- you know, again, I think just like the 7 other drugs, you have people who said, "I took my 8 drugs, Doc, and I was on the right levels, and I 9 rejected." 10 And I don't think we understand at a cellular 11 level what the adequacy is based on these troughs and 12 why it's so variable for some patients. 13 DR. SAMANIEGO-PICOTA: What is your opinion 14 about these CD86 oversaturation story? 15 DR. MANNON: I'm not sure I can -- I'm not 16 sure I know what you're asking, and maybe Stuart knows 17 better. I'm not sure if you're thinking that -- you 18 mean in regards to -- you mean like there's a loss of a 19 negative signal. Yeah. I mean, I don't know, you 20 know. Probably in animal models, in these small animal 21 models, like rodents, you could probably show 22 something.</p> |

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| <p>1 I think it's been -- you know, Allan has tried</p> <p>2 to look at risk -- Allan Kirk -- tried to look at, you</p> <p>3 know, sort of risks based on cell populations</p> <p>4 pretransplant. And we've tried to support that</p> <p>5 substantiation in the CTOT studies and haven't been</p> <p>6 able to. So I'm not sure that we know.</p> <p>7 And there's another company that has a</p> <p>8 different pathway that they're interested in looking</p> <p>9 at, and you do worry that maybe there is suppression of</p> <p>10 a negative signal that you're hoping to have that isn't</p> <p>11 there. But we tried it.</p> <p>12 But Steve Woodle has a lot of data with</p> <p>13 belatacept. I'll put you on -- since we're putting</p> <p>14 each other on the spot, you know.</p> <p>15 (Laughter.)</p> <p>16 DR. WOODLE: I was waiting for Stuart to go</p> <p>17 first.</p> <p>18 DR. KNECHTLE: Allan Kirk has that data, yes,</p> <p>19 that CD57-positive cells, as a memory cell subset that</p> <p>20 doesn't express the CD28 and is resistant to a</p> <p>21 blockade, and that may be a pathway. I know that's</p> <p>22 somewhat controversial and hasn't been settled yet.</p> | <p>1 that's the direction that they're headed, and it's</p> <p>2 certainly the direction that we're in, to try to sort</p> <p>3 that out.</p> <p>4 What I can tell you is that I've never seen</p> <p>5 rejections of 2A or 2B under CNI that didn't show a</p> <p>6 response to Thymo. I saw that for the first time in my</p> <p>7 career under a bela-treated patient, and the responses</p> <p>8 to Thymo under bela are not what we would expect. And</p> <p>9 we've used a lot more tacrolimus rescue, which is the</p> <p>10 first thing we went to. And it's not the same</p> <p>11 tacrolimus rescue that we saw back in 1995 when we</p> <p>12 first started doing it, it's different.</p> <p>13 One thing that these cells do appear to be --</p> <p>14 so there's a story in the literature about these cells</p> <p>15 being mTOR-pathway-dependent and potentially mTOR-</p> <p>16 pathway susceptible. We've seen that in a few</p> <p>17 patients, but even that is not. So putting patients on</p> <p>18 mTOR sometimes makes these cells go away very rapidly,</p> <p>19 but not always. And so the picture is complex.</p> <p>20 We've looked at the CD4-CD57-positive paper</p> <p>21 that Allan has published, and it's interesting, but</p> <p>22 we've got to know the cell and we've got to put it in</p> |
| Page 403 | Page 405 |
| <p>1 And then there are, of course, thoughts that you're</p> <p>2 blocking a T regulatory pathway, which is probably</p> <p>3 true, with belatacept. And so that's why they're also</p> <p>4 looking at non-agonistic CD28s as well.</p> <p>5 Steve.</p> <p>6 DR. WOODLE: So we've followed this story of</p> <p>7 the CD28-negative effector memory T-cell population</p> <p>8 that basically escapes, and watched the literature, and</p> <p>9 looked in our population. In monitoring peripheral</p> <p>10 blood, we see a CD28-negative, CD38-positive, CD8-</p> <p>11 positive cell population that arises under bela that</p> <p>12 never arises under CNI. Now, that's, say, 20 patients</p> <p>13 on a CNI, but that population is unique to bela.</p> <p>14 That's in the peripheral blood.</p> <p>15 We've actually seen a patient have rejection</p> <p>16 in which they had a small population of CD28-negatives</p> <p>17 in the peripheral blood, but a tremendous number in the</p> <p>18 graft.