sefh
Sociedad Española
de Farmacia Hospitalaria

POSTMIDYEAR

15
febrero
2023

ASHP

More than a meeting

POSTMIDYEAR

ASHP

More than a meeting

15 febrero 2023

sefh Sociedad Española de Farmacia Hospitalaria

MÁS FARMACOTERAPIA

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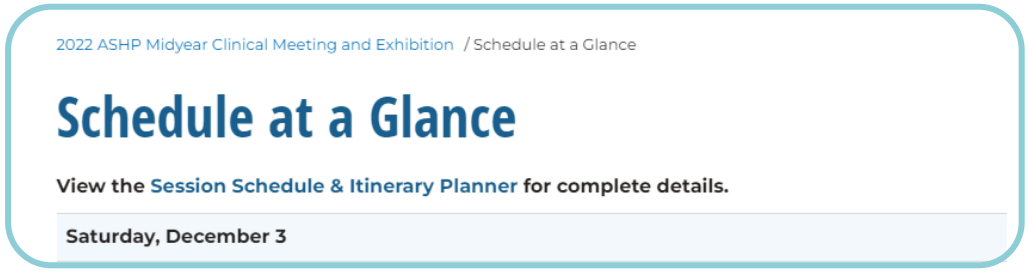
Servicio de Farmacia

Hospital General Universitario Gregorio Marañón

1. Anemia en la enfermedad renal crónica
2. Alergias a β-lactámicos
3. Perlas en Oncología
4. Anticoagulación y sangrados

1. Anemia en la enfermedad renal crónica



2022 ASHP Midyear Clinical Meeting and Exhibition / Schedule at a Glance

Schedule at a Glance

View the Session Schedule & Itinerary Planner for complete details.

Saturday, December 3

Novel Strategies for Managing Patients With CKD-Associated Anemia: What Do Health-System Pharmacists Need to Know About HIF-PH Inhibitors?

Let's Iron It Out: Updates for Anemia in Chronic Kidney Disease

IV Iron Replacement Therapy to Mitigate the Burden of IDA: Updates for Health System Pharmacists

Exploring the Efficacy and Safety of Iron Replacement Therapies for the Treatment of Iron Deficiency Anemia in Chronic Kidney Disease

- ✓Disminuye la calidad de vida
- ✓Aumenta la morbimortalidad
- ✓Aumenta la progresión de la ERC

1. Anemia en la enfermedad renal crónica

Cambios en el manejo de la anemia

"WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

- Chronic Kidney Disease:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL [see Warnings and Precautions (5.1)].
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks [see Dosage and Administration (2.2)].
- Use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions [see Warnings and Precautions (5.1)]."

