



UW TASP
tele-antimicrobial stewardship program

echo

December 20, 2022

Drug Compatibilities and Sepsis

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Saline vs Lactated Ringers for Sepsis

Maybe Saline?

Hypochloremic metabolic
alkalosis



Brain Injury



Hyperkalemia



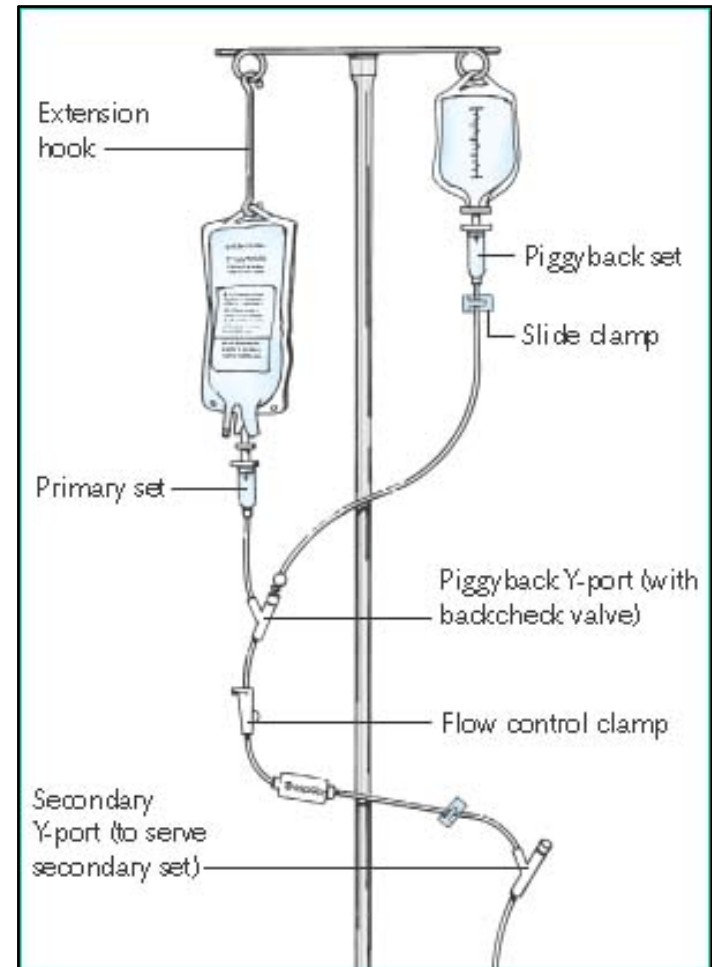
Blood & Medication
Compatibility



What is IV drug compatibility?

Compatibility information is based on four ratings:

Compatible	- No change in visible or electronically determined particulates, haziness or turbidity, frank precipitation, color, or evolution of a gas - Chemically stable: less than 10% loss of intact drug for at least 24 hours under the conditions being tested
Incompatible	A change in visible or electronically (even if not visible) particulates, haziness, or turbidity, frank precipitation, color or gas evolution occurred.
Uncertain or Variable	Research results do not fit conventional guidelines, apply judgement in using these results
No data	No data for administration methods chosen



Consequences of incompatibility

- Drug incompatibilities can lead to:
 - Reduced drug activity or inactivity
 - Formation of new toxic or nontoxic active ingredient
 - Increased toxicity of one or more of the involved drugs
 - Significant consequences including: multiorgan failure, severe liver dysfunction, toxic shock, local embolus, myocarditis, respiratory difficulties, systemic allergic reactions, local allergic reactions, thrombosis, thrombophlebitis, phlebitis, and local redness.

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Murney P. To mix or not to mix – Compatibilities of parenteral drug solutions. *Aust Prescr*. 2008;31:98–101.
Newton DW. Drug incompatibility chemistry. *Am J Health Syst Pharm*. 2009;66:348–57.
Trissel LA. *Handbook on Injectable Drugs*. Bethesda, Maryland: American Society of Hospital Pharmacists, Inc; 1994.
Lisa C. Compatibility of Commonly Used Intravenous Drugs. *Pharmacy Practice News*. 2011
Rosenthal K. One size doesn't fit all and other perils of IV administration. *Nurs Made Incredibly Easy*. 2006;4:18–21.
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Many challenges with IV drug compatibility data

IV drug compatibility and stability information is scarce, outdated, and inconsistent

- No consensus on which tests should be performed to check for incompatibility

Different studies apply different methods, and the results are interpreted relative to their test set

- Observation with matt black panel, automatic particle count or turbidimetry, optic microscopy, spectrophotometry, turbidimetry, visual inspection, gas formation, pH change and measurements, precipitate formation, color change, light obscuration, dynamic light scattering, and MORE!

