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Knowledge, attitudes, and practices related to augmented renal clearance among pediatricians in China

A cross-sectional study

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Abstract

Our purpose was to assess pediatricians' knowledge of augmented renal clearance (ARC).

We conducted cross-sectional analyses of 500 pediatricians from 16 tertiary hospitals in Anhui Province, China. Pediatricians provided demographic information and were asked questions about their knowledge of ARC, including risk factors, evaluation tools, and the impact on patient prognosis, with a focus on the attitude and practice of pediatricians related to adjusting vancomycin regimens when ARC occurs.

A total of 491 valid questionnaires were finally included, only 276 pediatricians stated that they "know about ARC." Compared with the "do not know about ARC" group, the "know about ARC" group was younger (43.7 ± 8.0 vs 48.0 ± 7.9, $P < .001$), and their main source of ARC knowledge was from social networking platforms. A total of 193 (70%) chose at least 4 of the following factors as risk factors for children with ARC: severe trauma, sepsis, burns, major surgery, lower disease severity, and hematological malignancies. A total of 110 (40%) and 105 (38%) pediatricians chose the Schwartz formula and cystatin C, respectively, as the indicators to evaluate the renal function of ARC children. Concerning the estimated glomerular filtration rate threshold to identify ARC children, 201 (73%) pediatricians chose 130 mL/min/1.73 m^2, while 55 (20%) chose "age-dependent ARC thresholds." Overall, 220 (80%) respondents indicated that ARC would impact the treatment effect of vancomycin, but 149/220 (68%) were willing to adjust the vancomycin regimen; only 22/149 (8%) considered that the dose should be increased, but no one knew how to increase. Regarding the prognosis of ARC children, all respondents chose "unclear."

ARC is relatively common in critically ill children, but pediatricians do not know much about it, as most of the current knowledge is based on adult studies. Furthermore, ARC is often confused with acute kidney injury, which would lead to very serious treatment errors. Therefore, more pediatric studies about ARC are needed, and ARC should be written into official pediatric guidelines as soon as possible to provide reference for pediatricians.

Abbreviations: AKI = acute kidney injury, ARC = augmented renal clearance, CrCl = creatinine clearance, DK-ARC = "do not know about ARC" group, eGFR = estimated glomerular filtration rate, K-ARC = "do know about ARC" group.

Keywords: clearance, critical care, knowledge, pediatricians, surveys and questionnaires, vancomycin

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Due to their immature growth and development, their complex conditions, and the combined effect of multiple organ support methods in the intensive care unit, the safe and effective use of drugs in critically ill children has become a serious challenge for pediatricians.[1] Past studies have only focused on children with acute kidney injury (AKI), which requires a decrease in the drug dose according to renal function to reduce the drug-related nephrotoxicity, but have rarely paid attention to the hyperfiltration of the glomerulus.

In the past 10 years, augmented renal clearance (ARC) was considered to be a common phenomenon in critically ill patients, and its incidence was reported to be approximately 20% to 65%.[2] ARC is characterized by an increased estimated glomerular filtration rate (eGFR) and enhanced clearance of drugs by the kidneys.[3] However, creatinine clearance (CrCl) is commonly used as a surrogate indicator of eGFR in the clinic. In adult patients, studies have consistently defined ARC as CrCl $\geq$130 mL/min/1.73 m^2. It was proposed that ARC may lead to insufficient drug dose even or treatment failure in critically ill patients.[2,4]

It is worth noting that ARC not only exists in adults but may also be ubiquitous in children.[5,6] However, pediatricians pay little attention to ARC, and as a result, substandard drug concentrations are often not detected.[7] Therefore, this study investigated pediatrician's knowledge of ARC, including risk factors, evaluation tools, and the impact on children's prognosis, with a focus on the attitude and practice of pediatricians related to adjusting vancomycin regimens when ARC occurs.

