Antimicrobial Dilution for Intravenous Administration in Children

KV Sruthy[1], Jeeson C Unni[2], Priya Karunakaran[3]

Abstract

There are very few guidelines available that focus on recommended diluents for intravenous (IV) administration of the various antimicrobial used in pediatric practices. This article attempts to detail ideal diluents for commonly used antimicrobials; the amount of diluent to be added for IV administration; analyze various methods of IV administration; explains how diluents could be reduced while treating children in whom fluid restriction improves outcome; and suggests methods of reducing wastage of costly antimicrobials and thereby economizes therapy of sick children.

Keywords: Antibiotics, Antimicrobials, Diluent, Dilution, Pediatric.

Pediatric Infectious Disease (2022): 10.5005/jp-journals-10081-1300

Introduction

Antimicrobials are commonly administered intravenous (IV) medications. Intravenous antibiotics in children are usually given to sick children with sepsis. They may be given as bolus push, slow IV push, and as intermittent or continuous infusions depending on the condition of the child, the infection for which it is prescribed; with due consideration to the pharmacokinetics and pharmacodynamics of the given antimicrobial.[1] Beyond the application of best practice recommendations to guide safe use and optimize the clinical outcome, several issues are better addressed through evidence-based policies, procedures, and practices.

Childhood is unique in that there is rapid growth, maturation, and development; the ability to handle active drugs changes during childhood and is recognized in developmental pharmacology.[2] The magnitude changes in dosages required during the pediatric age group could vary >50-fold between the neonate and the adolescent. Fluid management is an important aspect in critically ill patients.[3] Most recommendations for antibiotic dilution cater to adults.[4] There are very few pediatric guidelines for IV medication administration.[5–7]

It would be most appropriate if pediatric IV preparations are available in the ready-to-administer form. Preparation and dilution of the IV medication need to take place in a clean, uncluttered area with clear instructions on the type and volume of appropriate diluent. Syringes should be promptly labeled and this necessitates the availability of blank, ready-to-apply labels.[8,9]

Materials and Methods

A list of 36 injectable antimicrobials available in our hospital formulary was generated. FDA approved package inserts and other drug resources like Lexicomp, Micromedex, emc, and PDR.net were used as the primary reference for information on diluents for initial reconstitution and final dilution; maximum concentration of drug for intravenous administration (MCIA); and, for a few select drugs, the maximum concentration for fluid restricted patients.[10–13] Maximum concentration of drug for intravenous administration of an antimicrobial was used to determine the minimum volume of the diluent required for IV administration by employing the formula given below.

[1,3]Department of Clinical Pharmacy, Aster Medcity, Kochi, Kerala, India

[2]Department of Child and Adolescent Health, Aster Medcity, Kochi, Kerala, India

Corresponding Author: Jeeson C Unni, Department of Child and Adolescent Health, Aster Medcity, Kochi, Kerala, India, Phone: +91 9847245207, e-mail: jeeson1955@gmail.com

How to cite this article: Sruthy KV, Unni JC, Karunakaran P. Antimicrobial Dilution for Intravenous Administration in Children. Pediatr Inf Dis 2022;4(2):47–61.

Source of support: Nil

Conflict of interest: None

The 36 antimicrobials were sorted in alphabetical order and their presentation as marketed in India, fluid for initial dilution, fluid for final dilution, MCIA, MCIA in fluid restricted patients, MCIA for IV push, rate of infusion, stability, monitoring parameters, and additional remarks, if any, were generated.

Antimicrobial dilution protocol for pediatrics was prepared and submitted before Pharmacy and Therapeutic Committee (P&TC). After getting the approval, it was circulated through the Hospital Intranet so that Doctors, Nurses, and Clinical Pharmacists could access it. Training classes for nurses were conducted to educate them on the concepts of maximum concentration and other aspects of the protocol.

While prescribing an antimicrobial, instructions for dilution and mode of IV administration were made mandatory. Clinical pharmacists checked and ensured that the dose, drug product which is being indented, dilution and administration techniques, storage conditions, and monitoring parameters were adhered to. Recommendations for storage of partly used vials of expensive drugs were formulated to reduce the cost of therapy.

Results

The results of all parameters studied for the 36 antimicrobials are given in Table 1. For beta-lactam-beta-lactamase inhibitor combinations, MCIA of the beta-lactam content is provided separately.

