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*Original article*

# Operating characteristics of pediatric continuous arteriovenous hemofiltration in an animal model

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**Abstract.** Continuous arteriovenous hemofiltration (CAVH) is an increasingly popular technique in the care of critically ill children. The operating characteristics of the available circuits are largely unknown. Prior to introducing CAVH into our pediatric intensive care unit, we investigated the performance of three CAVH circuits: CAVH with postfilter dilution, CAVH with prefilter dilution ($CAVH_{pre}$) and CAVH with dialysis counterflow. Using a neonatal lamb model, we measured filter blood flow ($Q_B$), ultrafiltrate rate ($Q_U$), arterial, venous and ultrafiltrate compartment pressures, oncotic pressure, plus urea levels in blood and ultrafiltrate fluid for the three CAVH circuit designs. Transmembrane pressure and urea clearance were calculated for various values of $Q_B$ after varying a clamp on the arterial side of the circuit. The major finding, applicable to all circuits, was the wide variability of $Q_B$. Constant attention was required in order to obtain a consistent $Q_B$. Fluid clearance was effective with all three circuits. Urea clearance averaged 5–10 ml/min and was principally dependent on $Q_U$ and independent of $Q_B$. The addition of dialysis counterflow did not increase urea clearance. The most convenient circuit we tested was $CAVH_{pre}$, but the problem of unstable $Q_B$ is common to all unpumped arteriovenous filtrate circuits. It is a major limiting factor in the practical application of this technology to critically ill children.

**Key words:** Hemofiltration – Continuous arteriovenous hemofiltration – Predilution – Transmembrane pressure – Hemodiafiltration – Pediatric hemofiltration

## Introduction

Continuous arteriovenous hemofiltration (CAVH) has gained wide acceptance in the fields of pediatric critical care [1, 2] and pediatric nephrology [3]. Adult CAVH filters and circuits have been studied extensively [4], and much of this knowledge has been extrapolated for use in children. In an attempt to increase urea clearance, alternative circuits have been developed, including CAVH with predilution (prefilter dilution of blood, $CAVH_{pre}$) [5] and CAVH with counterflow dialysis (CAVHD) [6, 7]. These, subsequently, have also been applied to children [1, 8].

However, the small filter sizes and low filter blood flows ($Q_B$) associated with pediatric circuits might combine to produce functional characteristics that differ significantly from adult circuits. Although several pediatric case descriptions have been published [1, 8–10], to our knowledge the operating characteristics of various CAVH circuit designs have not been systematically studied in a pediatric-sized animal model.

Prior to introducing this technology into our pediatric intensive care unit, we used a lamb model to investigate the performance of three separate circuit designs: CAVH with postfilter fluid replacement ($CAVH_{post}$), $CAVH_{pre}$ and CAVHD.

## Methods

The study was approved by the University Animal Care Committee.

*Animal preparation.* Five 4-week-old lambs (weight 12.5 ± 1.2 kg) were anesthetized with 10–15 mg/kg thiopental sodium i.v. After tracheotomy, the animals were connected to a Harvard ventilator. Anesthesia was maintained with halothane and nitrous oxide, ventilation was adjusted to maintain $PO_2$ between 100 and 150 mmHg and $PCO_2$ between 35 and 45 mmHg. Arterial and venous access was achieved with standard pediatric vascular catheters (Deseret, Sandy, Utah, USA) via femoral cutdown. Routine cannula size was 16 gauge (length 58 mm) unless otherwise stated. Each animal was given 200 units/kg heparin i.v. as a bolus, followed by an infusion of 20 units/kg per hour.