Dosis dependiente

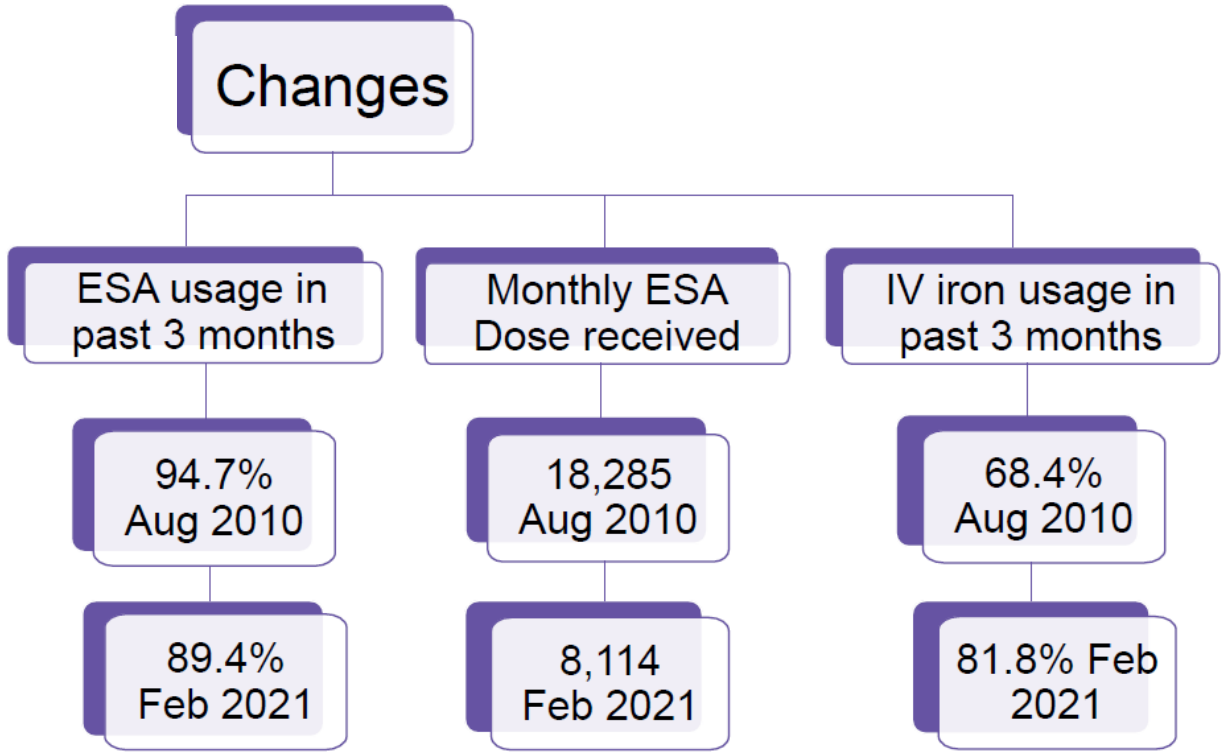
Pacientes Hiporespondedores

- No aumento de Hb tras 1 mes con ESA
- Dosis estable de ESA: necesidad posterior de aumentar 50% de la dosis

ESA: Agentes estimulantes de la eritropoyetina

1. Anemia en la enfermedad renal crónica

2009 ⇨ 2022



Reservas de hierro adecuadas

⇩

Menos dosis de ESA

ESA: Agentes estimulantes de la eritropoyetina

DOPPS Practice Monitor https://www.dopps.org/DPM-HD/DPMSlideBrowser.aspx?type=Topic&id=1 Accessed Oct 2 2022

1. Anemia en la enfermedad renal crónica

¿Cuándo tratamos con Hierro?

Guideline	Treat when…		
	TSAT		Ferritin
KDIGO 2012	< 30%	AND	<= 500 mcg/L
Europe (ERPB) 2013	< 20% OR *increase Hgb without ESA* < 25%	AND AND	< 100 mcg/L (absolute) < 200 mcg/L (300 D)
Canada (CSN) 2013	< 20%	AND	> 200 mcg/L (100
British RA 2017	*Iron replete when* > 20%	AND	> 100 mcg/L

¿Con qué Hierro tratamos?

Product	Elemental iron	Unique attributes
Ferrous sulfate	65 mg/tablet	Over the counter (OTC)
Ferrous fumarate	106mg/tablet	OTC
Ferrous gluconate	27-38 mg/tablet	OTC
Polysaccharide iron-complex	50-200 mg/tablet	More difficult to find, often combined with other vitamins/minerals
Ferric citrate	210 mg/tablet	Prescription Phosphate binder for CKD-D
Ferric maltol	30 mg/capsule	Prescription Higher bioavailability

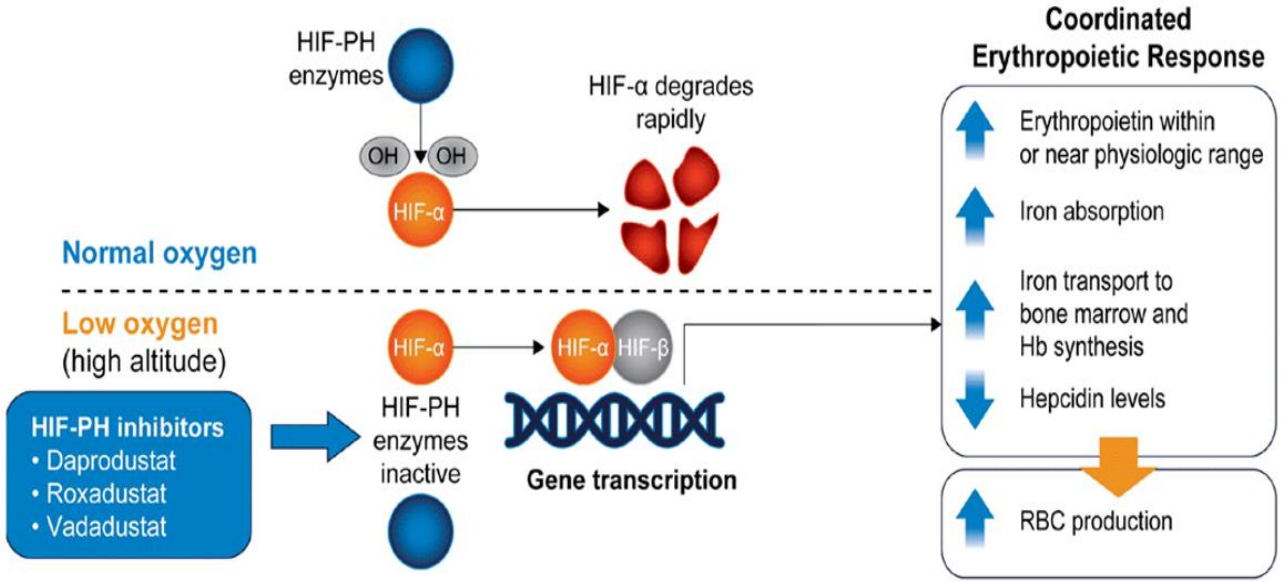
SE RECOMIENDA NO INICIAR NUEVOS TRATAMIENTOS CON ▼MONOFERRO® (HIERRO-ISOMALTÓSIDO) DEBIDO AL RIESGO DE REACCIONES GRAVES DE HIPERSENSIBILIDAD