Variety of dosage forms and formulations

- Product availability varies depending on country of origin
- Need to consider drug concentration, duration of stability, condition studied in (ex. temperature), and inactive ingredients

Multiple factors should be considered before concurrently administering two or more drugs



Ceftriaxone and LR

INTRAVENOUS ADMINISTRATION											
U N S P	D 5 W	D 1 0 W	D 5 L R	D 5 ¼ S	D 5 ½ S	D 5 N S	D 5 R	L R	R	N S	S L
	C		X		Ø	Ø	X	X	X	C	

...But why?

 = Compatible  = Incompatible  = Conflicting Reports NA = No Data



Calcium and Ceftriaxone

- 2007 FDA warning
 - Ceftriaxone and calcium containing products should NOT be co-administered to any patients due to risk of precipitation based on report of fatality in neonates.
- FDA retracted warning in 2009
 - Based on in vitro studies assessing precipitation of ceftriaxone and calcium-containing products in vials and infusion lines of both neonatal and adult plasma
- **New recommendation: ceftriaxone and calcium-containing products **may be sequentially administered** in patients older than 28 days if the infusion lines are flushed between infusions.**
 - Removed alert from the OR at UW Medicine



Ceftriaxone Package Insert

Interaction with Calcium-Containing Products

- **Do not use diluents containing calcium** to reconstitute Rocephin vials or to further dilute for IV administration because a precipitate can form.
- **Precipitation of ceftriaxone-calcium** can also occur when Rocephin is mixed with calcium-containing solutions **in the same IV administration line**.
 - Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site.
- However, **in patients other than neonates**, Rocephin and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.



What is in LR?

TABLE 1.

**COMPOSITION OF 1 LITER OF SELECTED
BALANCED FLUID SOLUTIONS.**

DRUG	LACTATED RINGERS (LR)	PLASMA- LYTE A
Acetate	-	27
Calcium	3	-
Chloride	109	98
Gluconate	-	23
Lactate	28	-
Magnesium	-	3
Potassium	4	5
Sodium	130	140

^aUnits expressed in mEq/L

- Does ceftriaxone pose a compatibility issue with LR given small amount of Ca+?



Pip/tazo and LR

U N S P	D 5 W	D 1 0 W	D 5 L R	D 5 ¼ S	D 5 ½ S	D 5 N S	D 5 R	L R	R	N S	S L
C	C							Ø		C	

...But why?

C=Compatible X=Incompatible Ø=Conflicting Reports NA=No Data

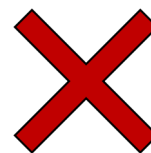


If pip/tazo has EDTA, then compatible with LR

Compatibility of piperacillin-tazobactam and lactated ringer's: dependent on whether the pip/tazo formulation contains the inactive ingredient edetate disodium dihydrate (EDTA) → stabilizing excipient



EDTA



NO EDTA

NOTE: most generic products are marketed without EDTA, therefore, are incompatible with LR.

Conclusion: look at product specific Package Insert, ensure that formulations with EDTA are the only forms of the drug mixed with this diluent



Parenteral Antimicrobial Y-Site Compatibility Chart

	Ampicillin	Ampicillin-sulbactam	Aztreonam	Caspofungin	Cefepime	Ceftriaxone	Ciprofloxacin	Ertapenem	Fluconazole	Levofloxacin	Linezolid	Meropenem	Metronidazole	Piperacillin-tazobactam	Tobramycin	Vancomycin
Ampicillin			U	I	U	U			I	C	C		C		U	U
Ampicillin-sulbactam			U	I	C	U	I		U	C	C		C		U	U
Aztreonam	U	U		C	C	C	C	C	C	C	C		I	C	C	U
Caspofungin	I	I	C		I	I	C	I	C	C	C	C	U	I	C	C
Cefepime	U	C	C	I			I		C	C	C		C	C	C	U
Ceftriaxone	U	U	C	I					U	C	C		C		I	U
Ciprofloxacin		I	C	C	I			C	C		C	I	C	I	C	C
Ertapenem			C	I			C		C	C	C		C		C	C
Fluconazole	I	U	C	C	C	U	C	C		C	C	C	C	C	C	C
Levofloxacin	C	C	C	C	C	C		C	C		C		C	I	C	C
Linezolid	C	C	C	C	C	C	C	C	C		C	C	C	C	C	C
Meropenem				C			I		C		C		C			C
Metronidazole	C	C	I	U	C	C	C	C	C	C	C	C		C	C	C
Piperacillin-tazobactam			C	I	C		I		C	I	C		C		I	U
Tobramycin	U	U	C	C	C	I	C	C	C	C	C		C	I		C
Vancomycin	U	U	U	C	U	U	C	C	C	C	C	C	C	U	C	
Dextrose 5% in Water*	U	U	C	I	C	C	C	I	C	C	C	I		C	C	C
0.9% Sodium Chloride*	U	C	C	C	U	C	C	U	C	C	C	U		C	C	C
Lactated Ringer's	U	U	C	U		U	U		C		C	C	C	C	C	C