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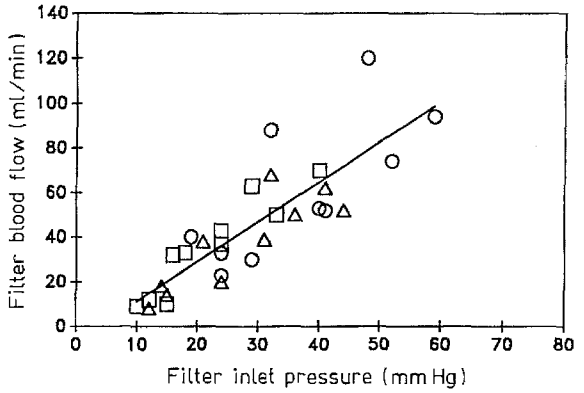


**Fig. 1.** Combined plot of blood flow against filter inlet pressure for three sizes of arterial catheter [14 gauge × 58 mm (○), 16 gauge × 58 mm (□), 18 gauge × 32 mm (△)]. Venous catheter was 16 gauge for all readings

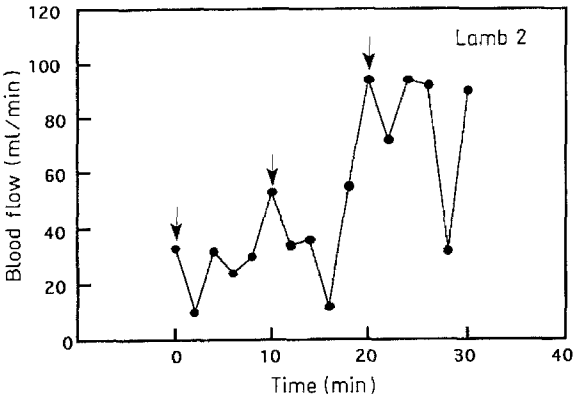


**Fig. 2.** Ultrasonic filter blood flow at 2-min intervals. *Arrows* denote gate clamp adjustments

*Circuit preparation.* Arteriovenous hemofiltration was performed using a pediatric hemofilter (membrane area 800 $cm^2$) (Minifilter plus, Amicon, Beverly, Mass., USA) which had been flushed with 1 l normal saline containing 5,000 units heparin and primed with normal saline containing heparin 1 unit/ml. Pressure was measured with strain-gauge transducers (Gould, Oxnard, Calif., USA) at filter inflow ($P_A$), filter outflow ($P_V$) and in the ultrafiltrate compartment ($P_U$), then displayed on a multichannel recorder (HP 7758 B, Hewlett Packard, Waltham, Mass., USA). $Q_B$ through the inflow tubing was measured with an ultrasonic Doppler flow probe (T201, Transsonic Systems, Ithaca, N. Y., USA) at the junction of the arterial line and circuit tubing. The probe had been calibrated for this tubing by pumping lamb's blood at 37° C into a graduated cylinder. Dialysis flow rate ($Q_D$), ultrafiltrate rate ($Q_U$) and replacement fluid rate ($Q_R$) were set by high accuracy volumetric pumps (IVAC Corp, San Diego, Calif., USA).

During $CAVH_{post}$, ultrafiltrate was not pumped but drained passively into a container. On these occasions, $Q_U$ was measured by timed collection into a graduated cylinder.

For each circuit design, blood flow was varied with a clamp on the arterial limb. After a 10-min stabilization period, blood samples were taken from the filter inflow and outflow ports. These were analyzed for hematocrit, urea and oncotic pressure (by depression of freezing point). Simultaneous ultrafiltrate samples were also taken and analyzed for urea concentration. Urea clearance was calculated as:

$$\text{Clearance}_{\text{Urea}} = \frac{\text{Urea}_{\text{Filtrate}}}{\text{Urea}_{\text{Plasma}}} \times Q_{\text{Filtrate}}$$

Transmembrane pressure ($P_{TM}$) was calculated for filter inlet and outlet using the following equations:

$P_{TM}(\text{inlet}) = (P_A - P_U) - \pi_A$

$P_{TM}(\text{outlet}) = (P_V - P_U) - \pi_V$

where $\pi_A$ and $\pi_V$ are inflow and outflow oncotic pressures, respectively.