Fecha de publicación: 19 de julio de 2017

Ferric carboxymaltose	750 mg x 2	Give doses at least 7 days apart Can alter MRI studies for up to 3 months
Ferric derisomaltose	1000 mg x 1 500 mg x 3	If multiple doses, give over 7 days
Ferris pyrophosphate citrate	1 packet in every 25 gallons of bicarbonate concentrate	For patients on dialysis only – administered through dialysate No iron sequestration

1. Anemia en la enfermedad renal crónica

Nuevos Tratamientos: HIF-PHI



Roxadustat[1-3]

- NDA rejected by the FDA on August 11, 2021 because of safety concerns
- NDA approved by EMA 2021
- App Japa Kore

Vadadustat[4,5]

- NDA rejected by the FDA on March 29, 2022 because of safety concerns
- Undergoing EMA

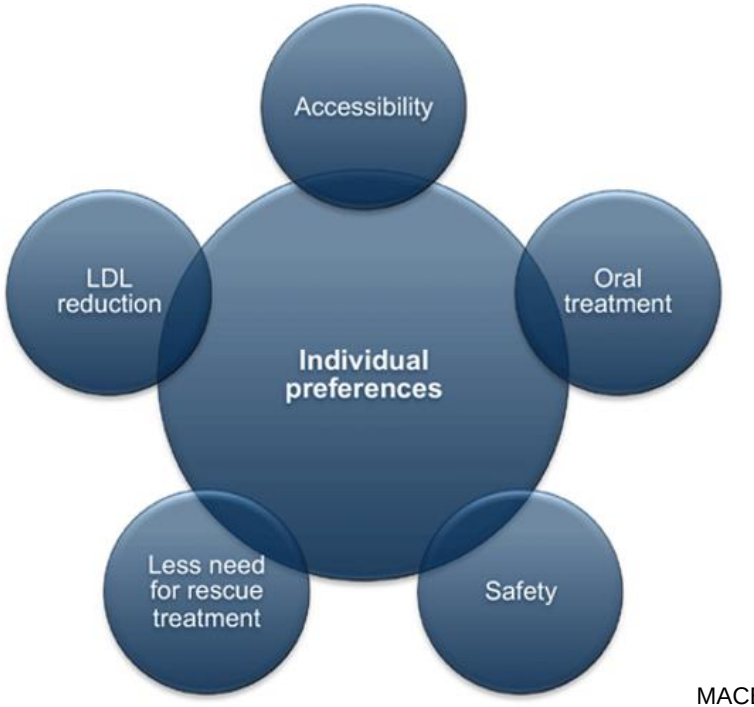
Daprodustat[6]

- FDA CRDAC held on October 26, 2022; recommended 13-3 for approval in DD-CKD and 11-5

New Drug Application (**NDA**)

1. Anemia en la enfermedad renal crónica

- ✓Superioridad frente a placebo y no inferioridad frente AEE
- ✓Mantenimiento de los niveles de Hb cuando se hace switch desde AEE
- ✓EA: Hipertensión, eventos tromboembólicos, infecciones, MACE



