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Antimicrobial Stewardship Strategies for Managing the Intravenous (IV) Fluid Shortage

On September 20th, 2017, Puerto Rico was devastated by Hurricane Maria, the strongest storm to make landfall in Puerto Rico in 85 years. The medical products industry has a significant presence in Puerto Rico, and the disruption to this industry has had ramifications on the island and throughout the U.S. Most significant to date, hospitals across the country are reporting shortages of intravenous fluids, particularly small volume parenteral (SVP) fluids such as 50 mL and 100 mL preparations.

The limited availability of these products has presented significant antibiotic administration challenges for stewardship programs in DASON hospitals. The goal of this newsletter is to review strategies to preserve SVP fluids as well as provide guidance on alternative antibiotic administration modalities.

General Recommendations

DASON encourages antimicrobial stewardship programs to consider implementing the following strategies to preserve SVP fluids:

1) Order premixed antibiotics or alternative formulations such as Baxter Mini-Bag-Plus from the manufacturer if they are available.
2) Screen all patients on IV antibiotics to ensure ongoing IV antibiotic treatment is needed. This review should consider opportunities to convert to an agent that can be administered via an alternative route, preferably **oral** when possible.
3) Increase staff awareness of the SVP fluid shortage with education for physicians, nurses, and pharmacists that encourages conserving IV fluids when possible.
4) Consider flushing IV medication lines with the patient's maintenance IV fluid if it is compatible with the patient's antibiotic therapy.

   When alternative agents are needed, use an agent with the same spectrum of activity whenever possible. Converting to drugs with a much broader spectrum during the shortage is discouraged. If broad spectrum drugs are needed, always include a plan for prompt review and de-escalation whenever possible.

Considerations for Alternative Administration

Beyond conservation, alternate administration strategies for antibiotics may be needed. These include converting agents to be given by intramuscular (IM) injection, as a slow IV push (IVP) over several minutes, or as a continuous infusion. There are several factors that go into assessing how to best implement these conversions. Several of these are discussed below:

1) Which antibiotics will our hospital administer by alternate routes?

Table 1 lists antibiotics that are often administered via rapid IV infusion. Hospitals may choose to begin by converting IV antibiotics that are prescribed in high volumes (e.g. cefazolin) or by targeting specific patient populations (e.g. patients receiving surgical prophylaxis).

2) When multiple options are available for an agent, how should I choose between IM, IVP, and continuous infusion?

It is important to consider several drug-specific factors in this decision including local availability of large volume parenteral fluids, pharmacodynamic properties, and compatibility with other potential medications and infusions required for the patient. For example, since β-lactam antibiotics have pharmacodynamic properties that are optimized with extended infusions, IV push of this class may not be appropriate in targeted patient populations such as the critically ill and those infected

FDA Suggestions for Management of SVP Solutions Shortage:
https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM582461.pdf

ISMP Safe Practice Guidelines:
http://www.ismp.org/Tools/guidelines/ivsummitpush/ivpushmedguidelines.pdf

with organisms that have a higher MIC if there are other options available for treating the patient.[1]

DASON endorses the ISMP Safe Practice Guidelines for Adult IV Push Medications.[2] These factors should be discussed with nursing as part of developing any IVP protocol.

3) Is there a medication that can easily be given as a rapid IV infusion that is an appropriate substitution for a medication that requires slow IV infusion?

Some agents are unsuitable for IVP administration due to the potential for adverse events, lack of evidence, reconstitution and administration requirements, and/or stability; however, there are multiple therapy interchanges that can be adopted to help hospitals conserve fluids. For example, cefazolin is a suitable alternative to penicillin and ampicillin for prophylaxis of Group B Streptococcus in OB patient, and hospitals can use cefepime instead of piperacillin/tazobactam to treat most *P. aeruginosa* infections.[3-6]

4) What is the best route of administration for an antibiotic based on stability?