</p> <p>19 And so there is always the issue -- one of the</p> <p>20 problems is we always look in peripheral blood for</p> <p>21 these things, but the answer is really in the graft,</p> <p>22 and I think from my reading of Allan's papers, I think</p> | <p>1 the graft, and you've got to put it in the tubule that</p> <p>2 has tubulitis to hammer down what cells are driving --</p> <p>3 what are the primary effector cells driving this.</p> <p>4 Technologies are out that are available, it's</p> <p>5 just going to be something that somebody is going to</p> <p>6 have to work really hard and get a little bit lucky to</p> <p>7 show.</p> <p>8 Carla Baan actually has a nice case report of</p> <p>9 a patient that had a very aggressive rejection that</p> <p>10 went on to cause graft loss where they had done a</p> <p>11 fairly sophisticated analysis of these cell</p> <p>12 populations, and I think that's the type of data we</p> <p>13 need.</p> <p>14 But it's certainly interesting. In spite of</p> <p>15 that, the patients that don't reject, they just sail.</p> <p>16 They literally look great, they feel great, and I think</p> <p>17 this is sort of the one big remaining issue that's out</p> <p>18 there with bela that we've got to figure out. And once</p> <p>19 we're on the right track with that, I think that that</p> <p>20 drug is going to be used a lot more, once it's</p> <p>21 available.</p> <p>22 (Laughter.)</p> |

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| Page 406 | Page 408 |
| <p>1 DR. HAAS: Going back to these individual</p> <p>2 cases, one thing, as a pathologist, that I would</p> <p>3 certainly like to see a lot more follow-up biopsies</p> <p>4 because you cite a case where you're trying to type</p> <p>5 cells in highly aggressive rejections, and typing of</p> <p>6 cells may be very difficult if you have a graft that's</p> <p>7 just overwhelmed by inflammatory cells, but in a</p> <p>8 follow-up biopsy where you treat, and apparently</p> <p>9 incompletely treat because these patients don't</p> <p>10 necessarily improve, you will presumably be enriching</p> <p>11 the cell population within the graft for those</p> <p>12 particular cells that are really doing the damage.</p> <p>13 And seeing sort of before and after biopsies</p> <p>14 and seeing which cells seem to become enriched when you</p> <p>15 treat and can differentiate which cells seem to respond</p> <p>16 to treatment versus which cells don't may be very, very</p> <p>17 informative and may also allow us to try and develop</p> <p>18 therapies that are directed against those particular</p> <p>19 cell types that seem to be resistant to our current</p> <p>20 therapy.</p> <p>21 DR. WOODLE: You know, Mark, I couldn't agree</p> <p>22 more. I think one of the things that happens when we</p> | <p>1 thing about bela that's unique that I think serial</p> <p>2 biopsies when studied appropriately can give us insight</p> <p>3 into.</p> <p>4 DR. SAMANIEGO-PICOTA: Steve, in those</p> <p>5 patients you just mentioned, do they have normal</p> <p>6 function, and the only abnormality is this infiltrate</p> <p>7 on surveillance biopsies?</p> <p>8 DR. WOODLE: Yeah. So, you know, they start</p> <p>9 out with low creatinines to begin with --</p> <p>10 DR. SAMANIEGO-PICOTA: Yeah.</p> <p>11 DR. WOODLE: -- like .8, .9, and 1. They'll</p> <p>12 bump up to like 1.4 or 1.5, and they may sit there for</p> <p>13 a long time, not clearing the lesions, given Thymo,</p> <p>14 given TAC rescue --</p> <p>15 DR. SAMANIEGO-PICOTA: They stay there.</p> <p>16 DR. WOODLE: -- not clearing lesions, they</p> <p>17 stay there, but what doesn't happen as much is they</p> <p>18 don't have progressive deterioration of renal function</p> <p>19 associated with progressive fibrosis.</p> <p>20 DR. SAMANIEGO-PICOTA: Have you immunostained</p> <p>21 those tissues to how they --</p> <p>22 DR. WOODLE: We have not done as much as I'd</p> |
| Page 407 | Page 409 |