Long-Term Safety Questions

- Theoretical oncogenic risk
- Predisposition to pulmonary arterial hypertension and thromboembolic disease
- Increased angiogenesis → diabetic retinopathy
- Increased CKD progression
- Increased cyst size in polycystic kidney disease patients
- Metabolic effects: hyperglycemia, hyperuricemia, hyperkalemia

MACE: major adverse cardiovascular event

2. Alergias a β-lactámicos

90% de los pacientes que refieren alergia a penicilinas

Implicaciones

- Aumento de efectos adversos
- Aumento de la estancia hospitalaria
- Mayor uso de antibióticos de amplio espectro
- Desarrollo de infecciones multirresistentes
- Aumento del gasto farmacéutico

2. Alergias a β-lactámicos

Penicillin Allergy Evaluation

Patient/Room #: _____

Preliminary (Assess Health Record)

- PCN allergy - What specific agent did the patient take? How long ago? What was their reaction?

_____

_____

□ Yes □ No: Patient has documented PCN/Cephalosporins taken during prior visits

- If yes, _____

Does patient have pharmacy on file: _____ Phone: _____

Talk to patient

- Ask which PCN they remember taking. How long ago was it?

_____

- Ask, in detail: What was their reaction?
  - □ Rash □ Hives □ Anaphylaxis □ Patient was hospitalized
  - Localized or full body? _____
  - □ Other: _____

□ Yes □ No: Reaction >10 years ago

□ Yes □ No: Patient has had an episode of anaphylaxis within the last month

□ Yes □ No: Patient recalls taking other PCN/Cephalosporins

- Ask about common brand/generics (Keflex, Amoxicillin, Augmentin, etc.)
- If yes, which med? When? Any reaction? _____

_____

Assess if Patient is candidate for intervention

- Can allergy be removed (i.e. adverse reaction)?
  - □ Yes □ No
- Is patient candidate for re-challenge or graded challenge?
  - □ Yes □ No _____
- Is patient candidate for penicillin skin test (PST)?
  - □ Yes □ No: Patient is willing to do PST _____
  - If yes, determine a proper timing for the test: _____

Post-Intervention

- Educate patient if allergy removed
  - Ensure allergy field updated in medical record
  - Answer applicable questions and give handout or wallet card (PST)
  - Encourage patient to inform their PCP, dentist, pharmacist, etc.

Evaluación de la alergia

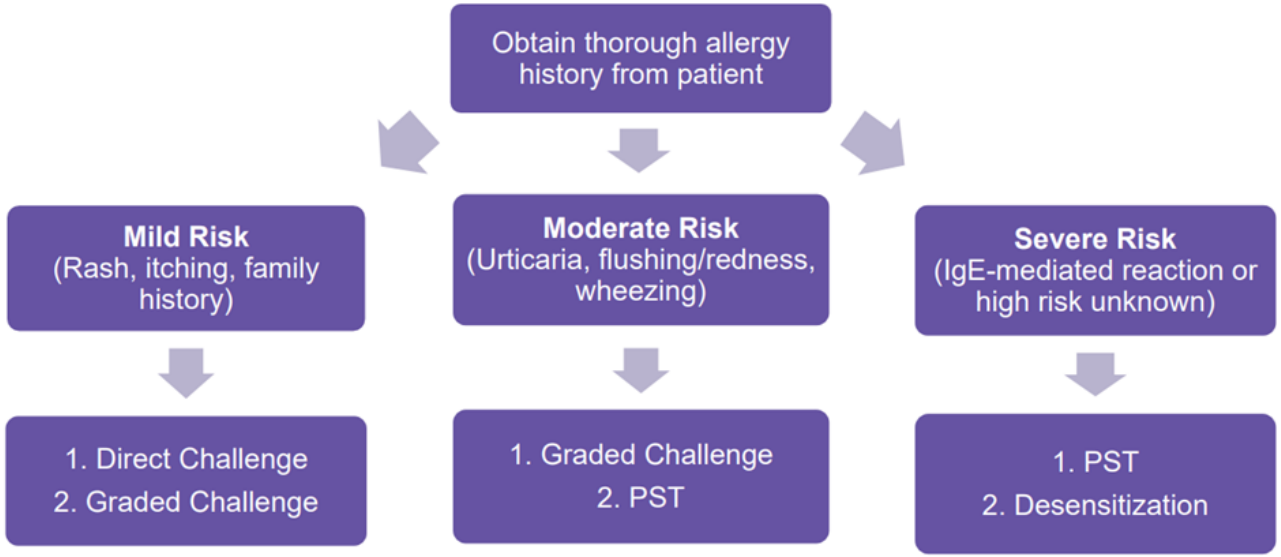
- ✓Estandarizada
- ✓Educación al paciente
- ✓Desetiquetado