Reference values for MCIA in fluid restricted conditions of 6 antimicrobials were used to calculate the volume of diluent required

Table 1: Pediatric antimicrobial drug dilution manual

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
1	Acyclovir	250 mg PFI 500 mg PFI 1,000 mg	SWFI	NS, D5W, DNS	7 mg/mL	10 mg/mL	NA	60 minutes	Reconstituted solution: 12 hours at room temperature. Final diluted solution: 24 hours at room temp	CBC, RFT, LFT, Monitor for neurotoxicity and nephrotoxicity when using high-dose therapy, neutrophil count at least twice weekly in neonates receiving acyclovir 60 mg/kg/day IV	Rapid infusion is associated with nephrotoxicity Maintain adequate hydration during therapy. Extravasation may cause inflammation and phlebitis at the injection site Do not use bacteriostatic water for injection (contains paraben or benzyl alcohol)	Lexicomp, emc, PDR.net, Teddy Bear, Micromedex, Package insert
2	Amikacin	100 mg in 2 mL 250 mg in 2 mL 500 mg in 2 mL	NA	NS, D5W	5 mg/mL	10 mg/mL	IM can be given	30–60 minutes	Final diluted solution: 24 hours at room temp	RFT, peak and trough serum amikacin concentrations, be alert to ototoxicity	Infusion over 1–2 hours is recommended in infants If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered	Teddy Bear, Lexicomp, PDR.net, emc, Package insert
3	Amoxicillin clavulanic acid	150 mg PFI 300 mg PFI 600 mg PFI 1.2 g PFI	SWFI	NS	10 mg Amoxicillin/mL	NA	IV Pushover 3–4 minutes No IM	30–40 minutes	Reconstituted solution: 4 hours at room temp	CBC, LFT, RFT, INR	Should be administered as IV infusion only in children <3 months	Package insert (Clavam)

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
4	Amphotericin B Liposomal	50 mg PFI	D5W	D5W	1–2 mg/mL Infants and small children: 0.2–0.5 mg/mL	NA	NA	2 hours	Reconstituted solution: 24 hours at 2–8°C	RFT, LFT, Serum electrolytes	Do not reconstitute or mix with saline Flush line with D5W before infusion Begin infusion within 6 hours of dilution with D5W Infusion-related reactions may occur	Lexicomp, Teddy Bear, package insert, emc, PDR.net, Micromedex
5	Ampicillin	125 mg PFI 250 mg PFI 500 mg PFI 1 g PFI 2 g PFI	SWFI	NS, D5W	NS: 30 mg/mL D5W: 20 mg/mL	112 mg/mL	Doses ≤500 mg: IVP over 3–5 minutes; Doses >500 mg: IVP over 10–15 minutes; IM also recommended	15–30 minutes	Reconstituted solution: 1-hour Final diluted solution in NS: 8 hours at 25°C and 24 hours at 4°C; Final diluted solutions in D5W: 2 hours at 25°C and 1 hour at 4°C	RFT, LFT, Hematology function test	Rapid infusion may cause seizures; Adjust the rate of infusion so that the total dose is administered before admixture stability expires; Observe for signs of anaphylaxis with the first dose	Lexicomp, Teddy Bear, Package insert, PDR.net
6	Azithromycin	500 mg PFI	SWFI	NS, D5W	1 mg/mL	2 mg/mL	NA	1 mg/mL: over 3 hours; 2 mg/mL: over 1 hour	Reconstituted solution: 24 hours <25°C Diluted solutions: 24 hours when stored <30°C and 7 days at 2–8°C	CBC, LFT	Do not infuse over a period of <60 minutes	Lexicomp, emc, Package insert, PDR.net, Teddy Bear, Micromedex

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
7	Caspofungin	50 mg PFI 70 mg PFI	NS, SWFI	NS	0.5 mg/mL	NA	NA	1 hour (higher doses, e.g., 150 mg: 2 hours)	Reconstituted solution: 1 hour at ≤25°C Final diluted solution: 48 hours at 2–8°C	LFT, CBC, Serum potassium, signs of anaphylaxis or histamine-related reactions	Do not use any diluents containing dextrose	Lexicomp, Teddy Bear, Package insert, emc, PDR.net
8	Cefazolin	500 mg PFI 1 g PFI	SWFI	D5W, NS	20 mg/mL	138 mg/mL (IV Push with SWFI)	IV Push: 100 mg/mL over 3–5 minutes may also be given as IM	60 minutes	Reconstituted 24 hours at room temp and 10 days at refrigeration	RFT, LFT, CBC, PT	Monitor for signs of anaphylaxis during the first dose	Lexicomp, teddy Bear, PDR.net, Micromedex, Up to 40 mg/mL is recommended in Lexicomp
9	Ceftazidime	250 mg PFI500 mg PFI 1 g PFI	SWFI	D5W, NS	40 mg/mL	125 mg/mL (IV Push with SWFI, Peripheral line)	IV Pushover 3–5 minutes May also be given as IM	15–30 minutes	Reconstituted solution: 24 hours at room temperature and 7 days at refrigeration (Inj Fortaz)	RFT, LFT, PT (especially with warfarin)		Lexicomp, Teddy Bear, PDR.net, emc, Micromedex drug ref Storage vary by manufacturer
10	Ceftriaxone	250 mg PFI 500 mg PFI 1 g PFI	SWFI, DNS, NS	D5W, NS	40 mg/mL	NA	IV Push (100 mg/mL) over 5 minutes May also be given as IM	30 minutes	Reconstituted solution (100 mg/mL): stable for 48 hours at room temp of 25°C	CBC, PT (especially if on warfarin), LFT, RFT, Observe for signs and symptoms of anaphylaxis	Do not co-administer with calcium-containing solutions	Lexicomp, Teddy Bear, emc, pdr.net, Micromedex drug ref, Package insert, emc