2. Methods

2.1. Study design

A cross-sectional study was performed in pediatricians from 16 tertiary hospitals in Anhui Province, China, between July 17 and August 31, 2020. The study was approved by the Medical Research and Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China, which complies with the Declaration of Helsinki.

2.2. Study and population

We used a convenience sample; all pediatricians were eligible, and there were no restrictions on education background or professional title. Pediatricians who signed the informed consent were included. Pediatricians who did not accept participation or who did not sign the informed consent form were excluded from the study.

2.3. Measurement tool

The questionnaire was developed by researchers and then modified by 2 pediatric chief physicians and pediatric clinical pharmacists, with appropriate changes based on their expert opinions. A pilot test was conducted in pediatricians (n = 30) to test the intelligibility and practicality of the questionnaire. After conducting the preliminary research, the final version of the questionnaire was released to the research participants.

The online questionnaire was produced through the Wenjuanxing digital platform (www.wjx.cn). The questionnaire consisted of 3 parts with 15 questions (Table 1): the first part

Table 1

Questionnaire.

Part 1
1) Sex
Male
Female
2) Year
. . .
3) Education
Bachelor's degree
Master's degree
Doctorate degree or above
4) Professional title
Resident
Attending physician
Associate chief physician
Chief physician
Part 2
5) Do you know about ARC?
Yes
No (If this answer was selected, participants were directed to the end of the questionnaire.)
6) What is the source of your ARC knowledge?
Research literature
Academic conferences
Social networking platforms: WeChat, QQ, and forums
7) What are the risk factors for ARC in children?
Severe trauma
Sepsis
Burns
Major surgery
Lower disease severity
Hematological malignancies
Neutrophils with fever
Unclear
8) How do you accurately assess the renal function status of children with ARC?
Clearance of iohexol
CysC
Schwartz formula
Urine collection
Unclear
9) What is the eGFR threshold to determine ARC in critically ill children?
$\geq$110 mL/min/1.73 m^2
$\geq$130 mL/min/1.73 m^2
$\geq$160 mL/min/1.73 m^2
Age-dependent ARC thresholds
Unclear
Part 3
10) Have you encountered children with ARC?
Yes
No
11) Does ARC status affect the therapeutic effect of vancomycin?
Yes
No (If this answer was selected, participants were directed to Q15.)
12) Are you willing to adjust the vancomycin treatment regimen when ARC occurs?
Yes
No (If this answer was selected, participants were directed to Q15.)
13) Do you know how to adjust the vancomycin treatment regimen?
Increase the dose (If this answer was selected, participants were directed to Q14, otherwise they were directed to Q15.)
Reduce the dose
Change the frequency of administration or extend the infusion time
Unclear
14) Do you know how to increase the dose?
Yes
No
15) How does the status of ARC affect the prognosis of critically ill children?
Antimicrobial resistance even treatment failure
Improved prognosis
Unclear

ARC = augmented renal clearance, CysC = cystatin C, eGFR = estimated glomerular filtration rate.

collected demographic data related to the respondents sex, age, education, and professional title. The second part assessed the pediatrician's understanding of ARC. The third part assesses the respondent's practices regarding ARC, focusing on the attitude of pediatricians to adjust vancomycin regimens when ARC occurs.

2.4. Data collection

We collected data by sharing the online questionnaire on several social networking platforms (e.g., WeChat, QQ). On the first page of the questionnaire, the research purpose and research procedure were provided.

2.5. Statistical analysis

SPSS 19.0 (SPSS Inc., Chicago, IL) was used for data processing and analysis. Descriptive statistical methods were used to summarize the general information. The data are expressed as the mean ± standard deviation or frequency and percentage. Continuous variables were compared with Student *t* test. Chi-square tests were used to compare categorical variables. $P < .05$ was considered statistically significant.