*Compatibility information derived from administration in solution, not Y-site

Reference: Trissel's 2 Clinical Pharmaceutics Database, accessed 6/6/2020

Created by Emily Kaip, PGY1 Pharmacy Resident

Questions? kendall.gross@ucsf.edu

C	Compatible
U	Uncertain or variable
I	Incompatible
	No data

Check your product for EDTA!



Solution to the Solution

BE CREATIVE & INDIVIDUALIZE

- ✓ Hold IVF until Antibiotics are done
 - ✓ Flush before and after
- ✓ Use separate line for IVF and Antibiotics
 - ✓ If available
- ✓ Choose Antibiotic based compatibility
- ✓ Choose NS over LR

Could we change our practice?

- ✓ IV Push for antibiotics



Effect of IV Push Antibiotic Administration on Antibiotic Therapy Delays in Sepsis

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Characteristics	Baseline Characteristics	
	IV Piggyback (n = 143)	IV Push (n = 131)
Age (yr), median (IQR)	63.5 (50.7–74.7)	61 (52–75)
Male gender, n (%)	65 (45.5)	51 (38.9)
Body mass index (kg/m ²), median (IQR)	25.7 (22.1–32.1)	25.8 (21.3–31.2)
Initial serum creatinine, median (IQR)	1.6 (1.1–2.3)	1.3 (0.9–2.1)
Acute kidney injury, n (%)	69 (48)	57 (44)
Initial lactic acid, median (IQR)	2.4 (1.6–3.7)	2.5 (1.5–4.1)

Patients who did not receive β-lactam		
Within 1 hr, n (%) ^a	82 (57.3)	58 (44.6)
Within 3 hr, n (%) ^a	35 (24.5)	10 (7.6)
Before transfer from ED, n (%)	12 (8.4)	3 (2.3)

Clinical outcomes		
Time to first β-lactam dose (min), median (IQR) ^a	72 (8–180)	48 (19–96)
Time to broad-spectrum regimen (min), median (IQR)	114 (42–282)	108 (66–144)

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Before transfer from ED, n (%)	12 (8.4)	3 (2.3)
Length of stay		
ED (hr), median (IQR)	8.0 (6.1–10.2)	7.5 (6–9.7)
ICU (d), median (IQR) ^a	4.5 (2–6)	2.3 (1.0–2.6)
Hospital (d), median (IQR)	10.4 (4.3–11.8)	9.1 (3.9–10.1)
Overall mortality, n (%)	14 (9.7)	16 (12.2)
Septic shock mortality, n (%)	11 (12.9)	13 (16)
Adverse events, n (%)	0 (0)	0 (0)

Evaluation of First-Dose, Intravenous Push Penicillins and Carbapenems in the Emergency Department

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Table 4. Percentage of Orders Meeting 60- or 180-Minute Time Goals[▽].

	Pre-intervention: IVPB N = 351	Post-intervention: IVP N = 345	P-value
ED arrival to administration, <60 min	42 (12)	70 (20)	<0.01
Ampicillin/sulbactam	10 (7)	25 (19)	<0.01
Piperacillin/tazobactam	28 (17)	39 (23)	NS
Ertapenem	4 (8)	6 (13)	NS
ED arrival to administration, <180 min	219 (62)	255 (75)	<0.01
Ampicillin/sulbactam	87 (64)	92 (72)	NS
Piperacillin/tazobactam	113 (68)	137 (81)	<0.01
Ertapenem	19 (40)	29 (62)	<0.01
Order to antibiotic administration, <60 min	219 (67)	296 (86)	<0.01
Ampicillin/sulbactam	99 (73)	112 (87)	<0.01
Piperacillin/tazobactam	114 (68)	145 (86)	<0.01
Ertapenem	23 (48)	39 (83)	<0.01

[▽]Number (%).