| <p>1 get these difficult rejections under bela is we're</p> <p>2 biopsying the patient regularly. And I know there is</p> <p>3 one patient sitting at the table here that wouldn't</p> <p>4 like that very much. But we felt like we needed to do</p> <p>5 that. And what will happen is you'll look under the</p> <p>6 microscope and you look at this, and you go, "Man,</p> <p>7 that's a lot of inflammation, that makes me nervous,"</p> <p>8 and then you'll treat them, and you'll come back a</p> <p>9 couple weeks later and it's not much better. You come</p> <p>10 back 2 or 3 weeks later, and it's the same.</p> <p>11 But what doesn't happen -- and those are</p> <p>12 things that under a CNI, under TAC, you would see, you</p> <p>13 would go, okay, the next time I look at this in 2, 3</p> <p>14 weeks, I bet you there's going to be a lot of scar.</p> <p>15 But under belatacept these things seem to persist, but</p> <p>16 the scar doesn't develop. And so that's another thing</p> <p>17 that's fundamentally different about bela.</p> <p>18 And I don't know if it's the absence of TGF-</p> <p>19 beta induction that you get with a CNI that you don't</p> <p>20 get with bela, or what it is, but you see persistent</p> <p>21 inflammation without the progressive rapid onset of a</p> <p>22 lot of fibrosis in the graft. And so that's another</p> | <p>1 like to do. And so one of the things that we've had to</p> <p>2 do in our institution is basically gear up a program to</p> <p>3 start to be able to look at this. And so the rules are</p> <p>4 different. The rules under bela are different.</p> <p>5 The other thing that's a little bit different</p> <p>6 is viral responses. I think that our impression is we</p> <p>7 have to be more aggressive about your concomitant</p> <p>8 immunosuppression reduction to clear virus under bela</p> <p>9 as compared to CNI. Now, we haven't analyzed our data,</p> <p>10 and we need to do that. But that's our impression. I</p> <p>11 don't know if Stuart or if you other folks that have</p> <p>12 used bela have had that same impression about clearance</p> <p>13 of virus under bela also.</p> <p>14 DR. MANNON: I would respond, but I feel that</p> <p>15 this is not a bela session, and I feel guilty for</p> <p>16 starting it. So I will discuss after.</p> <p>17 DR. BELEN: Okay. So we'll give the last</p> <p>18 comment to Ergun, and we're going to move on to the</p> <p>19 next question.</p> <p>20 DR. VELIDEDEOGLU: Just one quick question to</p> <p>21 Professor Woodle.</p> <p>22 DR. WOODLE: Bela is a very important drug</p> |

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| <p style="text-align: right;">Page 410</p> <p>1 because there are several groups -- there are groups 2 poisoning to use that in combination as an antihumoral 3 therapy strategy. So I just would leave it there. I 4 think you're going to hear more about that tomorrow 5 certainly from Stuart and possibly from others. 6 DR. VELIDEDEOGLU: One very quick question, 7 clarifying question. When you say "TAC rescued," I 8 assume the patients are discontinued from bela, is that 9 right? No. They receive TAC plus bela. Okay. 10 Thanks. 11 DR. BELEN: Okay. So we're going to move on 12 to the next set of questions. 13 From a posttransplant DSA development 14 perspective -- and we're going to take it in two 15 different questions, the first one being, Should 16 induction treatment strategies be based on immunologic 17 risk? And then the second part, if you could discuss 18 CNI minimization and avoidance of corticosteroids from 19 the perspective of DSA development. But we'll start 20 with the induction question. 21 DR. SAMANIEGO-PICOTA: Yes. 22 (Laughter.)</p> | <p style="text-align: right;">Page 412</p> <p>1 effectively. 2 DR. SAMANIEGO-PICOTA: Yeah, absolutely. So I 3 don't know that the answer is clear. That's why in Dr. 4 Djamali's paper it's clearly established that 5 randomized clinical trials need to be done. I do not 6 know that there is an appetite in PhRMA to do these 7 kind of randomized trials mainly because the conflict 8 of interest in Sanofi being they are a company owning 9 both medications that may not be able to ever been 10 done, and not in the United States at least. 11 Whether we should combine a cell-depleting 12 agent at one point in time, give rituximab, you can 13 really only do that in the setup of desensitization. 14 You know, in a patient that gets the transplant 15 tomorrow -- today I mean, 2 days later have a recall 16 response or a memory response and has AMR, that is 17 really not induction, it gets then into the treatment 18 part of things, but if you think -- and I think 19 everybody here probably agrees -- that for antibody, de 20 novo antibody, these are T-cell-dependent antigens, you 21 need to have T-cell activity. T-cell control of T-cell 22 immunity is essential to prevent de novo antibody</p> |