3. Results

3.1. Study population

A total of 500 pediatricians participated in the study. A total of 491 valid questionnaires were finally included for analysis, for an effective response rate of 98%. The mean age of the participants was 45.6 ± 8.2 years, ranging from 25 to 60 years. A total of 294 (60%) participants were men.

3.2. Pediatricians' knowledge about ARC

A total of 215 pediatricians stated that they did not know about ARC (DK-ARC group), so they ended the questionnaire immediately. The remaining 276 pediatricians indicated that they "do know about ARC" (K-ARC group).

A comparison of sex, age, education, and professional title between the K-ARC group and the DK-ARC group was carried out. In the K-ARC group, the mean age was younger than that in the DK-ARC group (43.7 ± 8.0 vs 48.0 ± 7.9, $P < .001$), and the constituent ratios of pediatricians in each age group showed a downward trend, while in the DK-ARC group, the constituent ratios of pediatricians in each age group showed an upward trend, and the difference was significant ($\chi^2 = 37.28$, $P < .001$). However, there was no significant difference in sex, education, or professional title between the 2 groups (Table 2).

In the K-ARC group, 165/276 (60%) chose "social networking platforms" as the source of their ARC knowledge, 67/276 (24%) chose "the literature," and 44/276 (16%) chose "academic conferences." Analyzing the source of ARC knowledge, pediatricians under the age of 35 all obtained their ARC knowledge from "social networking platforms." However, as age increased, the constituent ratios of pediatricians who chose "social networking platforms" gradually decreased, the constituent ratios of pediatricians who chose "the literature" or "academic conferences" gradually increased, and the difference was significant ($\chi^2 = 135.11$, $P < .001$) (Fig. 1).

Regarding risk factors for children with ARC, 193 (70%) chose at least 4 of the first 6 risk factors. A total of 110 (40%) and 105 (38%) chose the Schwartz formula and cystatin C, respectively, as the indicator to evaluate the renal function status of children with ARC. For the threshold of eGFR to identify children with ARC, 201 (73%) chose 130 mL/min/1.73 m^2, while 55 (20%) chose "age-dependent ARC thresholds."

3.3. Pediatricians' ARC practices

Half of the pediatricians stated that they had met children with ARC. A total of 220/276 (80%) indicated that ARC would impact the treatment effect of vancomycin, but only 149/220 (68%) were willing to adjust the vancomycin treatment plan. It is worth noting that 124/149 (83%) thought that the dose of vancomycin should be reduced, while only 22/149 (15%) thought that the dose should be increased. As for how to

Table 2

Comparison of gender, age, education, and professional title between K-ARC group and DK-ARC group.

Characteristics	K-ARC n = 276, n (%)	DK-ARC n = 217, n (%)	χ^2	P
Sex			0.258	.611
Male	168 (57)	126 (43)		
Female	108 (55)	89 (45.2)		
Age group, yr			37.28	<.001
<35	18 (72)	7 (28)		
35–44	142 (71)	59 (29)		
45–54	78 (46)	91 (54)		
55–60	38 (40)	58 (60)		
Education			1.739	.419
Bachelor's degree	167 (59)	118 (41)		
Master's degree	97 (52)	88 (48)		
Doctorate degree or above	12 (57)	9 (43)		
Professional title			1.537	.674
Resident	47 (52)	43 (48)		
Attending physician	106 (60)	72 (40)		
Associate chief physician	67 (56)	53 (44)		
Chief physician	56 (54)	47 (46)		

DK-ARC = "do not know about ARC" group, K-ARC = "do know about ARC" group.