UW Medicine approach- OB sepsis

Situation:

We have two campuses with OB services, we want align antibiotic choices for sepsis



High rate of
MDROs

Montlake Campus
Pip-tazo
Fluids: NS



NW Campus
Amp-sulbactam
Fluids: LR





FRED HUTCHINSON CANCER RESEARCH CENTER / SEATTLE CANCER CARE ALLIANCE

Managing Sepsis in Adult BMT Patients in the SCCA Ambulatory Clinic

Allergies _____

MEDICATIONS: To be administered in: ☐ Infusion Room ☐ Triage

1. IV Fluids: Administer

☐ NS _____ ml at _____ ml/hr

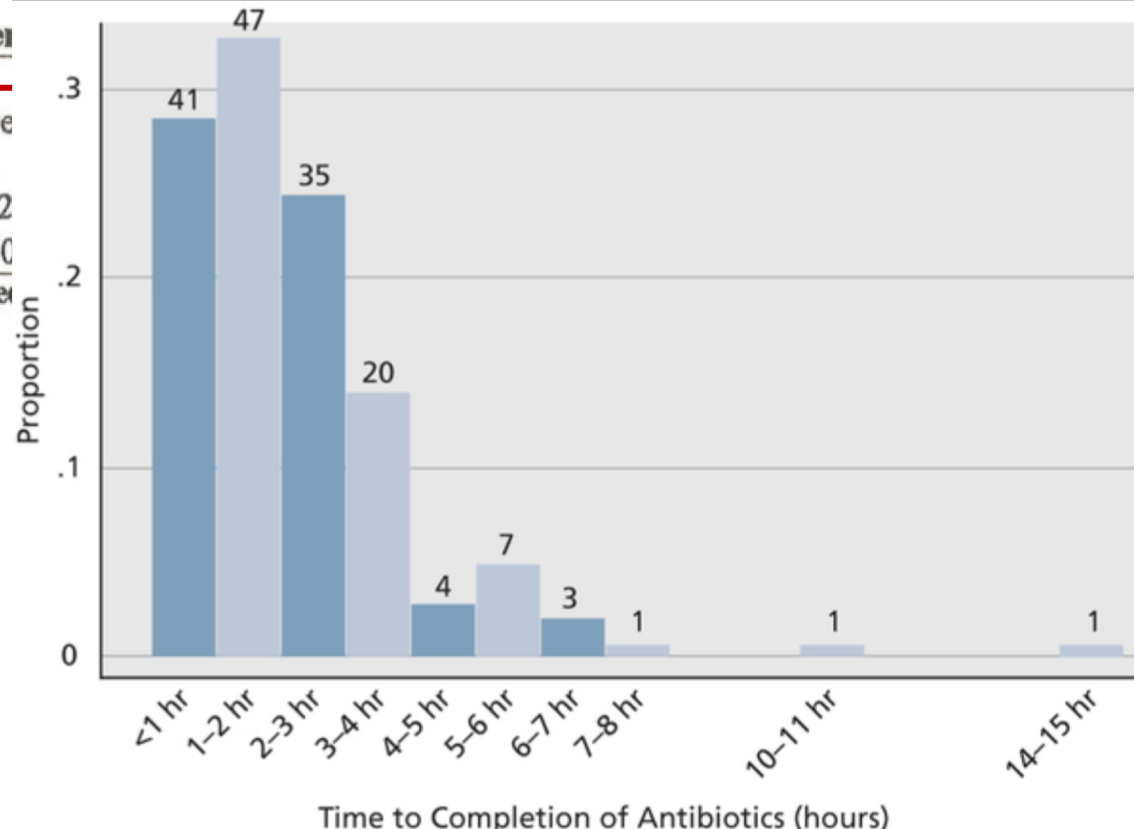
☐ Other _____ at _____ ml/hr

2. Antibiotic (Y-site compatible, administer

☐ **Adult Sepsis Protocol Standard***

- Meropenem 1000 mg IVPB STAT over minutes
- Tobramycin 160 mg IVP STAT over 2
- Linezolid 600 mg IVPB STAT over 30

*If these options are clinically contraindicated



Discussion



How is your site
approaching compatibility
issues for your septic
patients?

