Precision CRRT: Results from ADQI XVII

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Speaker 1:	00:06	There is a website , Acute Dialysis Quality Initiative that you can visit, now, this is the list of the conferences and the many topics that we have developed over the years. The last one was in Asiago, a place that is a very dear to me because I spent 20 years of my very early life, playing hockey and singing and playing guitar and, in this place we tried to figure out what the precision medicine can do for CRRT. Now I will try to be fast because you can find every single word of this conference published already in Blood Purification so you can go and get those papers and they are open access, so they are very easy to get. But the problem was, large randomized trial that provide evidence for clinical guidelines. Although these guidelines had often characterized by expert opinion rather than strong solid evidence, and in fact controversies remain.
Speaker 1:	01:11	The practice of CRRT remains variable. , some new trials did not give definitive conclusions. There are heterogeneous results that underscore the limitations of randomized trial. So a single best solution may not exist for all or even for most patients and the lack of one size fits all answer to complex problems is not uncommon. We have seen already for there is no best dose for insulin or no best antibiotic and so on. So treatments should be tailored to a specific patient specific condition. In this case, for example, in oncology, this is very, very clear and they should explain also why a device can work in a given patient and not in another patient. So search for one dose, one modality, one time for initiation, the best number simply may be not fruitful. And, so this are the editorial that John Kellum and I wrote about introducing precision renal replacement therapy. Precision medicine takes into account individual differences, geno and phenotype.
Speaker 1:	02:22	It targets illness by selecting drugs and those specifically for an individual and therefore precision CRRT use patient information like solute load, fluid balance, residual renal function to personalize treatment, prescription more, patient needs change over time. So it's not just individualizing the treatment, but prescriptions should be dynamic in the very same patient. And using this framework, we cannot speak about optimal dose in general recommendations that are based on expert experience become more important rather than stringent evidence that cannot be achieved sometime and therefore we are much more looking on the application and the pathophysiological

foundations of the mechanism involved in the syndrome rather than trials result, because sometimes these trials in order to be perfect and statistically meaningful, they lose a little bit of clinical significance. So there is an apparent paradox in modern medicine because in one side we have a big data and we did one ADQI meeting in Banff, Canada on big data analysis.

Speaker 1: 03:39 And on the other hand we have single patient, single electronic medical record evaluation. By trying to combine these two things with technology, we can probably provide the quality assurance program and CQI programs, evaluating policies, changing policies, but also managing outliers. So we move towards the single patient rather than towards a large populations. So what came out from ADQI was that as previously suggested, the application of large database and big data should be done but in light of specific data for each patient. And we need to make a big effort to standardize terminology. So the concept of terminology standardization has been dealt with two publication in Critical Care that are also open access and I think they are very important to keep on the desk in order to use the same terminology. Consensus was reached on the fact that a continuous balance between patient demand and capacity should be made.

Speaker 1: 04:53 Then I will explain this in a moment. So the purpose of ADQI 17 was to develop this framework and to set a research agenda to answer key questions, need to refine the framework for clinical use. Why is it important to have a consensus terminology to increase safety of CRRT, to increase accuracy and efficiency of delivery, to attain a shared language among all parties, physicians, nurses, technician engineers, to uniform clinical research and data reporting. In the big data world, you want to have the same terminology and to facilitate communication and technological progress. So this is a document that has been signed by many people and many industries in the so-called a Nomenclature Standardization Initiative Alliance were practically, they agreed on trying to get the same terminology and to call the same things with the same name. Given this, consideration we got a nice Cappuccino, as you can see here in Asiago and the group, Ashita is just a seating near me.

Speaker 1: 06:07 The group was going through specific questions, 1- patient selection for CRRT , 2- solid control technical aspects and fluid management. Now again, I will try to go fast through this things, but just to tell you the highlights of these aspects and again, every point that is in a publication in Blood Purification. About patient selection, when should that acute renal replacement therapy be initiated, what is the most appropriate therapy to meet demand and capacity imbalance? How should renal replacement therapy be integrated to other extracorporeal