Interventions	As of 9/1/22
Verbal	655
Re-Challenge	18
Graded Challenge	16
Penicillin Skin Testing	23
Desensitization	1
Allergy Removal	194

2. Alergias a β-lactámicos

Clinical Decision Support – Penicillin Allergy

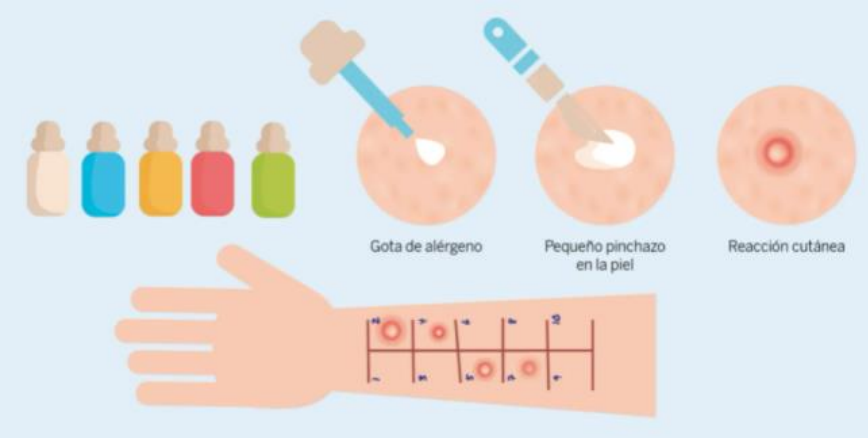
- PEN-FAST – validated tool to help identify low-risk penicillin allergies that do not require PST
- PEN = subjective penicillin allergy
- F = ≤5 years since reaction
- A = Anaphylaxis/angioedema
- S = Severe cutaneous reaction
- T = Treatment required secondary to reaction
- Score of <3 associated with low risk patient



PST = Penicillin Skin Test

Curr Treat Options Infect Dis 2019 June, Vol. 11, Issue 2:103-114.

2. Alergias a β-lactámicos



Penicillin Skin Testing - IDSA Guidelines

XII. In Patients With a Reported History of ß-Lactam Allergy, Should ASPs Facilitate Initiatives to Implement Allergy Assessments With the Goal of Improved Use of Frst-Line Antibiotics?

Recommendation

13. In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and penicillin (PCN) skin testing when appropriate *(weak recommendation, low-quality evidence)*.

Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should promote such assessments with providers. In facilities with appropriate resources for skin testing, the ASPs should actively work to develop testing and treatment strategies with allergists.

Barlam TF, et al. *Clin Infect Dis* 2016;62:e51-77.

Pharmacists and PST: State Laws

- Varies tremendously state by state
- Recent survey showed only 19 out of 50 were definitive “Yes”
- Lots of “maybes”
- 16 states did not respond despite multiple efforts to contact via phone or email
- Interesting considering vaccination allowed in all 50 states plus D.C.