Hospital pharmacies must determine their own best practices in terms of reconstitution, stability, and administration rates of antibiotic therapies. While this document provides data and references regarding stability for some products, hospitals should always review data for their specific products since multiple factors impact product stability, including: selected product, storage container, storage temperature, diluent, and final concentration. Reconstitution and stability information can typically be found in the drug's package insert and your DASON liaison clinical pharmacist can provide additional literature on this topic upon request.

Considerations for Continuous Infusion Antibiotics

Administering antibiotics by continuous infusion is a means of optimizing PK/PD properties of the drug; however, there are many logistical concerns that may need to be considered.[7]

1) Patients need continuous intravenous access when they are on continuous infusions.
2) Compatibility of the continuous infusion with co-administered drugs must be addressed.
3) Drug stability at room temperature must be considered. Keep in mind that refrigerated medications should be kept at room temperature for one hour prior to administration.
4) Drug waste is a concern when medications are reconstituted in larger volumes.
5) Dosing recommendations are based on clinical trials and may be validated in small patient populations with very specific indications.
6) The following guidance is to assist sites during the fluid shortage. If a more comprehensive continuous infusion protocol is desired, please work with your DASON liaison for additional development and implementation guidance.

Table 2 lists antibiotics that are suitable for extended- and/or continuous infusion for adults.

Please note the tables include are intended to provide guidance for adult patients only. For dosing in pediatric patients, refer to manufacturer labeling. Standardizing antibiotic dilution volumes and administration times of rapid IV infusion is a strategy to reduce medication errors. If possible, consider administering only medications with similar diluents, reconstitution volumes, and IV push rates to avoid errors.

Table 1. Rapid IV Infusion Antimicrobials for Adults

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Amikacin[8]	NOT RECOMMENDED	N/A	Yes	Although select clinical trials are available to support rapid IV infusion of aminoglycosides, IM route is preferred due to risk of toxicity. Injection site pain may occur.
Amphotericin B (all preparations)[8]	NOT RECOMMENDED	N/A	No	Infusion rates vary based on product selection.
Ampicillin[8-10]	NOT RECOMMENDED: 1 GM vial + 10 mL Sterile Water	10 minutes	Yes	Infusing ampicillin more rapidly than recommended may cause seizures (>100 mg/min). Ampicillin has limited stability once reconstituted. Consider administering on a syringe pump since it must be given over at least 10-20 minutes (>100 mg/min). Consider switching to oral option if appropriate.
	NOT RECOMMENDED: 2 GM vial + 20 mL Sterile Water	20 minutes		
Ampicillin/ Sulbactam[8,10,11]	NOT RECOMMENDED	N/A	Yes	Ampicillin/sulbactam has limited stability once reconstituted. Consider administering on a syringe pump since it should be given over at least 10-20 minutes (>100 mg/min). Consider switching to oral option if appropriate.
Azithromycin[8]	NOT RECOMMENDED	N/A	No	Consider switching to oral option if appropriate Should not be administered IM or as an IV bolus
Aztreonam[8,12-14]	1 GM vial + 10 mL Sterile Water 2 GM vial + 10 mL Sterile Water	3-5 minutes	Yes	May cause phlebitis/thrombophlebitis
Cefazolin[8,15,16]	1 GM vial + 10 mL Sterile Water	3-5 minutes	Yes	May cause thrombophlebitis or injection site pain. Diluted solution should be translucent and yellow.
Cefepime[8,12,17,18]	1 GM vial + 10 mL Sterile Water 2 GM vial + 20 mL Sterile Water	5 minutes	Yes	IV push administration may not optimize PK/PD, consider continuous infusion (see Table 2). May cause localized phlebitis.
Cefotaxime[8,10,19]	1 GM vial + 10 mL Sterile Water 2 GM vial + 10 mL Sterile Water	3-5 minutes	Yes	May cause injection site pain. There are post-marketing reports of a potentially life-threatening arrhythmia in 6 patients who each received a rapid bolus injection over < 1 minute.