*Study design.* $CAVH_{post}$: to assess the relationship between $Q_B$ and urea clearance, blood flow was varied while ultrafiltrate was collected passively into a container positioned 100 cm below the filter. Replacement fluid (Ringer's lactate) was given into the venous limb at a rate that replaced ultrafiltrate production ($Q_U = Q_R$). Urea clearance and $Q_U$ were measured over a wide range of $Q_B$. The effect of arterial catheter size on the circuit characteristics was also studied by altering $P_A$ and measuring $Q_B$ with three sizes of arterial catheter (14-gauge × 58 mm length, 16-gauge × 58 mm length, 18-gauge × 32 mm length).

$CAVH_{pre}$: for this circuit, ultrafiltrate flow was controlled by volumetric pump at three predetermined levels (200, 400 and 600 ml/h). Replacement fluid was added to the arterial limb so that $Q_R$ was equal to $Q_U$. For each $Q_U$, urea clearance was measured at different blood flow rates. Arterial and venous catheters were both 16 gauge.

CAVHD: ultrafiltrate flow was controlled at a constant rate of 1,000 ml/h using a volumetric pump. Replacement fluid was added to the venous limb at three flow rates (200, 400, 600 ml/h). Dialysate (Dianeal 1.5%, Baxter Corp. Mississauga, Ontario, Canada) was "pumped" through the filtrate compartment at 800, 600 and 400 ml/h (so that $Q_U = Q_R + Q_D$ = 1,000 ml/h). For each of the three flow settings, urea clearance was measured at different blood flow rates. Arterial and venous catheters were both 16 gauge.

The order of sequence of circuit design was chosen randomly for each animal.

*Statistics.* All values are expressed as mean plus or minus one standard deviation. Comparison between groups was made by ANOVA. Graphical regression lines were calculated by the method of least squares. Comparison between actual slopes of regression lines and slope of zero was made by *t*-test with a 5% level of significance.

## Results

All animals survived the duration of the experiment and in no case was early termination of filtration required. No filter clotting or rupture was noted.

### *$CAVH_{post}$*

The general relationship between pressure in the arterial tubing and blood flow is shown in Fig. 1. Although the highest values for $Q_B$ were obtained with the largest catheter (14 gauge), there was no clear difference between the three catheters at lower flow rates. A finding common to all three circuits was marked sensitivity of $Q_B$ to factors such as catheter position, tension on the circuit or slight kinking of the tubing. A representative tracing of $Q_B$ is shown in Fig. 2. Stable flow rates could often only be achieved by constant attention. Decreases in $Q_B$ were paralleled by decreases in circuit blood pressures.

Urea levels measured in blood and ultrafiltrate fluid were usually very similar, consequently urea clearance was almost identical to ultrafiltrate rate. As filter blood flow increased, passive $Q_U$, and consequently urea clearance, also increased (Fig. 3).

Mean $P_{TM}$ varied from 59 to 110 mmHg (mean 87.4 ± 11.3 mmHg) over the range of blood flow rates