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
11	Cefuroxime	750 mg PFI 1.5 g PFI	SWFI	NS, D5W	30 mg/mL	137 mg/mL (SWFI/Peripheral dilution)	IV Push (95 mg/mL) over 3–5 minutes May also be given as IM	15–60 minutes	Reconstituted solution: 24 hours at room temp and 48 hours when refrigerated. Final diluted solution: 24 hours at room temp and 7 days when refrigerated	LFT, RFT, Hematology function test	Observe for signs and symptoms of anaphylaxis during the first dose	Lexicomp, Teddy Bear, PDR.net, emc, Micromedex drug ref, Package insert
12	Ciprofloxacin	200 mg in 100 mL	NA	NA	2 mg/mL	NA	NA	60 minutes	Discard unused portion	RFT, LFT, Hematopoietic function periodically		Lexicomp, Package insert, Teddy Bear, PDR.net, Micromedex
13	Clarithromycin	500 mg PFI	SWFI	NS, D5W	2 mg/mL	NA	NA	60 minutes	Reconstituted solution: 6 hours at 25°C Final diluted solutions: 24 hours if stored at 5°C	LFT, RFT, QT interval	Do not use diluents containing preservatives or inorganic salts	emc, Package insert
14	Clindamycin	150 mg in 1 mL300 mg in 2 mL 600 mg in 4 mL	NA	NS, D5W	18 mg/mL	NA	IV Push not recommended undiluted solution may be used as IM	10–60 minutes	Final diluted solution: 16 days at room temp and 32 days when refrigerated	CBC, RFT, LFT	Hypotension and cardiopulmonary arrest have been reported following rapid IV administration	Lexicomp, Package insert, Teddy Bear, PDR.net, emc, Micromedex

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
15	Colistin	1 MIU PFI 2 MIU PFI 3 MIU PFI 4.5 MIU PFI	SWFI	D5W, NS	IV Push: 75 mg/mL (2,25,000 IU)	NA	IV Push-over 3–5 minutes IM can be given	30 minutes	Reconstituted solution: 7 days at 2–8°C or at 20–25°C	CBC, RFT, CBC	Continuous IV infusions should be completed within 24 hours of preparation	Lexicomp, PDR.net, emc, Micromedex, Package insert Duration: 90–180 in PDR.net
16	Doxycycline	100 mg PFI	SWFI	D5W, NS	1 mg/mL	NA	NA	1–4 hours	Final diluted solution: 72 hours when refrigerated	BUN, LFT, Hematology function test	Avoid rapid infusion Phlebitis occurs frequently; Reconstituted solution should be protected from sunlight and artificial light	Lexicomp, package insert, Teddy Bear
17	Ertapenem	1 g PFI	NS, SWFI	NS	20 mg/mL	NA	No IVP IM can be given	30 minutes	Reconstituted solution: 6 hours at room temp or 24 hours at 2–8°C	RFT, LFT, Hematology function test	Do not infuse with dextrose-containing solutions	Lexicomp, Teddy bear, PDR.net, emc
18	Fluconazole	200 mg in 100 mL 400 mg in 200 mL	NA	NA	2 mg/mL	NA	NA	1–2 hours	Discard unused portion	LFT, RFT, CBC, ECG	Do not unwrap unit until ready for use	Lexicomp, Package insert, emc, PDR.net, Teddy Bear
19	Ganciclovir	500 mg PFI	SWFI	NS, D5W	10 mg/mL	NA	NA	60 minutes	Reconstituted solution: 12 hours at room temperature. Final diluted solution: 24 hours when refrigerated	CBC, LFT, RFT	Follow the same precautions utilized with antineoplastic agents when preparing and administering ganciclovir; Too rapid infusion can cause increased toxicity and excessive plasma levels	Lexicomp, Package inset, emc, PDR.net, Teddy Bear