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Cefotetan[8,10,20]	1 GM vial + 10 mL Sterile Water 2 GM vial + 20 mL Sterile Water	3-5 minutes	Yes	
Cefoxitin[8,10,21]	1 GM vial + 10 mL Sterile Water 2 GM vial + 10 mL Sterile Water	3-5 minutes	Yes	
Ceftaroline[8,22]	NOT RECOMMENDED	N/A	No	Ceftaroline 400 MG and 600 MG vials may be reconstituted in Sterile Water, but must be further diluted with ≥250 mL of appropriate diluent prior to administration. Administer as a slow IV infusion over 5-60 minutes.
Ceftazidime[8,12,23]	500 MG vial + 5.3 mL Sterile Water 1 GM vial + 10 mL Sterile Water 2 GM vial + 10 mL Sterile Water	3-5 minutes	Yes	Keep separate from aminoglycosides. Consider administration via continuous infusion (Table 2).
Ceftazidime/ avibactam[7,8]	NOT RECOMMENDED	N/A	No	Administer by intermittent infusion over 2 hours.
Ceftolozane/ tazobactam[7,8]	NOT RECOMMENDED	N/A	No	Pharmacodynamic data support administration by continuous infusion, but has not been studied compared with intermittent dosing. Administer by intermittent infusion over 60 minutes.
Ceftriaxone[8,25-27]	1 GM vial + 10 mL Sterile Water 2 GM vial + 20 mL Sterile Water **(see comments for adverse events with 2 GM dose)**	1-4 minutes	Yes	IV push administrations over 4 minutes in adults have been reported, primarily in patients outside the hospital. Administration of a 2 GM IV push dose over 5 minutes resulted in tachycardia, restlessness, diaphoresis, and palpitations in one patient.
Cefuroxime[8,10,29]	750 MG vial + 10 mL Sterile Water 1.5 GM vial + 20 mL Sterile Water	3-5 minutes	Yes	May cause local thrombophlebitis.
Chloramphenicol[8,10,30]	1 GM vial + 10 mL Sterile Water	>1 minute	No	IVP over > 1 minute at a concentration of 100 mg/mL. Do not administer IM.
Ciprofloxacin[8]	NOT RECOMMENDED	N/A	No	Administer by slow IV infusion over 60 minutes. Administer into a large vein to reduce the risk of irritation.
Clindamycin[8,31]	NOT RECOMMENDED	N/A	Yes	Clindamycin must be diluted to a final concentration of no more than 18 mg/mL and administered slowly at a rate not to exceed 30 mg/min. Consider switching to oral option if appropriate.

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Colistimethate sodium[8,32]	150 MG vial in 2 mL Sterile Water	3-5 minutes (50% of dose)	Yes	May inject 50% of total daily dose over 3-5 minutes q12h. Colistimethate sodium is associated with CNS toxicity, renal toxicity, and respiratory arrest. **Use this agent with caution in patients without other viable treatment options.** Potential for dosing errors due to lack of standardization in literature. Colistimethate and colistin base strengths are not interchangeable.
Dalbavancin[8]	NOT RECOMMENDED	N/A	No	Infuse over 30 minutes. Usual infusion concentration: 1-5 mg/mL.
Daptomycin[8,33]	500 MG vial + 10 mL Normal Saline	2 minutes	No	Injection site pain/rash may occur. Pay attention to diluent.
Daptomycin RF[8,34]	500 MG vial + 10 mL Sterile Water	2 minutes	No	Injection site pain/rash may occur Pay attention to diluent.
Doripenem[8]	NOT RECOMMENDED	N/A	No	Infuse over 1 hour.
Doxycycline[8]	NOT RECOMMENDED	N/A	No	Consider switching to oral option if appropriate. Prolonged IV administration may lead to thrombophlebitis.
Ertapenem[8,35,36]	1 GM vial + 10 mL Normal Saline	5 minutes	Yes	May cause phlebitis/thrombophlebitis. Pay attention to diluent.
Fluconazole[8]	NOT RECOMMENDED	N/A	No	Consider switching to oral option if appropriate. May be administered IV over ~1-2 hours at a rate not to exceed 200 mg/hr.
Gentamicin[8,37,38]	NOT RECOMMENDED	N/A	Yes	Although select clinical trials are available to support rapid IV infusion of aminoglycosides, IM route is preferred due to risk of toxicity. Injection site pain may occur.
Imipenem/ cilastatin[8]	NOT RECOMMENDED	N/A	No	Do not administer as IV push or bolus injection.
Isavuconazole[8]	NOT RECOMMENDED	N/A	No	Infuse over a minimum of 1 hour via an infusion set with a 0.2-1.2 micron in-line filter. Do not administer as an IV bolus injection.