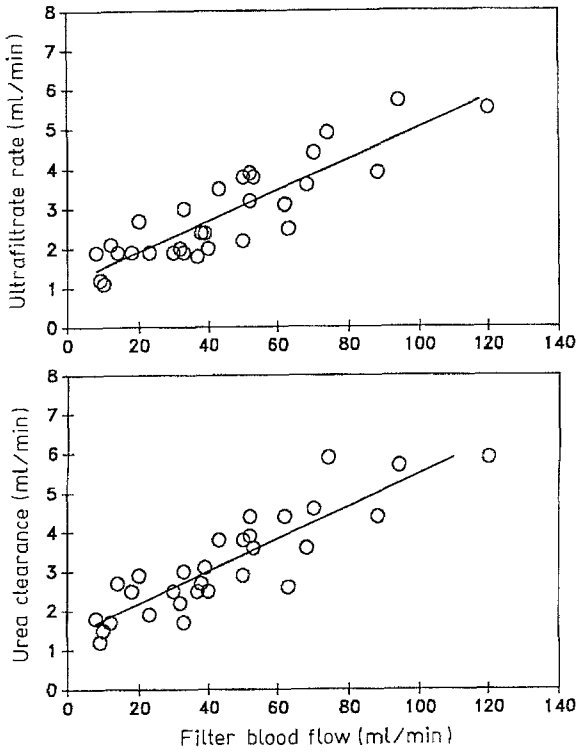


**Fig. 3.** Passive ultrafiltrate rate (*top*) and urea clearance (*bottom*) plotted against filter blood flow for the continuous arteriovenous hemofiltration with postfilter dilution ($CAVH_{post}$) circuit design

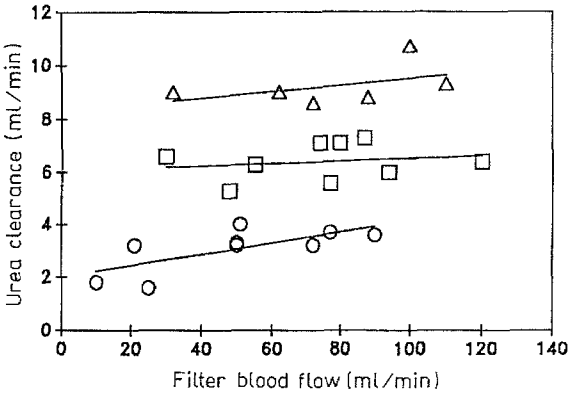


**Fig. 4.** Urea clearance plotted against filter blood flow using the CAVH predilution ($CAVH_{pre}$) circuit at three levels of ultrafiltrate flow [replacement fluid rate ($Q_R$) = ultrafiltrate rate = 200 (○), 400 (□), 600 (△) ml/h]. No regression line slope was significantly different from zero (slope for $Q_R200$, $P = 0.18$)

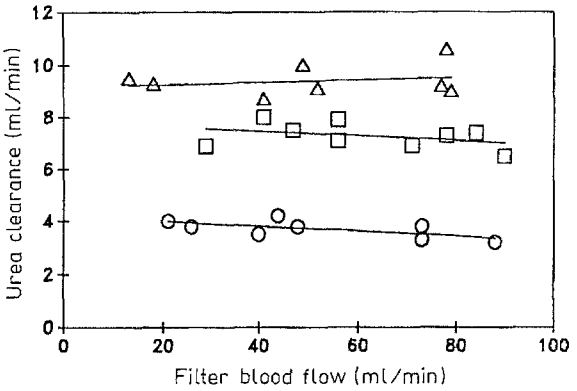


**Fig. 5.** Urea clearance plotted against filter blood flow for three combinations of $Q_R$ (200, 400, 600 ml/h) and dialysis flow ($Q_D$ = 800, 600, 400 ml/h). △, $Q_R$ 600 / $Q_D$ 400; □, $Q_R$ 400 / $Q_D$ 600; ○, $Q_R$ 200 / $Q_D$ 800

studied. It decreased by 5%–7% from filter inlet to outlet. $P_{TM}$ at the filter outlet remained positive as it did during $CAVH_{pre}$ and CAVHD, i.e., neither pressure equilibrium nor reverse filtration occurred.

### *$CAVH_{pre}$*

Over the range of flows studied, urea clearance was independent of $Q_B$ (Fig. 4). Urea levels in blood and ultrafiltrate were again very similar so that urea clearance was numerically identical to $Q_U$. For the three values of $Q_R$ an $Q_U$ that were used (10, 6.7, 3.3 ml/min), the corresponding mean values for urea clearance were 9.4±0.8 ml/min, 6.6±0.7 ml/min and 3.2±0.9 ml/min (Fig. 5).

Mean $P_{TM}$ varied from 37 to 295 mmHg (mean 215±160 mmHg) over the range of blood flows studied. It decreased by 5%–10% over the length of the filter.