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
20	Gentamicin	60 mg in 1.5 mL 80 mg in 2 mL	NA	NS, D5W	10 mg/mL	NA	IV push over 5 minutes; IM can also be given	30–120 minutes	Final diluted solution: 48 hours at room temperature and refrigeration	CBC, RFT, peak and trough serum gentamicin concentrations, Signs of nephrotoxicity or ototoxicity	Avoid formulations with preservatives in neonates and infants, consider longer infusion time with higher doses	Lexicomp, Teddy Bear, PDR.net, emc, Package insert
21	Imipenem/ Cilastatin	250 mg PFI 500 mg PFI	10 mL NS, D5W	NS, D5W	5 mg/mL	10 mg/mL	Do not administer IV Push IM can also be given	≤500 mg: 20–30 minutes; >500 mg: 40–60 minutes	Reconstituted solution: 4 hours at room temp and 24 hours when refrigerated at 5°C	LFT, RFT, Hematology function test	Monitor for signs of anaphylaxis during first dose If nausea and/or vomiting occurs during administration, decrease the rate of IV infusion; Do not use diluents containing benzyl alcohol for reconstitution when administering to neonates due to toxicity	Lexicomp (10 mg/mL), Teddy Bear, PDR.net, emc, Package insert Primaxin inj for IM and IV vials available separately
22	Levofloxacin	250 mg in 50 mL 500 mg in 100 mL 750 mg in 150 mL	NA	NA	5 mg/mL	NA	NA	60–90 minutes	Discard unused portion	RFT, LFT, the possibility of crystalluria should be assessed, hydration status	Avoid rapid or bolus IV infusion due to risk of hypotension; Avoid administration through an intravenous line with a solution containing multivalent cations (e.g., magnesium, calcium)	Lexicomp, Package insert, emc, PDR.net, Micromedex
23	Linezolid	200 mg in 100 mL 400 mg in 200 mL 600 mg in 300 mL	NA	NA	2 mg/mL	NA	NA	30–120 minutes	Discard unused portion	CBC	Keep infusion bags in overwrap until ready for use	Lexicomp, Package insert, Teddy Bear, emc, PDR.net, Micromedex

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
24	Meropenem	125 mg PFI 250 mg PFI 500 mg PFI 1 g PFI 2 g PFI	SWFI	D5W, N S	20 mg/mL	NA	IVP: Administer reconstituted solution (50 mg/mL) up to 1 g over 3–5 minutes	30 minutes	Reconstituted solution in NS: 1 hour at up to 25°C or 15 hours at up to 5°C Final diluted solution in NS: 1 hour at up to 25°C or 15 hours at up to 5°C	RFT, LFT, Hematology function test	Solutions reconstituted with D5W should be used immediately Monitor for signs of anaphylaxis during the first dose.	Lexicomp (final diluted solution for 24 hours), Teddy Bear (50 mg/mL for infusion over 15–30 minutes), Package insert, pdr.net, emc Extended infusion over 4 hours (Lexicomp)
25	Metronidazole	500 mg in 100 mL	NA	NA	5 mg/mL	NA	NA	30–60 minutes	Discard unused portion	CBC, LFT, RFT	Avoid contact of drug solution with equipment containing aluminum; Remove from foil wrapping just before administration	Lexicomp, Package insert, emc, PDR.net, Micromedex, Teddy bear
26.	Minocycline	100 mg PFI	SWFI	NS, DNS	100–1,000 mL	NA	NA	60 minutes	Final diluted solution: 4 hours at room temp and 24 hours at 2–8°C	CBC, LFT, RFT, Monitor magnesium concentrations in patients with renal impairment	Avoid rapid administration. Prolonged IV administration may result in thrombophlebitis Do not dilute with any calcium-containing solutions due to the risk of precipitation	Lexicomp, Package insert, Micromedex

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
27	Piperacillin tazobactam	1.125 g PFI 2.25 g PFI 3.375 g PFI 4.5 g PFI	NS, D5W, SWFI	NS, D5W	80 mg/mL	NA	NA	30 minutes	Reconstituted solution: 24 hours up to 25°C and 48 hours at 2–8°C	Serum electrolytes, CBC, LFT, RFT, Hematology function test	Should not be administered with aminoglycosides; Extended infusion over 3–4 hours; Coagulation parameters should be frequently monitored during co-administration with large doses of heparin and oral anticoagulants Monitor for signs of anaphylaxis during the first dose	Lexicomp, emc, PDR. net, Package insert, Teddy Bear, Micromedex
28	Polymyxin B	500,000 IU PFI	D5W, NS (can be directly dissolved)	1,667 IU/mL	NA	IM can be given (but not recommended for routine use)	60–90 minutes	Reconstituted solution: 48 hours at 2–8°C	RFT, Serum Polymyxin concentrations, Signs of superinfections, Neurologic adverse effects		Lexicomp, package insert, PDR.net,	
29	Teicoplanin	200 mg PFI 400 mg PFI	SWFI	NS, D5W	67 mg/mL	NA	IV push over 3–5 minutes	30 minutes	Reconstituted and diluted solution: 24 hours at 2–8°C	CBC, RFT, teicoplanin trough concentrations (on day 3, 4, or 5, then weekly), Auditory function tests	Must infuse over 30 minutes in neonates. Do not administer bolus inj or IM in neonates	Lexicomp, Package insert,
30	Tigecycline	50 mg PFI	NS, D5W	NS, D5W	1 mg/mL	NA	NA	60 minutes	Reconstituted solution: 24 hours at room temperature (up to 6 hours in the vial and the remaining time in the intravenous bag) Final diluted solution: 48 hours at 2–8°C	Hypersensitivity reactions, LFT, Coagulation parameters, tooth enamel (pediatric patients <8 years)	Administer intravenously through a dedicated line or via Y-site Administer IV line before and after with NS or D5W if IV line is used for sequential infusions for several drugs	Lexicomp, Package insert, Micromedex, emc, PDR. net