| <p style="text-align: right;">Page 411</p> <p>1 DR. BELEN: Okay. 2 DR. SAMANIEGO-PICOTA: Let me see how -- 3 really, all the data we are getting about development 4 of DSA and induction agents is from retrospective data, 5 most of them, from postdoc analysis from previous 6 studies. Logic suggests that, yeah, induction therapy 7 is important and it's useful. Which is the ideal agent 8 for induction therapy? Whether if you're looking at T- 9 cell depletion, is it Campath? is it Thymoglobulin? It 10 is possible that both are equally good depending on 11 what type of maintenance immunosuppression you put that 12 patient on, Campath, (inaudible), and MMF, seems to be 13 doing fairly decently based on the Cedars-Sinai 14 experience. 15 Thymoglobulin works very well, has certain 16 advantages, and Campath does as well, and is the 17 targeting of natural killer cells. And I do not know 18 how -- Stuart probably knows very well -- how well is 19 Campath at depleting natural killer cells vis-à-vis 20 Thymo? 21 DR. KNECHTLE: I don't know the comparison of 22 that, Millie, but alemtuzumab does target NK cells</p> | <p style="text-align: right;">Page 413</p> <p>1 formation. Induction can help to certain level to 2 that. 3 DR. BELEN: Thank you. Anyone? 4 DR. KNECHTLE: Don't you think one answer to 5 that question is, what's happening clinically? I mean, 6 just look at drug in the United States; 70 to 80 7 percent of patients are getting depleting induction 8 therapy. I think that gives you the opinion of most 9 clinicians in the United States regardless of what the 10 co-called experts today think. 11 DR. BELEN: Okay. 12 DR. DJAMALI: If I may add a comment here. 13 DR. BELEN: Yeah. 14 DR. DJAMALI: I agree that the vast majority 15 get T-cell depletion. And the main question is, Which 16 T-cell depletion is the right approach for the 17 induction of sensitized patients? One of them is 18 effective, and both of them are effective, but one of 19 the would be much more costly than the other one. And 20 the best randomized trial we have comparing Campath to 21 Thymo in sensitized patients, this is patients with a 22 PRA of less than 20 percent, so they are not that</p> |

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| <p style="text-align: right;">Page 414</p> <p>1 sensitized. I would really love to see that.</p> <p>2 I don't know. I think you're right,</p> <p>3 absolutely have to do a T-cell depletion, but which</p> <p>4 one?</p> <p>5 DR. BELEN: So we'll move on to the next</p> <p>6 section of questions regarding the avoidance, CNI</p> <p>7 minimization, and steroid avoidance. No? I think this</p> <p>8 was touched upon a little bit, but --</p> <p>9 DR. NICKERSON: So I would say we would all</p> <p>10 love to do CNI minimization, and we'd like to do it as</p> <p>11 much as we can, but every attempt that we've tried to</p> <p>12 do it has failed, I would say, so far, especially as it</p> <p>13 relates to being at risk for DSA. The data around the</p> <p>14 HLA matching of donors and recipients I think may be a</p> <p>15 window into where there might be some selective</p> <p>16 opportunities.</p> <p>17 But, again, and I've made this point, the data</p> <p>18 that's been generated so far has been largely in a</p> <p>19 Caucasian-based population. We don't know whether</p> <p>20 that's going to be true in other genetic backgrounds.</p> <p>21 And certainly I think there needs to be more study in a</p> <p>22 more diversified cohort of patients more like what we</p> | <p style="text-align: right;">Page 416</p> <p>1 done the right thing after the fact. And until we have</p> <p>2 ways to decide for point for number A to define</p> <p>3 immunologic risk better than we do right now, or, B,</p> <p>4 who to minimize in, then we're going to be sort of</p> <p>5 operating blindfolded.</p> <p>6 DR. HAAS: I think one of the problems we have</p> <p>7 in addressing the possibility of CNI minimization is I</p> <p>8 don't think that we really know in the current era of</p> <p>9 CNIs, that is, tacrolimus at its current dosage versus</p> <p>10 higher doses of cyclosporine in the past, how much</p> <p>11 chronic damage CNIs really do to the allograft.</p> <p>12 And if you go back to the studies, the</p> <p>13 protocol biopsy studies, that Brian Nankivell and his</p> <p>14 colleagues did now 20 years ago, they concluded that</p> <p>15 chronic CNI toxicity was a major contributor to IFTA</p> <p>16 and ultimately to graft loss. But this was done,</p> <p>17 cyclosporine, and it was also done when higher doses of</p> <p>18 CNIs were done.</p> <p>19 Phil Halloran has suggested on numerous</p> <p>20 occasions, based mainly on molecular data, that in</p> <p>21 today's environment CNI nephrotoxicity contributes very</p> <p>22 little to graft loss.</p> |