### *CAVHD*

Over the range of flows studied, urea clearance was independent of $Q_B$ (Fig. 5). Ultrafiltrate urea levels were much lower than simultaneous blood levels because of the diluting effect of dialysis. The addition of dialysis counterflow did not increase the urea clearance which, in keeping with $CAVH_{pre}$, was only dependent on the ultrafiltrate rate. For each of the three values of $Q_R$ studied (10, 6.7, 3.3 ml/min), the corresponding mean urea clearances were 9.4±0.5 ml/min, 7.3±0.5 ml/min and 3.7±0.3 ml/min. These did not differ significantly from the clearances achieved during $CAVH_{pre}$ using the same values of $Q_R$ (ANOVA, $P > 0.05$). $P_{TM}$ varied from 69 to 601 mmHg (mean 271±190 mmHg). It decreased by 3%–5% across the filter.

## Discussion

This study was undertaken to determine the functional characteristics of arteriovenous filtration circuits in a pediatric-sized animal model. Our general aim was to assess the suitability of this technology for a pediatric intensive care unit.

Values of $Q_U$ and clearances in this study were similar to those described in previous clinical reports [1, 2]. Our main finding however, applicable to all circuit designs, was the wide variability of $Q_B$ following small disturbances in the circuit. Some clinical studies reported on blood flow rates achieved [1] but did not use continuous flow monitoring. In this study, changes in the angle of the intravascular

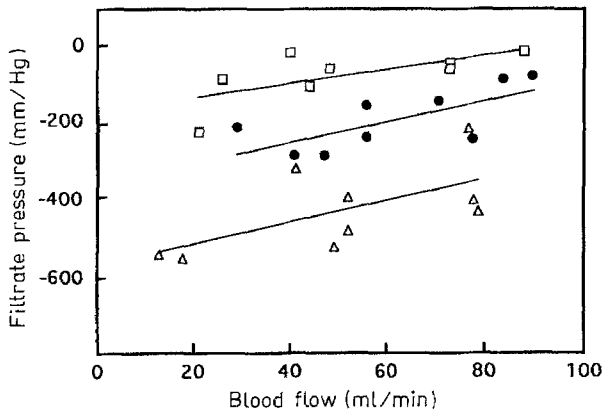


**Fig. 6.** Ultrafiltrate compartment pressures plotted against blood flow at three different ultrafiltrate pump rates (□, 200 ml/h; ●, 400 ml/h; △, 600 ml/h) during $CAVH_{pre}$. The lowest recommended pressure is −500 mmHg

cannulae as they entered the skin or apparently minor kinking of some portion of the tubing was followed by a rapid decrease in blood flow and filtration pressure. Constant attention was required in order to obtain consistent values of $Q_B$ (see Fig. 2). In clinical practice, the situation would probably be worse because the driving pressure across the filter is often low due to the cardiovascular instability of the pediatric population that requires dialysis.

Although continuous flow monitoring by a Doppler flow probe is not a common practical option, an approximation of filter flow can be obtained by monitoring arterial and venous pressures (Fig. 1). In the absence of flow or pressure monitoring, early changes in $Q_B$ are missed and the first sign of decreased filter flow is often significant filter coagulation with decreased ultrafiltrate formation. Controlling $Q_U$ by pump would initially remove the dependence of urea clearance on $Q_B$. This however only applies as long as low $Q_B$ has not yet led to filter clotting and to unacceptably high filtrate fraction and filtrate compartment pressure. Figure 6 illustrates the relationship between $Q_B$ and ultrafiltrate pressures and shows that high ultrafiltrate demand and low $Q_B$ can combine to cause excessively negative ultrafiltrate compartment pressures.

Some improvement in the flow variability was achieved by interposing flexible tubing between the cannulae and the more rigid circuit tubing. However, the only permanent solution to the problem is to control the blood flow using a roller pump [11]. In our opinion, the flow instability of unpumped arteriovenous filtration circuits is a major limiting factor in the practical application of this technology to critically ill children.