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
31	Trimethoprim sulfamethoxazole	5 mL WFI (Each mL contains 80 mg Sulfamethoxazole and 16 mg Trimethoprim)	NA	D5W	Dilute to 1:25 dilution (5 mL drug to 125 mL D5W)	Dilute to 1:15 dilution (5 mL drug to 75 mL D5W)	NA	60–90 minutes	5 mL/125 mL D5W: stable for 6 hours 5 mL/100 mL D5W: stable for 4 hours 5 mL/75 mL D5W: stable for 2 hours	CBC, RFT, LFT	Must be diluted in D5W only	Lexicomp, Package insert, emc, PDR. net, Teddy Bear, Micromedex
32	Vancomycin	500 mg PFI 1 g PFI	SWFI	D5W, NS	5 mg/mL	10 mg/mL	NA	60 minutes	Reconstituted solution: 48 hours if refrigerated	RFT, serum vancomycin concentrations, WBC, audiogram, Fluid status	Red man syndrome may occur if the infusion is too rapid. Administration of antihistamines just before the infusion may also prevent or minimize this reaction	Lexicomp, emc, PDR. net, Package insert, Teddy Bear, Micromedex
33	Voriconazole	200 mg PFI	SWFI	NS, D5W	5 mg/mL	NA	NA	3 mg/kg/hour (1–2 hours)	Reconstituted solution: 24 hours if refrigerated	LFT, RFT, Serum electrolytes, Serum levels, Drug toxicity	Do not dilute with 4.25 sodium bicarbonate infusion. Do not infuse voriconazole concomitantly with blood products or short-term infusions of concentrated electrolytes, even if the 2 infusions are running through separate lines. Associated with infusion-related events resembling anaphylactoid reactions	Lexicomp, Micromedex, emc, Package inset, PDR. net, Teddy Bear

(*Contd…*)

(*Contd…*)

S. no	*Drug*	*Presentation*	*Initial reconstitution*	*Final dilution*	*Maximum concentration for intermittent IV infusion*	*Fluid-restricted patients*	*Bolus*	*Rate of infusion*	*Stability*	*Monitoring parameters*	*Remarks*	*References*
34	Anidulafungin	50 mg PFI 100 mg PFI	SWFI	NS, D5W	0.77 mg/mL	NA	NA	50 mg: 45 minutes 100 mg: 90 minutes 200 mg: 180 minutes	Reconstituted solution: 24 hours at up to 25°C Final diluted solution: 72 hours at 2–8°C	Anaphylactic reactions, Possible histamine-mediated symptoms, Infusion-related adverse reactions, LFT	To reduce occurrence of infusion-related adverse reactions, do not exceed infusion rate of 1.1 mg/minute	Lexicomp, Teddy bear, Package insert, PDR.net, emc, Micromedex
35	Cefotaxime	250 mg PFI 500 mg PFI 1 g PFI2 g PFI	SWFI	D5W, NS	40 mg/mL	50 mg/mL (intermittent infusion) 200 mg/mL (IV Push)	IV Push over 3–5 minutes IM can also be given	15–30 minutes	Reconstituted solution: 24 hours at room temp and 7 days when refrigerated. Final diluted solution: 24 hours at room temp and 5 days when refrigerated	RFT, LFT, Hematology function test, monitor infusion site for extravasation	Avoid rapid injection (<1 minute) due to association with arrhythmias; Observe for signs and symptoms of anaphylaxis during first dose	Lexicomp, PDR.net, emc, Teddy Bear, Micromedex drug ref, Package insert
36	Ceftazidime avibactam	2.5 g PFI	NS, D5W, SWFI	NS, D5W	Ceftazidime ~167 mg/mL	40 mg/mL	NA	2 hours	Reconstituted solution: should be used immediately. Final diluted solution: 12 hours at room temp and 24 hours at 2–8°C	RFT, signs/symptoms neurotoxicity	Signs of anaphylaxis during first dose	Lexicomp, emc, PDR.net, Package insert, Micromedex

PFI, powder for injection; SWFI, sterile water for injection; NS, normal saline; DNS, dextrose normal saline; D5W, dextrose 5% in water; NA, not applicable; IVP, intravenous push; SubQ, subcutaneous; IM, intramuscular; NA, not applicable

Table 2: Volume of diluent saved in fluid restricted patients with intermittent infusion and IV push

