is not a model of AAV, both Th17 and Th1 cells have been implicated in human and experimental AAV. However, significant experimental work supports a role for B cells in driving renal injury in AAV. The use of B cell-depleting agents has significantly improved the outcomes of patients with AAV, implicating B cells in the pathogenesis of AAV. The authors found that miR-155 was required for the complete development of humoral immunity, although humoral immunity has a limited role in this model. The therapeutic potential of miR-155 inhibition could extend to renal diseases in which B cells promote renal injury.

In summary, silencing miRNA has exciting clinical potential and this study has extended the potential benefits to include treatment of crescentic GN. Although the authors used antagonists, several other strategies have been trialed experimentally, including the use of decoy technologies with the transgenic introduction of tandem miRNA binding site repeats. Targeting miRNAs could potentially form part of the therapeutic armamentarium available to nephrologists.

DISCLOSURES
None.

REFERENCES


Cloudy Peritoneal Dialysate: In Search of a Clear Cause?

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Peritoneal dialysis–associated peritonitis is usually caused by infection. It is characterized by abdominal pain and cloudy peritoneal effluent caused by an increased peritoneal leukocyte count (>100 million cells/L, more than 50% of which are neutrophils), as well as positive effluent microbiological cultures. Empirical treatment with antibiotics is promptly started with antibiotics that cover both gram-positive and gram-negative bacteria. The role of Treg cells and tryptophan degradation is a critical role in the cross-regulation of Th1 and Th17 immune responses in murine crescentic glomerulonephritis. Kidney Int 82:72–83, 2012

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In approximately 10%–20% of cases, however, no causative microorganism can be identified, even though the introduction of concentration methods has improved the recovery of microorganisms.\(^1\)

It is generally assumed that the culture-negative peritonitis is caused by bacterial infection; therefore, continuation of antibiotic treatment is recommended. The fact that clinical course and response to therapy do not significantly differ between patients with culture-positive and culture-negative peritonitis supports a bacterial infection as the main cause of culture-negative peritonitis. Culture-negative peritonitis has been related to recent use of antibiotics or failure to culture microorganisms because of the small number in the continuously renewed dialysis fluid.\(^2\) Although the introduction of “flush before fill” connection systems has drastically reduced infectious peritonitis because of the decreased risk of contamination via inflow of fresh dialysis fluid, the relative numbers of culture-negative peritonitis versus culture-positive peritonitis have not significantly increased over the past few years.

In this issue of JASN, Lin et al. question the validity of the widely held view that culture-negative peritonitis is caused by microbial infection.\(^3\) They report in much detail a meticulous study on the inflammatory cellular and humoral responses in the peritoneal cavity on the first day of peritonitis, in the context of the culture results. Humoral responses were analyzed by measuring the concentrations of various cytokines and chemokines in cell-free peritoneal effluent. Cytokine release in culture-negative peritonitis was significantly lower than in culture-positive peritonitis. As a consequence, the authors challenge the widely held belief that culture-negative peritonitis is usually caused by bacterial or fungal infection.

If their contention is true, which conditions could be considered alternative causes of “sterile” peritonitis? Various disorders, including juxtaperitoneal inflammatory processes (such as renal allograft rejection or intestinal viral infections) have occasionally been identified as nonbacterial infection-related causes.\(^4,5\) In addition, many outbreaks of culture-negative peritonitis have been reported, which were caused by contamination of fresh dialysis fluid with endotoxin or peptidoglycan.\(^6,7\) These latter episodes of peritonitis, however, did not respond to antibiotics, and the leukocyte population was usually not dominated by neutrophils. In contrast, all the cases in the study of Lin et al. (except one with a low relative frequency of neutrophils) met the other conventional criteria for infectious peritonitis.

On the other hand, holding to the widely held belief that culture-negative peritonitis is caused by bacterial infection, how can failure to culture a causative microorganism be directly related to the observed limited cytokine response in the effluent? Of note, the innate immune system is able to tune in the intensity of the inflammatory response to the severity of infectious threat. How does it sense and assess microbial menace?