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Levofloxacin[8]	NOT RECOMMENDED	N/A	No	Infuse 250-500 MG doses over 60 minutes and infuse 750 mg IV solution over 90 minutes. May cause hypotension if infused too rapidly.
Linezolid[8]	NOT RECOMMENDED	N/A	No	Linezolid IV is available as a pre-mixed solution from the manufacturer.
Meropenem[8,12,40-42]	500 mg vial + 10 mL Sterile Water 1 GM vial + 20 mL Sterile Water	3-5 minutes	No	May cause phlebitis/thrombophlebitis. Final concentration must be 50 mg/mL. May be administered via continuous infusion (see Table 2).
Metronidazole[8]	NOT RECOMMENDED	N/A	No	Administer over 30-60 minutes. Avoid contact of drug solution with aluminum equipment.
Micafungin[8]	NOT RECOMMENDED	N/A	No	Administer over 1 hour.
Moxifloxacin[8]	NOT RECOMMENDED	N/A	No	Administer over 60 minutes. Do not administer as a rapid or bolus infusion.
Nafcillin[8,10,43]	NOT RECOMMENDED: 1 GM + 25 mL Normal Saline	10 minutes **(central line only)**	Yes	Limited data support rapid IV administration of nafcillin. Administration via continuous infusion is preferred (see Table 2) Administer IV push through **central venous catheter only**.
Oritavancin[8]	NOT RECOMMENDED	N/A	No	Infuse over 3 hours.
Oxacillin[8,10,44]	NOT RECOMMENDED: 1 GM + 10 mL Sterile Water 2 GM + 20 mL Sterile Water	10 minutes	Yes	Administration via continuous infusion is preferred (see Table 2)
Penicillin G Potassium[8,45]	NOT RECOMMENDED	N/A	Yes	Potassium salts may cause cardiac issues with rapid administrations, so give these agents as an IV infusion. Up to 100,000 units of penicillin per mL of diluent may be administered IM with minimum discomfort. When large doses are required, the aqueous dose is preferable. 20 million Unit dosage form may be administered by IV infusion ONLY.