S. no.	*Drug*	*MCIA in normal patient*	*MCIA in fluid-restricted patient*	*Volume saved (mL/kg/day)*
1	Acyclovir (10 mg/kg/dose thrice daily)	7 mg/mL	10 mg/mL	1.2
2	Amikacin (15 mg/kg/dose once daily)	5 mg/mL	10 mg/mL	1.5
3	Azithromycin (10 mg/kg/dose once daily)	1 mg/mL	2 mg/mL	5
4	Imipenem/cilastatin (25 mg/kg/dose four times a day)	5 mg/mL	10 mg/mL	10
5	Cotrimoxazole (5 mg/kg/dose twice daily)	Dilute to 1:25 dilution (5 mL drug to 125 mL D5W) [Trimethoprim 80 mg + Sulfamethoxazole 400 mg/5 mL]	Dilute to 1:15 dilution (5 mL drug to 75 mL D5W) [Trimethoprim 80 mg + Sulfamethoxazole 400 mg/5 mL]	6.4
6	Vancomycin (15 mg/kg/dose thrice daily)	5 mg/mL	10 mg/mL	4.5
S. no	*Drug*	*MCIA in intermittent infusion*	*MCIA in IV push*	*Volume saved (mL/kg/day)*
1	Ampicillin (50 mg/kg/dose four times daily)	NS: 30 mg/mL	100 mg/mL	4.68
2	Cefazolin (50 mg/kg/dose thrice daily)	20 mg/mL	100 mg/mL	6
3	Ceftazidime (50 mg/kg/dose thrice daily)	40 mg/mL	170 mg/mL	2.85
4	Ceftriaxone (50 mg/kg/dose twice daily)	40 mg/mL	100 mg/mL	1.5
5	Cefuroxime (30 mg/kg/dose thrice daily)	30 mg/mL	90 mg/mL	2.01
6	Cefotaxime (50 mg/kg/dose thrice daily)	40 mg/mL	200 mg/mL	3

for intermittent infusion in these states. The volume of fluid infusion that could be reduced by this calculation is 1.25, 1.5, 6.5, 10, and 4.5 mL/kg/day for acyclovir, amikacin, trimethoprim-sulfamethoxazole, imipenem/cilastatin, and vancomycin, respectively. Similar calculations using MCIA for drugs where values are available for IV push suggested a saving of 4.7, 6, 2.85, 1.5, 2, and 3 mL/kg/day for ampicillin, cefazolin, ceftazidime, ceftriaxone, cefuroxime, and cefotaxime, respectively (Table 2). The MCIA reference values for fluid restricted patients for the latter set of antimicrobials and reference values for generating the amount of volume saved by IV push for amoxiclav and IV infusion for colistin were not available. The significance of the reduced volume for dilution, in these fluid restricted states, is pronounced when a sick child requires the administration of multiple antimicrobials along with other drugs.

A few drugs could be stored, some at 2–8°C and others at room temperature, and reused either after reconstitution and/or final dilution. Since the duration of stability of the final diluted solution is much longer than for its reconstituted solution, storage after final dilution and administration as and when required ensured less wastage and increased cost saving. The cost-saving thus achievable for costly antimicrobials such as anidulafungin, caspofungin, ceftazidime, clarithromycin, ganciclovir, minocycline, and tigecycline was significant for resource-poor settings (Table 3).

Antimicrobials that require monitoring of serum concentration levels include amikacin, gentamicin, teicoplanin, polymyxin B, vancomycin, and voriconazole. Complete blood count (CBC), serum electrolytes, liver function test (LFT), renal function test (RFT), hematology function test, coagulation test, and signs of anaphylaxis are the common monitoring parameters for most antimicrobials. Echinocandins such as anidulafungin and caspofungin are prone to cause histamine-related reactions and one must be aware of the possibility of Redman syndrome with vancomycin (Table 1).

Discussion

To standardize protocols and reduce errors associated with the administration of antimicrobials in our hospital, an "Antimicrobial Dilution Manual for Pediatrics" was prepared and circulated.

Ciprofloxacin, fluconazole, levofloxacin, linezolid, and metronidazole are available as ready-to-use solutions and do not require further dilution for IV administration. Presentation of all the other antimicrobials is either as a powder for injection (PFI) or water for injection (WFI); the former requiring both reconstitution and final dilution while the latter requires only final dilution before IV use.

Fluid resuscitation, as part of fluid management, may be needed to maintain intravascular volume in critically ill children. Unfortunately, this often leads to fluid overload,[3] with consequent negative effects for children admitted in PICU.[3,14,15] These children would be on numerous IV medications. Reduction in volume of diluent for each drug, including the antimicrobials, would benefit fluid restriction. This approach is, however, not possible for drugs marketed as premixed infusions.

Antimicrobials may be administered via IV push, intermittent IV infusion, and/or continuous IV infusion depending on the individual drug recommendation. Intravenous push of antimicrobials provides the advantage of a minimum fluid volume which can be particularly useful for fluid-restricted patients. In addition, the faster administration time may provide advantages in the emergency department, so that time-to-first-dose can be shortened. There may also be interest in IV push administration in the setting of drug or fluid shortages, such as the current shortage of small-volume parenteral solutions.[1] The relevance of the antimicrobial dilution protocol for children requiring fluid restriction is hereby emphasized.