| <p style="text-align: right;">Page 415</p> <p>1 would see in the United States and what we see in our</p> <p>2 program in Canada.</p> <p>3 And then I think to do this properly, it</p> <p>4 should be done in a prospective, randomized, controlled</p> <p>5 trial where we use selection of these patients for</p> <p>6 enrollment into a CTOT-09-like study where we do it</p> <p>7 under very careful conditions to monitor for immune</p> <p>8 reactivity.</p> <p>9 So I think there are opportunities, and</p> <p>10 certainly we should be pursuing those in the absence of</p> <p>11 some new medication that's going to all of sudden show</p> <p>12 up and replace CNI. Whether that ultimately might be</p> <p>13 bela, I think we're going to wait and see. So I think</p> <p>14 there's opportunity, but I think it needs to be done in</p> <p>15 proper studies and shown in more than just one or two</p> <p>16 populations.</p> <p>17 DR. GASTON: So when I look at question A and</p> <p>18 question B there, to me, the issue is, as Peter just</p> <p>19 said, the issue I think is yes, we should base</p> <p>20 induction on the immunologic risk. We would love to</p> <p>21 eliminate, to minimize or eliminate, CNIs, but we don't</p> <p>22 have any guideline. We only seem to know whether we've</p> | <p style="text-align: right;">Page 417</p> <p>1 So before I think we can consider whether CNI</p> <p>2 minimization is a worthwhile pursuit, it would be worth</p> <p>3 knowing, how much chronic damage can CNIs do to the</p> <p>4 graft? And we don't know that.</p> <p>5 And just one plug into point C, I can't really</p> <p>6 speak as to the significance of corticosteroid</p> <p>7 avoidance regarding DSA development, but my other hat</p> <p>8 is as somebody who's interested in glomerulonephritis</p> <p>9 and particularly IgA nephropathy. And one of the</p> <p>10 biggest problems that at least I perceive with</p> <p>11 corticosteroid avoidance is recurrent disease, and I</p> <p>12 think that needs to be a consideration beyond just DSA.</p> <p>13 DR. BELEN: Dr. Matas?</p> <p>14 DR. MATAS: Well, I can't let the comment</p> <p>15 about the Nankivell paper go by without pointing out</p> <p>16 that there was significant inflammation in those</p> <p>17 biopsies that they ignored when they did the study. I</p> <p>18 think a preconceived notion of what they were looking</p> <p>19 for, and if I remember correctly, 25 percent of the</p> <p>20 biopsies between 1 and 5 years had inflammation, which</p> <p>21 clearly is hard to discriminate what was cause and</p> <p>22 effect.</p> |

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1 But I think it's important to minimize the
 2 drugs. I mean, we all know that. We've seen the
 3 benefit of steroid-free protocols. You can't tell in
 4 clinic anymore who's on prednisone -- I mean, who is a
 5 transplant patient like you could 20 years ago when
 6 people showed up with all the puffy face and so on.
 7 And CNJ minimization can't be bad if we do it
 8 well. And the trick is going to be how to define the
 9 subpopulation. And to give you a reason why, the
 10 flipside of Tom Nevin's (ph) data, where we looked at
 11 immunosuppression adherence using the MEMS Cap, we
 12 recently looked at -- and this was presented at ATC
 13 last year -- malignancy in relation to adherence and
 14 nonadherence, and, in fact, the perfectly adherent
 15 patients had more malignancy. And interesting in just
 16 looking at it recently, they also had more CMV
 17 infections.
 18 So we really need to find the right balance
 19 between minimization and preventing rejection.
 20 To address your comment about IgA nephropathy,
 21 I think we have to define who, which subgroups -- and I
 22 certainly agree with you about potential recurrent

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1 diseases. There is just a paper published looking at
 2 steroid-free immunosuppression in patients with IgA
 3 nephropathy, and I wish I could remember where, maybe
 4 JASN, showing increased recurrence in the steroid-free
 5 group.