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Penicillin G Sodium[8,46]	NOT RECOMMENDED	N/A	Yes	The 10-million-unit preparation should be administered by IV infusion. Intramuscular doses of 100,000 units of penicillin per mL of diluent will produce minimum discomfort. The administered IM volume should not exceed 4 mL per single site of administration. Doses up to 500,000 units per mL have been administered IM.
Piperacillin/ tazobactam[1,8,47]	NOT RECOMMENDED	N/A	No	IM administration data has been recorded for piperacillin alone, which is not available in the United States. May be administered via continuous infusion (see Table 2)
Polymyxin B[8]	NOT RECOMMENDED	N/A	Yes	This drug may cause neurotoxicity and nephrotoxicity and patients are at increased risk when they are on other agents that cause neurotoxicity or nephrotoxicity. Respiratory paralysis and neuromuscular blockade can occur, especially when this drug is given soon after anesthesia or muscle relaxants. The IM route is not typically recommended due to severe pain at the injection site.
Posaconazole[8]	NOT RECOMMENDED	N/A	No	Infuse over 90 minutes through a central line. Do not administer as an IV push or bolus.
Rifampin[8]	NOT RECOMMENDED	N/A	No	Do not administer IM or subcutaneously. Avoid extravasation. Administer by slow IV infusion over 30 minutes to 3 hours at a final concentration ≤6 mg/mL.
Tedizolid[8]	NOT RECOMMENDED	N/A	No	Administer over 1 hour. Do not administer as an IV push or bolus.
Televancin[8]	NOT RECOMMENDED	N/A	No	Review boxed warning. Administer as IV infusion over 60 minutes.
Tigecycline[8]	NOT RECOMMENDED	N/A	No	This drug should be reserved for situations when alternative treatments are not appropriate. Administer as IV infusion over 30-60 minutes

Medication	Reconstitution for Rapid IV Administration*	IV Push Rate	IM option	Comments*
Tobramycin[39]	NOT RECOMMENDED	N/A	Yes	Although select clinical trials are available to support rapid IV infusion of aminoglycosides, IM route is preferred due to risk of toxicity. Vestibular toxicity and some hearing loss was noted in one patient 16 h after her last dose of 320 mg tobramycin in Loewenthal et al.[38]
Trimethoprim/ Sulfamethoxazole[8]	NOT RECOMMENDED	N/A	No	Infused diluted solution over 60-90 minutes Do not administer as an IM injection
Vancomycin[8,48,49]	NOT RECOMMENDED	N/A	No	Oral vancomycin should not be used for systemic infections. Consider switching patients to the premixed IV or oral linezolid, if appropriate. Extended infusion may be an option (see Table 2) Irritant, avoid extravasation. Vancomycin should be administered with a final concentration ≤5 mg/mL by intermittent IV infusion over at least 60 minutes (recommended infusion time of ≥30 minutes for each 500mg administered). In fluid-restricted adult patients, a concentration up to 10 mg/mL may be used; however, this increases the risk of infusion-related reactions.
Voriconazole[8]	NOT RECOMMENDED	N/A	No	Administer as an IV infusion over 1-2 hours. Do not administer as an IV bolus injection.

* Hospitals should always review reconstitution and stability data for their specific products since multiple factors impact product stability, including: selected product, storage container, storage temperature, diluent, and final concentration since these will all impact the stability of the final preparation.

Table 2. Agents Suitable for Extended and/or Continuous IV Infusion for Adults

Medication	Creatinine Clearance	Dose and Interval	Expected Stability at Room Temperature**	Comments**
Cefepime[8,50-53]	>50 mL/min	2 GM IV q8h over 4 hours	Suggest changing infusion at least q12h	Studied reconstitutions: (1) Cefepime 4 GM or 3 GM in 1 L of 5% dextrose in water administered over 24 hours.[53] Many centers administer a single 2g bolus dose over 30 minutes as part of this regimen, which may not be feasible during the shortage.
	30-49 mL/min	2 GM IV q12h over 4 hours		
	15-29 mL/min or hemodialysis	1 GM q12h over 4 hours		
	< 15 mL/min or hemodialysis	1 GM IV q24h over 4 hours (dose after HD)		
Ceftazidime[8]	>50 mL/min	2 GM IV q8h over 8 hours	Suggested changing infusion at least q8h	Limited data are available to support this practice and evidence is primarily in patients with cystic fibrosis. Studies to inform optimal dosing are limited. May be given as a rapid IV infusion. Many centers administer a single 2g bolus dose over 30 minutes as part of this regimen, which may not be feasible during the shortage.
	30-50 mL/min	2 GM IV q12h over 8 hours		
	<30 mL/min or hemodialysis	Intermittent dose recommended		
Nafcillin[8,43]	No adjustment needed, use with caution in patients with concomitant hepatic impairment.[54,55]	6 GM IV q12h over 12 hours	Stable for up to 24 hours	High-dose nafcillin has been reported to decrease the effects of warfarin. Nafcillin is a vesicant. Ensure proper needle or catheter placement prior to and during IV infusion to avoid extravasation. If extravasation occurs, stop the infusion, gently aspirate the extravasated solution, initiate hyaluronidase antidote, remove needle/cannula (if not using hyaluronidase antidote), and apply cold, dry compresses, and elevate extremity.[56]