The main value of CAVH is in controlling fluid overload. The technique's ability to clear soluble substances from the blood is limited by the maximum achievable $Q_U$. A urea clearance of 5 ml/min is possible with the $CAVH_{post}$ circuit while values of 10–15 ml/min can be obtained with the $CAVH_{pre}$ circuit at high negative $P_{TM}$. While this range may maintain urea levels in small children with normal metabolic rates, it is probably insufficient for larger hypercatabolic patients.

We found that when $Q_U$ was pump controlled urea clearance was independent of blood flow, down to values as low as 15 ml/min, and was principally dependent on $Q_U$. The major determinant of solute clearance is the $Q_U$ which, in turn, is principally dependent on the characteristics of the ultrafiltrate volumetric pump and the maximum negative $P_{TM}$ that the filter can tolerate. Using the IVAC pump, the maximum flow rate is 1,000 ml/h, which limits the achievable urea clearance to 16.7 ml/min. We found that ultrafiltrate flow rates greater than 600 ml/h (10 ml/min) generated negative pressures in the ultrafiltrate compartment below −500 mmHg (Fig. 6). This was close to the maximum permitted for this particular filter design [12]. For a given value of $Q_U$, we also found that a reduction in $Q_B$ was associated with an increase in $P_{TM}$ (Fig. 6).

The calculated urea clearance during $CAVH_{pre}$ describes filter clearance only, as blood for urea was taken at the filter inlet. In order to determine the net urea clearance as seen by the animal during $CAVH_{pre}$, blood has to be sampled proximal to the dilution port.

It is interesting to note that the addition of dialysis countercurrent to the basic CAVH circuit did not increase the expected urea clearance. Our study animals were not uremic, and a higher urea gradient across the filter could arguably have led to a measurable increase in clearance by enhancing crossfilter diffusion. Hiyama et al. [13] used hemofiltration in uremic dogs and noted that addition of dialysis did not improve clearance. Zobel et al. [1] observed increases in urea clearance when adding dialysis, but used filters of 3–10 times the surface area than the pediatric filter tested here. In this study, even at low values of $Q_D$ urea did not equilibrate across the filter. Thus, higher dialysis flows were unlikely to have improved diffusion. These findings are probably due to the limitation of diffusive transport imposed by the small filter surface area. There was no difference between the urea clearances achieved at equal $Q_U$ between $CAVH_{pre}$ and CAVHD. The dialysis circuit added extra complexity without any measurable benefit.

The most convenient circuit that we tested was $CAVH_{pre}$. The use of accurate volumetric pumps to control $Q_R$ and $Q_U$ means that net fluid loss can be closely monitored. If high ultrafiltrate pressures are accepted, then a urea clearance of approximately 10 ml/min can be achieved with a small pediatric filter. However, the problems of unstable blood flow and low driving pressure still exist. Close monitoring of pre- and postfilter pressures can provide some early warning of decreased blood flow but the best solution might be to develop continuous venovenous hemofiltration devices for children.

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## References

1. Zobel G, Ring E, Zobel V (1989) Continuous arteriovenous replacement systems for critically ill children. Pediatr Nephrol 3: 140–143
2. Lieberman KV (1987) Continuous arteriovenous hemofiltration in children. Pediatr Nephrol 1: 330–338
3. Pascual JF, Lopez JD, Molina M (1987) Hemofiltration in children with renal failure. Pediatr Clin North Am 34: 803–818