Table 3: Cost saving when administering costly IV antimicrobials as final diluted solution

S. no.	*Drug and strength available*	*Dosage regimen (example)*	*Storage*	*Reconstituted solution*	*Final diluted solution*
1	Anidulafungin 50 mg PFI	15 mg once daily (Patient weight: 10 kg; 1.5 mg/kg/dose once daily)	Reconstituted solution: 24 hours at up to 25°C Final diluted solution: 72 hours at 2–8°C	Total doses available in the vial: 3, Total cost: Rs 10,518.20, Cost per dose: Rs 3,155.46	
				Maximum doses taken: 2 (30 mg)	Maximum doses taken: 3 (45 mg)
				No. of doses wasted: 1 (20 mg)	No. of doses wasted: 0 (5 mg)
				Cost of wastage: Rs 4,207.28	Cost of wastage: Rs 1,051.82
					Total money saved: Rs 3,155.46
2	Caspofungin 50 mg PFI	25 mg once daily (BSA: 0.5 m^2; 50 mg/m^2 /dose once daily)	Reconstituted solution: 1 hour at ≤25°C; Final diluted solution: 48 hours at 2 to 8°C	Total doses available in the vial: 2, Total cost: Rs 15,400, Cost per dose: Rs 7,700	
				Maximum doses taken: 1 (50 mg)	Maximum doses taken: 2 (50 mg)
				No. of doses wasted: 1 (25 mg)	No. of doses wasted: 0
				Cost of wastage: Rs 7,700	Cost of wastage: Rs 0
					Total money saved: Rs 7,700
3	Ceftazidime avibactam 2.5 g PFI	500 mg of Ceftazidime thrice daily (Wt: 10 kg; 50 mg/kg/dose thrice daily)	Reconstituted solution: should be used immediately Final diluted solution: 12 hours at room temp and 24 hours at 2–8°C	Total doses available in the vial: 4, Total cost: Rs 4,336.69, Cost per dose: Rs 1,084.17	
				Maximum doses taken: 1 (500 mg of ceftazidime)	Maximum doses taken: 4 (2 g of Ceftazidime)
				No. of doses wasted: 3 (1,500 mg of ceftazidime)	No. of doses wasted: 0
				Cost of wastage: Rs 3,252.51	Cost of wastage: Rs 0
					Total money saved: Rs 3,252.51
4	Clarithromycin 500 mg PFI	150 mg thrice daily (Wt: 10 kg; 15 mg/kg/day divided 2 doses)	Reconstituted solution: 6 hours at 25°C; Final diluted solution: 24 hours if stored at 5°C	Total doses available in the vial: 3, Total cost: Rs 1,144, Cost per dose: Rs 343.2	
				Maximum doses taken: 1 (150 mg)	Maximum doses taken: 3 (450 mg)
				No. of doses wasted: 2 (350 mg)	No. of doses wasted: Only 50 mg
				Cost of wastage: Rs 800.8	Cost of wastage: Rs 114.4
					Total money saved: Rs 686.4
5	Ganciclovir 500 mg PFI	50 mg twice daily (Wt: 10 kg; 5 mg/kg/dose twice daily)	Reconstituted solution: 12 hours at room temperature. Final diluted solution: 24 hour when refrigerated	Total doses available in the vial: 10, Total cost: Rs 1,663, Cost per dose: Rs 166.3	
				Maximum doses taken: 2 (100 mg)	Maximum doses taken: 3 (150 mg)

(*Contd…*)

(*Contd…*)

S. no.	*Drug and strength available*	*Dosage regimen (example)*	*Storage*	*Reconstituted solution*	*Final diluted solution*
				No. of doses wasted: 8 (400 mg)	No. of doses wasted: 7 (350 mg)
				Cost of wastage: Rs 1,330.4	Cost of wastage: Rs 1,164.1
					Total money saved: Rs 166.3
6	Minocycline 100 mg PFI	20 mg twice daily (Wt: 10 kg; 2 mg/kg/dose twice daily)	No data regarding reconstituted solution; Final diluted solution: 4 hours at room temp and 24 hours at 2–8°C	Total doses available in the vial: 5, Total cost: Rs 2,698, Cost per dose: Rs 539.6	
				Maximum doses taken: 1 (20 mg)	Maximum doses taken: 3 (60 mg)
				No. of doses wasted: 4 (80 mg)	No. of doses wasted: 2 (40 mg)
				Cost of wastage: Rs 2,158.4	Cost of wastage: Rs 1,079.2
					Total money saved: Rs 1,079.2
7	Tigecycline 50 mg PFI	10 mg twice daily (Wt: 10 kg; 1 mg/kg/dose twice daily)	Reconstituted solution: 24 hours at room temperature (up to 6 hours in the vial and the remaining time in the intravenous bag); Final diluted solution: 48 hours at 2–8°C	Total doses available in the vial: 5, Total cost: Rs 4,292, Cost per dose: Rs 858.4	
				Maximum doses taken: 3 (30 mg)	Maximum doses taken: 5 (50 mg)
				No. of doses wasted: 2 (20 mg)	No. of doses wasted: 0
				Cost of wastage: Rs 1,716.8	Cost of wastage: 0
					Total money saved: Rs 1,716.8

Sterile water for injection (SWFI), normal saline (NS), 5% dextrose in water (D5W), and dextrose normal saline (D5NS) are the common diluents used for initial reconstitution, whereas NS, D5W, and D5NS are used for the final dilution. Amphotericin B liposomal and cotrimoxazole should only be diluted with D5W; while caspofungin and ertapenem are incompatible with dextrose-containing solutions.