 6 And so I think we're going to need to have to
 7 look at individual recurrent diseases one-by-one
 8 because it may not apply across all recurrent diseases,
 9 to see if steroid-free immunosuppression can be done.
 10 But the definition of "steroid-free" has
 11 changed. So when we started steroid-free, we were
 12 giving whopping doses of prednisone, and it may be that
 13 simply 5 milligrams a day would be enough to prevent
 14 that recurrence of disease. I think those are all
 15 questions that need to be answered.
 16 DR. WOODLE: Arthur, I would make the point
 17 that our experience suggests -- and I think, if I'm not
 18 misquoting the IgA data, that there is a higher
 19 incidence of recurrence, but the progression to graft
 20 loss was not different within the first 3 to 5 years.
 21 Is that correct? Certainly that's what our data
 22 suggests.

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1 And, as you know, IgA recurrence is a pretty
 2 common thing. Graft loss to IgA recurrence is a
 3 different issue.
 4 DR. HAAS: That's because -- I think the
 5 problem with IgA recurrence in terms of interpreting
 6 the data in the literature, which is widely, widely
 7 varied, is how one defines a recurrence. Some centers
 8 define a recurrence simply by the presence of IgA in
 9 the mesangium. Now, these people have abnormally
 10 galactosylated IgA, and this is going to deposit
 11 frequently in the mesangium regardless of their
 12 immunosuppressive status. And those studies that
 13 define an IgA nephropathy recurrence simply by the
 14 presence of IgA will state that graft loss due to IgA
 15 recurrence is rare because IgA recurrence is so common.
 16 On the other hand, other studies will define
 17 IgA recurrence by either mesangial proliferation or by
 18 proteinuria, and now we're talking about IgA recurrence
 19 rates that are more down in the 10 to 20 percent range
 20 or even less, but that graft loss due to the IgA
 21 recurrence in these studies is greater.
 22 But one thing that was pointed out, I think it

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1 was in the Ponticelli in KI now about 10 years ago was
 2 that IgA recurrences that lead to graft loss tend to be
 3 late recurrences, usually recurring about 7 years and
 4 beyond posttransplant. So again when one considers how
 5 one wants to deal with steroid reduction in those
 6 cases, again, one has to consider the timing of the
 7 steroid reduction and also the timing of the recurrent
 8 diseases and how one defines a recurrent disease.
 9 DR. SAMANIEGO-PICOTA: I want to make a
 10 comment, Mark. We had made the same decision of not
 11 including patients with biopsy-proven GN in steroid-
 12 free, but there is really not too much data to show
 13 that that is the right decision. We assume it is. For
 14 instance, I don't think of IgA nephropathy primary
 15 disease as necessarily a steroid-responsive type of
 16 disease. I would like to hear what the other
 17 nephrologists in the group think.
 18 DR. DJAMALI: Actually, I think there is data
 19 from maybe Art's group, Aleksandra Kukla was the first
 20 author on this paper that looked at all patients with
 21 primary GN, and those that underwent steroid withdrawal
 22 as opposed to not, and those with steroid withdrawal

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| <p>1 had a higher recurrence rate. So all-comers GNs, now 2 what we do is that we keep them on low-dose steroids. 3 DR. SAMANIEGO-PICOTA: I agree, but what about 4 IgA? Do you consider IgA nephropathy a steroid- 5 responsive GN? 6 DR. DJAMALI: If I relied on that 7 observational study, yes, and the more recent study 8 that came out, yes. 9 DR. HAAS: It depends on the IgA. There are 10 -- I mean, the debate as to whether one uses steroids 11 in IgA and whether it's a potentially steroid- 12 responsive lesion depends on a number of different 13 factors. Endocapillary proliferation is one that seems 14 to be associated with steroid responsiveness. 15 Crescents, certainly associated with steroid 16 responsiveness. And there is some data also out there 17 that graft loss -- this is in Henoch-Schönlein purpura 18 rather than IgA, but I consider them sort of sister 19 diseases -- that crescents are associated with not only 20 an increased rate -- in the original biopsy, crescents 21 are associated with an increased rate of recurrence and 22 an increased rate of graft loss due to recurrent</p> | <p>1 listen to. 2 But, I mean, A, you know, yes, it should 3 definitely be based on immunologic risk. I don't know 4 why it wouldn't be. It seems to me a pretty cut and 5 straight answer. 