		therapies? When should transition to other modalities be considered and how should patients be liberated from renal replacement therapy? I think the key point of this discussion was the concept that we have the demand for blood purification, whether it is from a normal kidney or from an artificial kidney, and we have a disease burden. We have solute load and we have volume load, and here we have the capacity which can be meeting the expectation or not meeting the expectation and when there is a gap in this capacity, this is what requires renal replacement therapy and again, you can have a high demand or normal capacity or normal demand and low capacity and all these conditions create a gap that may require renal replacement therapy.
Speaker 1:	07:38	Indeed, of course, there are factors affecting metabolic and fluid demand like degree of fluid overload, solute load and comorbidities, and also other factors to be considered for initiation, like severity of illness, necessity of renal replacement therapy for other reasons, risk for the therapy and patient wishes overall goal of care and healthcare cost and so on. We made several different statements. I think, in the interest of time, I don't want to go through the statements, but you can find every point and statement documented in our publication. Just to make it clear, here you have three different conditions for the patient in blue CKD, in orange, super imposed AKI, and in green, the solute and fluid load in the patient. In the first two lines on top here, there is no renal replacement therapy as you can see here.
Speaker 1:	08:46	And kidney function is capable of coping with this or in this case progressively goes down towards an increased gap. In this case, renal replacement therapy is initiated rather early here or rather late here. And in some cases, as you can see here, continuous may be shifted into intermittent when the gap is decreasing, there were recommendations for future research in particular, we need to determine the thresholds for the demand capacity gap. This is what determines really the requirement for renal replacement therapy. And we recently published the concept that this time for precision medicine in indicating the initiation of therapy. And other point was that the continuous versus intermittent modalities may depend on the hemodynamic stability, intercranial pressure, risk of infection immobilization on one side and on the other side in favor of intermittent therapy. Rate of fluid removal, rapidity of metabolic correction, risk of osmolar shift and speed, the most solute clearance.
Speaker 1:	10:00	Now it is clear that this, a continuous prolong and intermittent and intermittent is a continuum for the patient. Also a machine should not become like a Christmas tree. They should be

integrating all the potential additional treatment, including CO2 removal or a treatment for liver dysfunction. For solute control. there were questions related to what is the ideal method to prescribe and measure delivered CRRT dose, what are the effect of the liver dose? Can procedure modification target dose be tailored to evolve in patient status? And finally, quality measures. There is a consensus on the fact that there is a dose dependent region and there is a breaking point and then there is a plateau which is mostly practiced dependent region. We don't know exactly for each patient where the breaking point is, we know where the population breaking point maybe, but the single patient may require what we call a dynamic prescription.

Speaker 1: 11:09 In any case, we have started in the past the delivery versus prescription, and we know today that if you prescribe 25 milliliters per kilogram per hour, you can get in every patient a kt/v of 1 every 24 hours, but for example, if you have fluid overload, this may impact the level of kt/v that you can deliver in that patient because the real volume in that patient is expanded compared to the ideal volume. The same is true for downtime and as you can see here, when you have a tool for six hours downtime, you're Kt/v delivery may really go down significantly. Even if you prescribe 25 milliliters per kilogram per hour. What are the effects that were solutes intended to clear? These are targets, restoration of homeostasis, and you have also harmful and unintended conditions like antibiotic removal or loss of micro nutrients. Are different target

Speaker 1: 12:17 those of CRRT needed that various stages. Well, yes, dynamic prescription may be required to achieve solute control. In other words, if you ever prescribed a certain dose and the patient starts climbing with azotemia or start climbing fluid overload, you need to reassess your prescription and change. And this is the figure that you will find in the publication showing three different patients with high variation of the demand compared to capacity and in which patient at every moment the prescription should be reassessed in order to try to keep the status like in patient B where there is a default zone. What indicator to monitor? Well, ratio delivered versus prescribed, effective treatment time and using generally specific indicator. You may use the reduction ratio in day one over day 2 ratio. I will go over the statements. I'm sorry they are too much.

Speaker 1: 13:21 Now, another point that was identified was what is adequacy, adequacy for what? Is adequacy target the same for every patient? is constant over time at prescription delivery, the same thing?, and therefore is the same to achieve adequacy target with different modalities? Now the idea is that we have a multidimensional view of adequacy today that includes, the molecules, cardiovascular condition, calcium, phosphate

control, nutrition, and several other aspects including control of sepsis and fluid balance. So treatments can have a different type of optimization. The best approach would be if you have a completely around the graph for your treatment, but if you have some alteration in the graph shows, for example, reduced kt/v or here, inadequate cardiovascular correction and fluid balance correction and so on. So dynamic prescription start form your original prescription, measure delivery looks at outcomes through quality measure continuously go back to reassessment of prescription and also through clinical reassessment of the patient.

Speaker 1: 14:43 Now, the concept of dynamic demand and capacity of the treatment stay on the fact that you want to stay as close as possible to the homeostasis line. Whether this is for uremia for volume or general electrolyzed, and acid base. That's why prescription here, where do you have average deviation from the almost static line, a much higher than here or here should be different, right? What in fact is the role of technology to do that? Well, the questions were basically how technology can help to perform and optimize therapy and this slide shows that technology can help from risk assessment to diagnosis, to indications to identification of therapy targets to prescription to delivery and to monitoring with the possibility to go back and reassess and identify new therapy targets, more defined prescription at the same time. The decision to start renal replacement therapy may depend on this blue part of the technology, so we have developed a kind of algorithm from the moment the patient is admitted to the ICU.