In brief, pathogen-associated molecular patterns (PAMPs) of microorganisms are recognized by pattern-recognition receptors (PRRs), which are evolutionary conserved germline-encoded innate immune receptors.\(^8,9\) It should be noted that one strain can display expression of several different PAMPs. Interaction of PAMPs and PRRs induces production of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and the anti-inflammatory cytokine IL-10. Toll-like receptors (TLRs) are PRRs that localize to plasma membranes or endosomal membranes, whereas nucleotide-binding oligomerization domain–like receptors are cytosolic proteins. The gram-negative bacterial cell wall component lipopolysaccharide, one of the PAMPs, is recognized by TLR4 and induces cytokine production in a dose-dependent fashion.\(^10\) In addition, viability of microorganisms is an important factor influencing the strength of inflammatory reactions: Living microorganisms evoke a more vigorous cytokine response than dead ones. This is sensed by various mechanisms: Detection of cytosolic bacterial mRNA that is released following phagocytosis of living bacteria triggers inflammasome activation and subsequent release of bioactive IL-1β. In addition to the detection of PAMPs, PPRs recognize damage-associated molecular patterns, endogenous molecules (such as ATP and IL-1α) that are released in response to tissue damage.\(^11\) Sensing of these indirect effects of virulence can trigger strong inflammatory responses. The nature, quantity, and viability of microorganisms as well as tissue damage are major determinants in scaling the inflammatory response to the microbial threat. Thus, slow intraperitoneal bacterial growth or diminished viability may provide an alternative explanation for the observed low cytokine responses in the presence of infection. Yet, the study of Lin et al. still challenges the widely held belief that all culture-negative peritonitis episodes associated with classic signs and symptoms of peritonitis are infection related.

Their finding that Vγ9/Vδ2 T cells were involved in the inflammatory response to acute peritoneal infection is very interesting. Vγ9/Vδ2 T cells are a subset of γδ T cells that exclusively occur in primates, including humans.\(^12,13\) Besides B cells and αβ T cells (two types of lymphocytes with rearranged antigen-specific receptors), a third rearranged receptor, the γδ TCR, was discovered in jawed vertebrates. γδ T cells integrate features reminiscent of both classic adaptive and innate immune cells.\(^14\) Vγ9/Vδ2 T cells, which make up the major γδ T cell subset in human peripheral blood, recognize, directly or indirectly, (E)-4 hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), a small microbial metabolite that is present in many microorganisms and is released upon ingesting and killing of microorganisms by other white blood cells. Interaction of HMB-PP with Vγ9/Vδ2 T cells amplifies various inflammatory and immune responses, including production and release of proinflammatory cytokines, such as TNF-α and chemokines. A significant expansion of the peritoneal Vγ9/Vδ2 T cell population was found in episodes of peritonitis caused by HMB-PP–positive bacteria, arguing for an important role of these cells in peritoneal dialysis–associated peritonitis.\(^13\) In addition, Lin et al. found that a selective enrichment of Vγ9/Vδ2 T cells among peritoneal T cells could discriminate between gram-positive and gram-negative...
infections. Although gram-negative bacteria are generally HMB-PP positive, most of the common gram-positive causative microorganisms of peritoneal dialysis–related peritonitis are indeed HMB-PP negative, including *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus* species, and *Enterococcus* species. Interestingly, the authors suggested that the natural antibiotic fosmidomycin, which targets the HMB-PP pathway, could also mitigate the inflammatory reactions by inhibiting Y9/V82 T cell–driven responses to HMB-PP–producing bacteria.

The study of Lin et al. deepens our understanding of the complex, local pathogen-host interactions. Such patient-based studies are important not only from a theoretical perspective but also for the prospect of future developments that could improve diagnosis and management of the various forms of peritonitis. The insights obtained by these patient-based studies may play an important role in the development of novel useful tests that may help to predict the causative microorganisms in an early stage of peritonitis (i.e., before the results of bacterial cultures have become available).

**DISCLOSURES**
None.

**REFERENCES**


**Sodium Reduction in CKD: Suggestively Hazardous or Intuitively Advantageous?**

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In the United States and most countries worldwide, mean dietary sodium intake is much higher than daily requirements. Although the potential consequences of high dietary sodium intake, including higher BP, fluid retention, and cardiovascular disease (CVD) risk, are much more common in individuals with CKD; few trials have been done, and to our knowledge, only one is underway in CKD patients based on a search of ClinicalTrials.gov.

In the absence of clinical trials, guidelines for dietary sodium intake in CKD are based on expert opinion, observational studies, and extrapolation from general population studies. For example, recent Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend “lowering salt intake to < 90 mmol (<2 g) per day of sodium, unless contraindicated.” This recommendation corresponds to 5 g of sodium chloride. The recommendation is graded “1C,” indicating that the KDIGO panel considered it important enough to serve as a candidate for making public policy decisions and as a performance measure, although

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