

Acute Dialysis Quality Initiative

2nd International Consensus Conference

REVIEWS

ADQI workgroup reports were sent to leading experts who served as external reviewers.

Reviewers were asked to provide reviews and editorial comment on the workgroup reports.

Seymour Rosen

Workgroup 4: Animal Models of Acute Renal Failure

My comments on this manuscript, because of space limitations, must be abbreviated. I would, therefore, urge the readers to consult references (1,2). The most utilized model of ATN is that of warm ischemia reperfusion and, the authors have listed a series of "advantages" of this method. Indeed, I do not completely agree with their conclusions.

Warm Ischemia Reperfusion

1. The reproducibility of this model depends on the length of the ischemic period. For instance, at 45 minutes of warm ischemia with subsequent reflow, there is extensive and consistent destruction of S3 but, there is irregular destruction of the proximal convoluted tubules as well, i.e., consistency in S3 destruction but inconsistency in S1, S2 injury (3). To achieve consistency, some investigators will use periods of 60 minutes or more, producing massive tubular injury never found in human ATN (1).
2. Intuitively, nephron repair processes in the rat likely resemble that found in human, but the statement of "recapitulation" confers an inappropriate certainty. Indeed, the renal anatomical differences of the rat versus human suggests that these processes cannot be identical: the outer stripe of the outer medulla (cellular mass, largely S3) in the human is extremely irregular in contrast to the well-defined corresponding zone in the rat. Furthermore, I find the statement "inflammatory response comparable to human autopsy data" as incorrect. The medullary inflammation typical of human ATN (4) is likely of intravascular hematopoietic origin (5). This type of inflammation is not the overt inflammatory response described in the warm ischemia reperfusion model (6).
3. I would agree that there is a correlation between functional injury and pathological changes, but that does not necessarily strengthen the relevance of this model since, in human ATN, such a correlation has not been shown. Indeed, substantial renal dysfunction in the clinical practice is usually associated with limited tubular damage. In this perspective, I regard the poor functional/morphological correlation found in less

severe models of selective outer medullary hypoxic damage as an advantage rather than disadvantage, resembling the human syndrome of ATN.

4. I consider the phrasing of the first two listed disadvantages of the warm ischemia-reflow model as being too modest. In fact, we hardly see ARF with pure warm ischemia alone and, ARF, due to warm ischemia with prolonged complete total cessation of renal blood flow, rarely occurs in the clinical practice.

Cold Ischemia-Reperfusion

On the other hand, the cold ischemia-warm reperfusion model of ATN parallels the situation of human renal transplantation. The findings of cold ischemia-warm reperfusion are dramatically different than those of warm ischemia-reperfusion, with predominant distal rather than proximal tubular injury (7).

Gentamicin

Regarding gentamicin nephrotoxicity, myeloid biopsies (characteristic of animal nephrotoxicity) in human renal tissues are unrelated to total dose of gentamicin, duration of therapy, serum drug concentration or overt evidence of gentamicin nephrotoxicity (8). Thus, while it is correct that myeloid bodies in human proximal tubular cells indicate gentamicin exposure, their presence does not necessarily reflect clinical toxicity.

Cis-Platinum

The statement of morphological similarity between animal and human nephrotoxicity of cisplatin is not completely supported by the literature (2).

General Comments

A functional/morphological dyssynchrony is characteristic of clinical ATN and is present in the milder models of distal tubular injury. Sequential studies of HIF-1 alpha indicate presence of this transcription factor in the outer medulla at early time periods in these models in concert with morphological intactness, both in severe and moderate (partial) ARF protocols (9, manuscript in preparation). At 24 hours, there is demonstrable injury, but HIF-1 alpha can no longer be demonstrated. These findings suggest that there are early time points in which hypoxia is present, initiating events which culminate in renal failure but not necessarily in concert with tubular necrosis.

Regarding Dr. Bonventre's personal remarks related to KIM-1, this technique, which may well identify proximal tubular damage, probably does not detect distal nephron injury (10). Finally, I wish to emphasize a critical question presented by Dr. Heyman related to the treatment issue: What is clinically more important? Pharmacologically manipulated increased GFR or the amelioration of medullary oxygen balance to minimize progression of mTAL and S3 injury at the price of diminished GFR?

References

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