2. Alergias a β-lactámicos

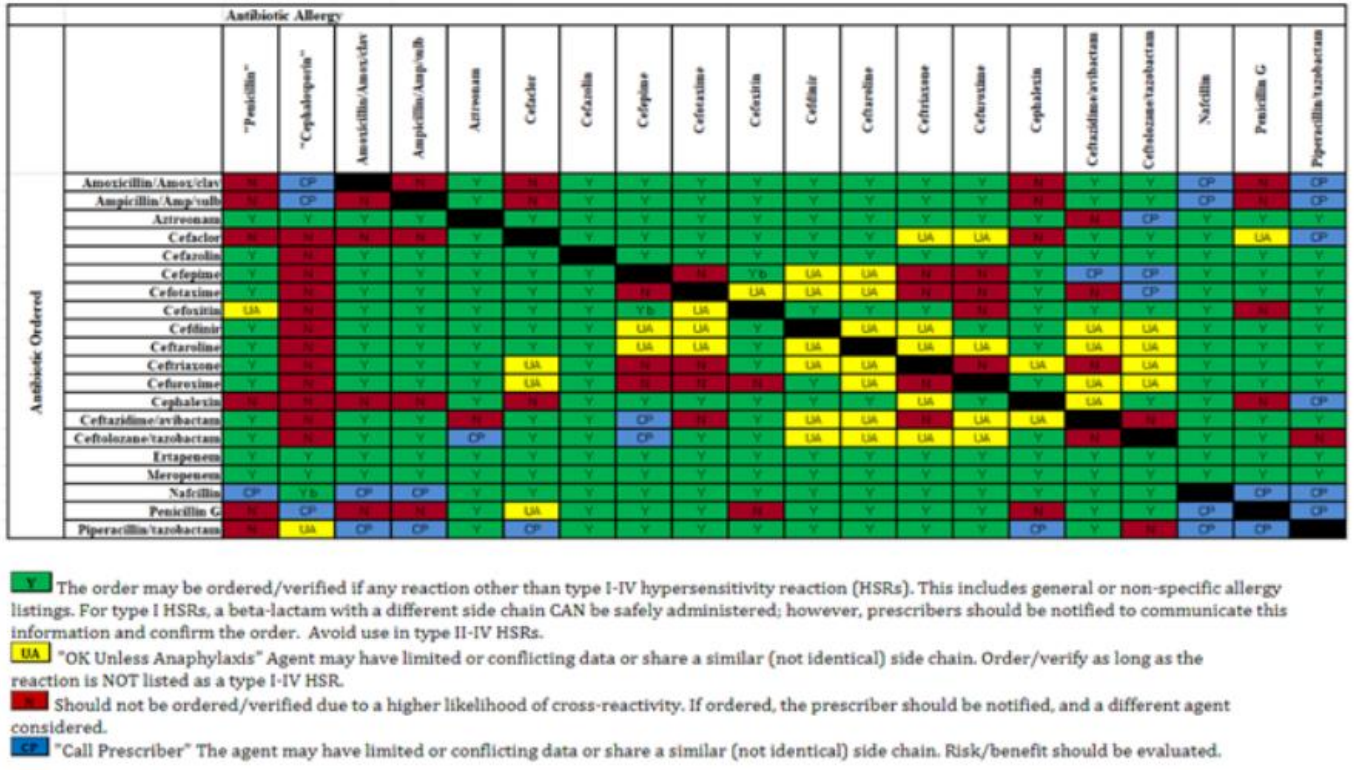
Evaluación de la reactividad cruzada

¿QUÉ β-LACTÁMICO FUE EL RESPOSABLE?

Los β-lactámicos con cadenas laterales del grupo R1 diferentes se asoc una baja reactividad cruzad

La **cefazolina** no comparte cadena lateral con ninguna otr penicilina o cefalosporina.

La **ceftazidima** comparte un cadena lateral común con el **aztreonam**



Y The order may be ordered/verified if any reaction other than type I-IV hypersensitivity reaction (HSRs). This includes general or non-specific allergy listings. For type I HSRs, a beta-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.

2. Alergias a β-lactámicos

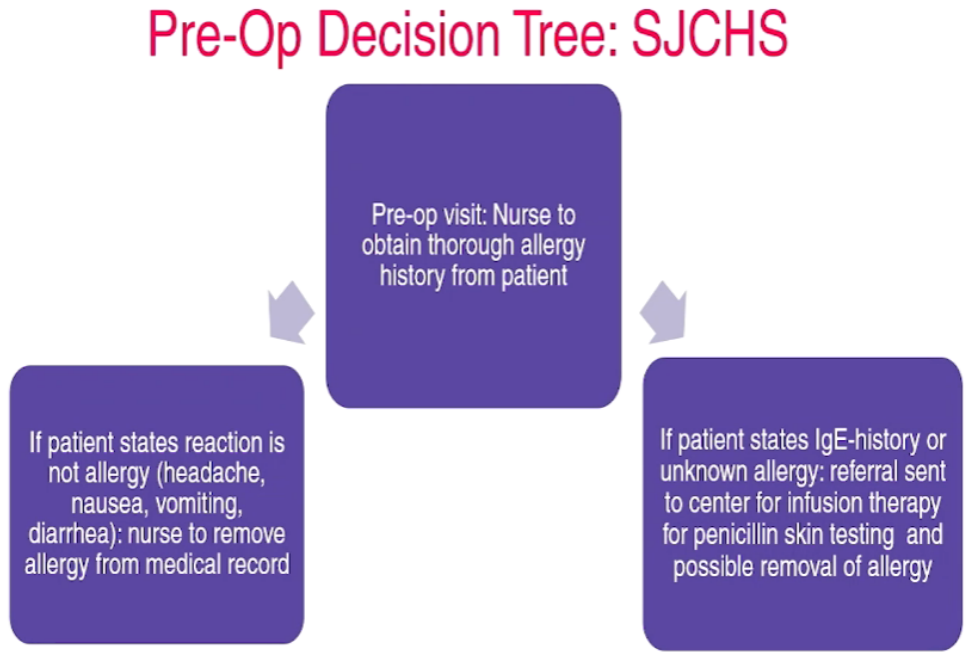
Profilaxis quirúrgica: **TODOS LOS PACIENTES RECIBEN CEFAZOLINA**