4. Bosch JP (1986) Continuous arteriovenous hemofiltration: operational characteristics and clinical use. Am Kidney Foundation Nephrol Lett 3: 15–26
5. Kaplan AA (1986) Clinical trials with predilution and vacuum suction. Enhancing the efficiency of CAVH treatment. Trans Am Soc Artif Intern Organs 22: 49–51
6. Peachey TD, Ware RJ, Eason JR, Parsons V (1988) Pump control of continuous arteriovenous haemodialysis. Lancet II: 878
7. Stevens PE, Riley B, Davies SP, Gower PE, Brown EA, Kox W (1988) Continuous arteriovenous haemodialysis in critically ill patients. Lancet II: 150–152
8. Assadi FK (1988) Treatment of acute renal failure in an infant by continuous arteriovenous hemodialysis. Pediatr Nephrol 2: 320–322
9. Lieberman KV, Nardi L, Bosch JP (1985) Treatment of acute renal failure in an infant using continuous arteriovenous hemofiltration. J Pediatr 106: 646–649
10. Ronco C, Brendolan A, Bragantini L, Chiaramonte S, Feriani M, Fabris A, Dell'Aquila R, La Greca G (1986) Treatment of acute renal failure in newborns by continuous arterio-venous hemofiltration. Kidney Int 29: 908–915
11. Golper TA, Ronco C, Kaplan AA (1988) Continuous arteriovenous hemofiltration: improvements, modifications, and future directions. Semin Dial 1: 50–54
12. Anonymous (1990) Operating instructions for the Amicon™ and Minifilter plus™. Package insert, Amicon Division, Grace
13. Hiyama DT, Weiss RG, Ryckman FC (1989) Factors affecting urea clearance during continuous hemodiafiltration in the canine model. J Pediatr Surg 24: 756–759

# Literature abstracts

Acta Paediatr (1992) 81: 402–406

## Normokalaemic pseudohypoaldosteronism is present in children with acute pyelonephritis

**J. Rodriguez-Soriano, A. Vallo, M.J. Quintela, R. Oliveros, and M. Ubetagoyena**

The present study demonstrates that renal tubular unresponsiveness to aldosterone, without associated hyperkalaemia, is present in children with acute pyelonephritis. We studied 32 children with a diagnosis of acute pyelonephritis established by high fever, flank pain/tenderness, increased blood levels of C-reactive protein and significant *Escherichia coli* growth in the urine culture. Renal tubular function tests and determinations of plasma renin activity and aldosterone concentration were performed at diagnosis (study 1), after three days of iv gentamycin (study 2) and after 21 days of antibiotic therapy (study 3). Findings were compared to those present in 32 normal children of similar age. Despite normal plasma potassium concentration, fractional potassium excretion and transtubular potassium concentration gradient were significantly decreased in studies 1 and 2, becoming normal in study 3. Decreased renal potassium excretion coexisted with increased values for plasma renin activity and aldosterone concentration. In study 3 these hormones remained elevated only in patients with scarred kidneys. The functional alteration present in acute pyelonephritis may be directly caused by the interstitial inflammation or be mediated by some *E. coli* endotoxin.

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## *Escherichia coli* virulence factors and $^{99m}$ TC-dimercaptosuccinic acid renal scan in children with febrile urinary tract infection

**Barbara A. Jantausch, Bernhard L. Wiedermann, Sheila I. Hull, Bogdan Nowicki, Pamela R. Getson, H. Gild Rushton, Massoud Majd, Naomi L. Luban, and William J. Rodriguez**

Correlation of virulence factors of *Escherichia coli* with renal inflammation documented by $^{99m}$Tc-dimercaptosuccinic acid renal scan was undertaken in 59 children with febrile urinary tract infections to identify more accurately the role of bacterial virulence factors in the development of pyelonephritis. P fimbriae were present in 63% of isolates from the positive scan group and 83% of those from the negative scan group ($P = 0.126$). Multivariate regression analysis showed no significant role for established *E. coli* virulence factors in the development of pyelonephritis. The *pap* genome was independently associated with negative scan ($P < 0.007$) and with the absence of reflux ($P = 0.031$). *E. coli* pyelonephritogenic clone 16:K1:H6 was isolated from negative scan patients and did not produce hemolysin. We conclude that P fimbriae are important in the development of febrile urinary tract infection regardless of the level of infection. Virulent *E. coli* clones described in prior Scandinavian urinary tract infection studies were not common causes of pyelonephritis in our patient population.