Speaker 1: 16:06 Volume is optimized, suspected or proven AKI, start AKI monitoring at this point, you assess severity in the patient including KDIGO staging. You personalize their valuation of patient demand capacity gap, and this is the area of research we have been identifying. We choose the therapy, whether it is conservative or substitutive and we prescribe renal replacement therapy, and then once you prescribe renal replacement therapy, you have your targets which are volume, solutes removal, electrolytes. Other. You choose the modality, you choose all the different aspects that are listed in the publication, you choose the therapy settings, and then you start delivery and collect the data and evaluate criteria for stopping or continuing and reevaluating the patient and the prescription. We have different technologies available today, right? So what we are looking forward is to have a technology that allow us to reach the minimum variation and the distance from the physiological targets.

Speaker 1: 17:18 So this is the ideal correction that we can have in a given patient and where technology can help. Well, once you have reached

almost close your physiological targets, what do you want to do is to avoid this alpha angle which moves the patient far from the condition of homeostatic control and anytime you find an angle greater than 15 degrees, you need reevaluation intervention and change prescription. This is what we call assisted dynamic prescription. In a more practical way. You get signals from the patient, clinical chemistry, the patient itself and the machine that go into a computer and combine the data and signal and making a true expert analysis, a potential feedback into the machine that can be nurse, manually operated, can be nurse authorized, biofeedback, or can't fully automatic biofeedback. This is the future of technology and by doing this there are already some machines that are designed to exactly meet the delivery to the prescription capacity and as you can see here, over time, the distance between prescription and delivery is minimized through the algorithms inside the machine. This is too long. Definitely.

Speaker 1: 18:58 What are the main areas for future research? Well, many areas basically I think that the electronic support for decision processes, one of the most interesting thing where information communication technology can meld information from the patient, from the machine, from the environment, and try to operate for a specific outcome. Today we have the possibility to collect the data into the machine card, into electronic medical records and even on the clouds. And we have tested recently a system called Shared Source that allow us to make statistics and to analyze our performance in terms filter life treatment, downtime, prescribed versus delivery, fluid removal parameters, alarm management, and different summaries, timing of CRRT initiation, fluid overload, management ventilator, vesopressor duration, CRRT initiation versus KDIGO stage, frequency of renal replacement therapy after CRRT and so on and so on. Finally, the last group was about fluid management, this is really a paper that is almost in secret and Ravi has made a lot of information in this paper.

Speaker 1: 20:19 So I invite you really to read. Just to summarize this, I think the goals for fluid management are to maintain circuit integrity, plasma composition and fluid balance and you don this is through the different operations that you can see here include the anticoagulation and the filtration fraction. You do this through the type of fluid content and site of administration. And finally you do this through removal regulation. Assuming that you have a removal you have refilling of the intravascular space and you might have imbalance at this point. What is important is that you can have different approaches that are designed. One is if you have fluid overload, the increased removal and varying ultrafiltration, or you may vary the replacement volume and speed in the patient.

Speaker 1:	21:22	Now there is another thing that is important entities. What is the fluid balance you can achieve with CRRT in the machine, and what is the fluid balance that you get in the patient. And this slide though, it seems a little bit complicated, simply shows that to achieve any integrated balance between the machine and the patient, it depends very much on the time gap that you may have before you achieved this thing. So this is the balance in the machine. This is the balance in the patient. The optimal situation is to get a minimum time gap in which actually the balance is fully integrated in the machine. So you need to do different steps, determining affluent rate, the fluid balance, composition, determine the timing of achievement of the goal. And then you can monitor an act in reprogramming the prescription. So in conclusion, I think that, I was a little bit running, but again, you can get every information in the series of publication in Blood Purification, 2016 and precision medicine is suggested in the evaluation starting and stopping renal replacement therapy, selecting the patients more is better until a certain point where the curve survival reach a plateau.
Speaker 1:	22:50	It means that CRRT cannot provide you in mortality. Dynamic prescription and strict control of delivery is recommended. Different modalities are available and you have to be ready to use them as a continuum rather than one against the other. And new technological advances should help clinicians to optimize prescription delivery and result evaluation. Today is Dr Kellum's Birthday. So I take this opportunity to wish him a happy birthday. And these are the four musketeers of ADQI, and also I have to really thank all of them. The idea about precision CRRT is to put together standardization with personalization in a melting pot. If you want to know more, follow us on youtube with a Cappuccino, with Claudio Ronco and again, thank you to Ravi that has made this 22 years fantastic meetings in California and I give you a date to come to which answer for this year in June, hopefully join us and be on the other side of the ocean with us. Thank you very much.