Intravenous and IM routes are used for bolus administration of antimicrobials. Antibiotics that may be administered IM include amikacin, ampicillin, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin, colistin, ertapenem, gentamicin, imipenem cilastatin, and polymyxin B. Drugs which are recommended for IV push are amoxicillin and clavulanic acid, ampicillin, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, colistin, gentamicin, teicoplanin, and meropenem.

Since pediatric dosage formulations are generally not available, the use of adult formulations leads to drug wastage, and in turn, higher costs of therapy; the most wasted group of medication being antibiotic.[16] Anidulafungin, caspofungin, and ceftazidime avibactam are expensive and their stability is longer as a final diluted solution than as the reconstituted solution. The benefit with regard to saving of drug and the cost was highlighted in our assessment.

Conclusion

An institutional antimicrobial dilution protocol for children is formulated to ensure the appropriate administration of IV medications for inpatient, emergency, and PICU settings. The factors considered include the appropriate diluent requirements and monitoring parameters after reviewing manufacturer labeling, primary literature, and drug information databases.

References

1. Spencer S, Ipema H, Hartke P, et al. Intravenous push administration of antibiotics: literature and considerations. Hospital Pharm 2018;53(3):157–169. DOI: 10.1177/0018578718760257
2. Crane E, Lehr TV, Mathew M, et al. Developmental pharmacology and therapeutics. In: Buonocore G, Bracci R, Weindling M, ed. Neonatology. Milano: Springer; 2012. DOI: 10.1007/978-88-470-1405-3_52
3. Dyah kanya wati. Measuring and Managing Fluid Overload In Pediatric Intensive care unit: Current topics in intensive care medicine. 2018. 3–12. https://www.intechopen.com/books/current-topics-in-intensive-care-medicine/measuring-and-managing-fluid-overload-in-pediatric-intensive-care-unit.
4. Administration of Antibiotic Injections. Compiled by Pharmacy Department Version 3 (July 2017). The Royal Liverpool and Broadgreen University Hospitals. NHS. https://secure.rlbuht.nhs.uk/

sites/Antibiotic/Documents/Antibiotic%20IV%20administration%20chart%202017%20a3%201%20sheet.pdf Accessed on 6.8.20.
5. Mass B, Gilchrist A, Hellinger A, et al., ed. Pediatric guidelines for IV medication administration. Pharmacy and Therapeutic Committee. UMass Memorial Medical Centre https://www.umassmed.edu/globalassets/anesthesiology/files/resources/2016-resources/pediatric-guidelines-for-medications.pdf. Accessed on 6.8.20.
6. IV Administration Guidelines. Pharmacy Department Cork University Hospital. Updated May 2017 http://emed.ie/Pharmacology/Docs/Pharm-CUH-IV-Guidelines-2017.pdf. Accessed on 6.8.20.
7. Lenz JR, Degnan DD, Hertig JB, et al. A review of best practices for intravenous push medication administration. J Infus Nurs 2017;40(6):354–358. DOI: 10.1097/NAN.0000000000000247
8. Grissinger M. Some IV medications are diluted unnecessarily in patient-care areas, creating undue risk. Pharm Therapeut 2017;42(8):490–492, 508.
9. Centers for Disease Control Prevention. One and only campaign. Centers for Disease Control and Prevention website; http://www.oneandonlycampaign.org/. Accessed on 7.8.2020.
10. Wolters Kluwer. Lexicomp. Available from: https://www.wolterskluwercdi.com/lexicomp-online/ [Accessed on 29 August 2020].
11. IBM Watson Health. Micromedex. Accessed from https://www.micromedexsolutions.com/home/dispatch/ssl/true [Accessed on 1 September 2020.
12. Datapharm Ltd. Electronic Medicines Compendium https://www.medicines.org.uk/emc/ [Accessed on 14 December 2019].
13. Prescribers' Digital Reference. Available from: https://www.pdr.net/ [Accessed on 12 December 2019].
14. Ker GL, Gangadharan S. Management of fluid overload in the pediatric ICU. Pediat Crit Carecur Contro 2019;193–209.
15. Raina R, Sethi SK, Wadhwani N, et al. Fluid overload in critically ill children. Front Pediatr 2018;6:1–18. DOI: 10.3389/fped.2018.00306.
16. Razieh D, Safoura A. Cost estimation related to drug waste in two major pediatric referrals centers and one adult hospital in southern Iran: a comparative cross-sectional study. Trends Pharmaceut Sci 2018;4(1):9–16.