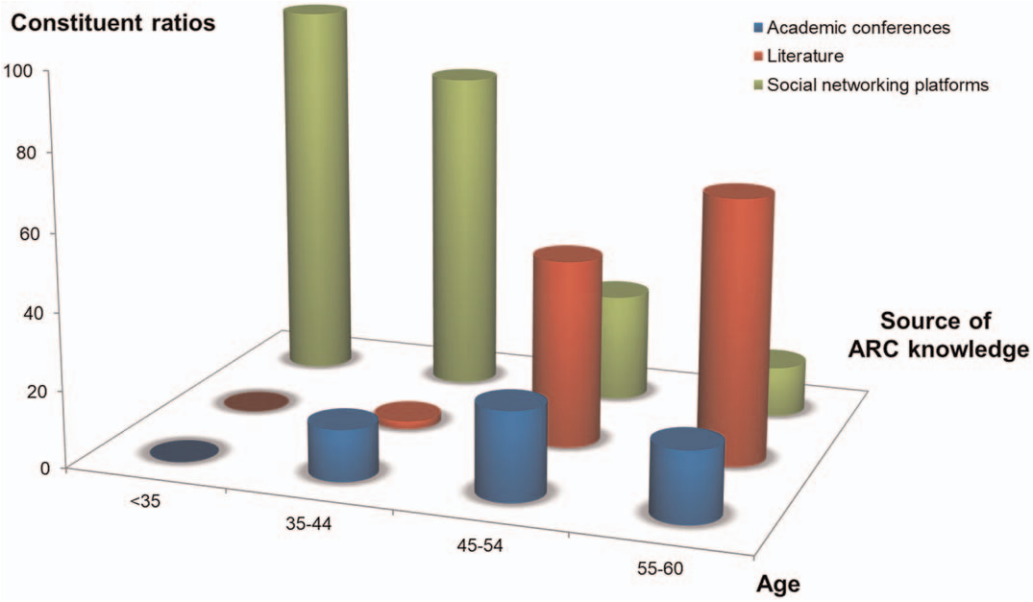

Figure 1. Constituent ratios of pediatricians acquiring ARC knowledge from different sources. In the <35 years group, 100% chose "social networking platforms." In the 35 to 44 year group, 84.5% of respondents chose "social networking platforms," 2.1% chose "the literature," and 13.4% chose "academic conferences." In the 45 to 54 year group, 28.2% of respondents chose "social networking platforms," 48.7% chose "the literature," and 23.1% chose "academic conferences." In the 55 to 60 year group, 13.2% of respondents chose "social networking platforms," 68.4% chose "the literature," and 18.4% chose "academic conferences." ARC = augmented renal clearance.

increase the dose of vancomycin, the respondents all chose "I don't know." Regarding the influence of ARC on the prognosis of the affected children, most pediatricians (222/276, 82%) chose "unclear."

4. Discussion

Our team reported the research progress regarding ARC in critically ill children.[8] To the best of our knowledge, this is the first survey of pediatricians' knowledge of ARC. Among the valid questionnaires, only 276 (56%) pediatricians stated that they have some understanding of ARC.

Unexpectedly, compared with the DK-ARC group, we found that the K-ARC group was younger, the source of ARC knowledge was mainly from social networking platforms, and there was no difference in sex, educational background, or professional title between the 2 groups. With the rapid development of social software such as WeChat, some of its functions, such as the "official account," have become new tools of knowledge dissemination; they can provide the latest medical knowledge quickly and efficiently and have become a new and indispensable resource for self-learning among modern pediatricians. Young pediatricians were better at using these advanced media for self-improvement, so new knowledge was easier to obtain. Therefore, obtaining knowledge through multiple channels was very important for the self-improvement of pediatricians, even more important than their original educational background.

Regarding the risk factors for children with ARC, 193 (70%) pediatricians chose "severe trauma," "sepsis," "burns," "major surgery," "lower disease severity," and "hematological malignancies." All of the above factors have been indicated to lead to the occurrence of ARC in adult patients.[9–14] However, for pediatric patients, Hirai et al[15] reported that neutrophils with fever were the only independent risk factor for the occurrence of ARC (OR = 5.86, 95% CI: 1.98–21.66; $P = .003$). Obviously, pediatricians did not know this information.