6 I mean, B, I take a CNI. So I would certainly 7 say that it should be applied to all, but with the same 8 extent, I'm almost 16 years out with this ABO- 9 incompatible transplant, and one of the surgeons was 10 here, and another one I think is going to be here 11 tomorrow, and their philosophy, and I agree with it, is 12 sort of if it isn't broken, don't fix it. 13 I'm on a really low dose, and I can tell you 14 from when I lost the second kidney, they switched me to 15 a drug and it screwed my kidney, because they thought 16 the other one would be so much better. 17 So if there's a little bit of toxicity or 18 potential risk for that, you're already sort of on 19 borrowed time, so why would you ruin something if it's 20 working well just because of a possible risk of -- 21 right? If you're not seeing it, don't kind of screw 22 with it, but minimize it.</p> |
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| <p>1 Henoch-Schönlein purpura nephritis. 2 And, finally, there's a paper in KI from the 3 Oxford group this month that podocytopathic segmental 4 sclerosis, which is basically segmental sclerosis with 5 overlying swollen and hyperplastic podocytes, is a 6 steroid-responsive lesion. But purely mesangial 7 proliferation IgA is not. 8 But then again, grafts are not usually lost to 9 purely mesangial proliferative IgA nephropathy. It's 10 those with the crescents, it's those with the 11 endocapillary proliferation, it's those with the 12 segmental glomerulosclerosis that lead to graft loss 13 and IgA. 14 So I think you need to consider the high-risk 15 IgA's that do lead to end-stage renal disease as being 16 the same ones that are more likely to recur in the 17 transplants. 18 DR. BELEN: Well, I think this is a wonderful 19 discussion, but we're going to give the last words to 20 one of our patients, Mr. Michael Mittelman. Please. 21 MR. MITTELMAN: Thanks. Man, I see this as 22 super cut-and-dry. I mean, the conversation is fun to</p> | <p>1 And, C, absolutely, corticosteroids are the 2 worst. Kids shouldn't be on them. I think you've 3 talked -- I've heard a lot about really only adult 4 usage, but, man, pediatric usage of corticosteroids 5 have screwed me big time, and I don't know why you 6 would ever put people on it, particularly if they're 7 posttransplant if it can be avoided. That's my 2 8 cents. 9 (Applause.) 10 Wrap Up -- Day 1 11 DR. BELEN: So we're going to wrap it up. 12 DR. ALBRECHT: Well, thank you very much. 13 We're now at 6:00 and closing. So again let me just 14 thank all the speakers for the outstanding 15 presentations, and, again, especially express our 16 sincere appreciation to the patients for sharing their 17 stories with us. 18 With that, I think we'll close and we'll come 19 back tomorrow -- and actually my apologies -- and 20 really good discussions, very much appreciate everybody 21 interacting and sharing viewpoints. 22 And with that, we'll close and we'll reconvene</p> |

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| <p>1 tomorrow morning here at 8:30. 2 Thank you. Have a good evening. 3 (Whereupon, at 6:02 p.m., the meeting was 4 adjourned.) 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p> | <p>1 CERTIFICATE OF TRANSCRIBER 2 I, DEBORAH ARBOGAST, do hereby certify that 3 this transcript was prepared from audio to the best of 4 my ability. 5 6 I am neither counsel for, related to, nor 7 employed by any of the parties to this action, nor 8 financially or otherwise interested in the outcome of 9 this action. 10 11 12 13 APRIL 24, 2017 DEBORAH ARBOGAST 14 15 16 17 18 19 20 21 22</p> |
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| <p>1 CERTIFICATE OF NOTARY PUBLIC 2 I, MICHAEL FARKAS, the officer before whom the 3 foregoing proceeding was taken, do hereby certify that 4 the proceedings were recorded by me and thereafter 5 reduced to typewriting under my direction; that said 6 proceedings are a true and accurate record to the best 7 of my knowledge, skills, and ability; that I am neither 8 counsel for, related to, nor employed by any of the 9 parties to the action in which this was taken; and, 10 further, that I am not a relative or employee of any 11 counsel or attorney employed by the parties hereto, nor 12 financially or otherwise interested in the outcome of 13 this action. 14 15 16 17 MICHAEL FARKAS 18 Notary Public in and for the 19 State of Maryland 20 21 22</p> | |

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