Oxacillin[8,44,58]	No adjustment available in manufacturer labeling; however, the manufacturer suggests that a lower total dose may be necessary in known or suspected renal impairment.	6 GM IV q12h over 12 hours	Stable for up to 24 hours	Continuous infusion of oxacillin was compared to intermittent infusion of oxacillin in a study of patients with *S. aureus* endocarditis. Continuous infusion was associated with greater microbiologic cure; however, clinical cure was not evaluated.
Piperacillin/ tazobactam (PTZ)[1,8,47,59]	>40 mL/min	3.375 GM IV q4h over 4 hours	Stable for up to 24 hours	Many centers administer a single 3.375 g bolus dose over 30 minutes as part of this regimen, which may not be feasible during the shortage. Grant et. al. determined that continuous infusion (CI) PTZ provided similar clinical and microbiologic outcomes to intermittent infusion. The study used PTZ 2.25 GM IV loading dose over 30 minutes, followed by: CrCl >40 mL/min: 12/1.5 GM IV in 150 mL normal saline at 7 mL/hr CrCl =20=40 mL/min: 8/1 GM in 150 mL normal saline at 7 mL/hr[46] Lau et. al. found that PTZ 12/1.5 GM administered continuously over 24 hours is a safe and reasonable alternative for the treatment of intra-abdominal infections.[1] A study by Lorente et. al. concluded the CI PTZ may be more effective than intermittent dosing for VAP with organism with MICs of 8-16 µg/mL in patients without renal failure. The dose of PTZ used was: PTZ 4/0.5g loading dose over 30 minutes, followed by 4/0.5 g infused over 360 minutes every 6 hours. The dose was diluted in 100 mL of 0.9% NaCl.[58]
	21-40 mL/min	3.375 GM IV q6h over 6 hours		
	≤20 mL/min or hemodialysis	3.375 GM IV q12h over 4 hours		

Meropenem[8,50,60-66]	>50 mL/min	2 GM IV q8h over 3 hours	Stable for up to 4 hours (see comments)	Data from Patel 1997 support the stability of meropenem (admixed with NS at a concentration of 20 mg/mL) at room temperature for ≤4 hours and under refrigeration for ≤24 hours. The manufacturer does not support stability at this concentration at room temperature for >1 hour or under refrigeration for >15 hours.[61]
	25-49 mL/min	2 GM IV q12h over 3 hours		
	10-24 mL/min	1 GM IV q12h over 3 hours		
	<10 mL/min or hemodialysis	1 GM IV q24h over 3 hours (give after HD)		
Vancomycin[8,48,49]	Normal renal function	15 mg/kg q12h	--	Vancomycin has pharmacodynamic characteristics that make continuous infusion attractive; however, there is literature suggesting that conventional regimens are equally effective. Irritant, avoid extravasation Vancomycin should be administered with a final concentration ≤5 mg/mL by intermittent IV infusion over at least 60 minutes (recommended infusion time of ≥30 minutes for each 500mg administered). In fluid-restricted adult patients, a concentration up to 10 mg/mL may be used; however, this increases the risk of infusion-related reactions.

** Hospitals should **always** review reconstitution and stability data for their specific products since multiple factors impact product stability, including: selected product, storage container, storage temperature, diluent, and final concentration since these will all impact the stability of the final preparation.

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