A similar situation appeared in the question "What is the eGFR threshold to identify ARC in critically ill children." A total of 201 (73%) pediatricians chose "130 mL/min/1.73 m^2" as the eGFR threshold for identifying children with ARC. However, as we know, "130 mL/min/1.73 m^2" is the eGFR threshold for identifying adults with ARC. Hirai et al[15] and Avedissian et al[16] have both proposed that eGFR ≥160 mL/min/1.73 m^2 can be used as a threshold for identifying children with ARC, while Lee et al[17] reported that eGFR ≥110 mL/min/1.73 m^2 can better predict the occurrence of ARC in critically ill children. For children, their kidneys continue to grow and mature, and renal clearance is in a continuous and fluctuating state. Therefore, age-dependent ARC thresholds for the pediatric population seemed preferable to a fixed cutoff value similar to that used in adults.[18] Notably, most pediatricians did not seem to know these thresholds.

A total of 220 (80%) pediatricians believed that ARC would impact the effect of vancomycin treatment, but only 149 (54%) were willing to adjust the vancomycin treatment plan to adapt to ARC. To our great surprise, 124/149 (83%) thought that vancomycin dose should be reduced; this would be a serious mistake. Hirai et al[15] proved that eGFR (≥160 mL/min/1.73 m^2) was related to a high clearance rate of vancomycin. To achieve the optimal therapeutic concentration in children with ARC, the initial dose of vancomycin needed to be increased. Avedissian et al[16] observed that compared with the non-ARC group, the vancomycin clearance rate in the ARC group increased by 50 mL/min/1.73 m^2 (141.3 mL/min/1.73 m^2 vs 91.7 mL/min/1.73 m^2), and the substandard rate of vancomycin concentrations was 27%

higher (79% vs 52%). Lee et al[17] found that there was a significant correlation between eGFR and vancomycin plasma concentration ($R^2 = 1.002$; $P < .001$), and elevated eGFR was an independent risk factor for a subtherapeutic vancomycin concentration (OR = 1.002, 95% CI: 1.001–1.003; $P = .001$).

Vancomycin is used as a first-line antibacterial drug for the treatment of gram-positive bacteria, such as methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative Staphylococcus, and a sufficient dose is important in the treatment of critically ill children.[19] We assume that most pediatricians made the choice to "reduce the dose of vancomycin" because they confused the concepts of ARC and AKI. Although they are both statuses of renal function, they had completely opposite meanings. Pediatricians do not truly understand ARC and its significant effect on the clearance of drugs, especially drugs metabolized by the kidneys.[20] This ARC effect can lead to further insufficient drug dose exposure, which required our attention and reflection.[2] Therefore, regarding the question "Do you know how to increase the dose?," it is not difficult to understand why nearly all pediatricians choose "unclear," as there is indeed a lack of reference data to tell them how to do so.

Our study has limitations. Due to geographical limitations, we only investigated the knowledge of ARC among pediatricians in one province of China, so the sample size was limited. Because there were not enough studies on children with ARC and many conclusions had not yet reached a consensus, we did not assign weights to each response to the questions related to ARC in the questionnaire, and it was difficult to further analyze the pediatrician's ARC knowledge.

5. Conclusions

ARC is relatively common in critically ill children, but little is known about it, as most current evidence is based on clinical data from adult studies. However, there was a more serious problem. When pediatricians encounter ARC children, they often confuse ARC with AKI and further reduce the drug dose, which will lead to very serious treatment errors. This issue needs to be taken seriously. Therefore, ARC should be written into the official pediatric guidelines as soon as possible, and more studies on children with ARC should be carried out to generate clinical experience for pediatricians.

Author contributions

Conceptualization: Chunyan Wang, Shusheng Zhou.
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Writing – original draft: Ran Zhou.
Writing – review & editing: Ran Zhou, Yuting Fang, Chunyan Wang, Shusheng Zhou.

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