* Excepto los que refieren alergia a penicilina

Surgical patients at UCHealth	Antibiotic prophylaxis	Immediate hypersensitivity
Labeled as allergic to penicillin	Cefazolin	1.7% (6/350)
	Clindamycin	2.4% (7/295)
n=734	Vancomycin	2.2% (2/89)

Vancouver General Hospital	Pre-policy HSR	Post-policy HSR
Policy change: cefazolin for all (minus PCN allergy with SJS/TEN, DRESS)	Cefazolin: 3/77 Clindamycin: 2/63 Vancomycin: 1/33	Penicillin allergy hx Cefazolin: 0/62 No allergy hx Cefazolin: 3/1386
	No life threatening HSR	All delayed HSR

PCN = penicillin, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug rash with eosinophilia and systemic symptoms



Kuruvilla MK, Sexton M, Wiley Z, et al. A Streamlined Approach to Optimize Perioperative Antibiotic Prophylaxis in the Setting of Penicillin Allergy Labels. *J Allergy Clin Immunol Pract.* Vol 8 (4): 1316-1322.

3. Perlas en Oncología

CARDIO-ONCOLOGIA: un campo en constante evolución

- Patients with both cardiovascular disease and cancer are exposed to complex medication regimens
- Drug interactions are possibly under-recognized or not discovered until widespread use after market approval
- Medications tend to have:
  - Narrow therapeutic indexes
  - Steep dose-toxicity curves
  - Complex pharmacologic profiles
  - Intra- and inter-patient variability

AHA Scientific Statement

Beavers CJ, Rodgers JE, Bagnola AJ, et al. Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association. *Circulation*. 2022; 145(15): e811-e838.

3. Perlas en Oncología

❑Interacciones farmacodinamicas

Hipertensión: Antihypertensives & VEGF Inhibitors

VEGF Tyrosine Kinase Inhibitors
Pazopanib (Votrient®)
Sunitinib (Sutent®)
Sorafenib (Nexavar®)
Regorafenib (Stivarga®)
Cabozantinib (Cabometyx®)
Lenvatinib (Lenvima®)
Axitinib (Inlyta®)

Anti-VEGF Monoclonal Antibodies
Bevacizumab (Avastin®)
Ramucirumab (Cyramza®)

VEGF Decoy Receptor
Ziv-aflibercept (Zaltrap®)

- VEGF inhibitors: 21-40% hypertension incidence, due to:
  - Vascular regression
  - Vasoconstriction
  - Renal parenchymal effect
- Management:
  - Close blood pressure monitoring
  - ACE inhibitor or ARB (first-line), CCB (second-line)

Sangrado: Anticoagulants/Antiplatelets & Bruton Tyrosine Kinase Inhibitors

Bruton Tyrosine Kinase Inhibitors (BTKs)
Ibrutinib (Imbruvica®)
Acalabrutinib (Calquence®)
Zanubrutinib (Brukinsa®)

- Off-target inhibition of Src alters platelet adhesion with ibrutinib:
  - **39%** incidence of any bleeding
  - **4.2%** incidence of major hemorrhage
- Newer generation BTK inhibitors (acalabrutinib and zanubrutinib) confer a lower bleeding risk

Prolongación QTc: Antiarrhythmics & Tyrosine Kinase Inhibitors (TKIs)

Vandetinib (Caprelsa®)
Black Box Warning: TdP & Sudden Death
EGFR/VEGF inhibitor - Medullary Thyroid Cancer

Nilotinib (Tasigna®)
Black Box Warning: TdP & Sudden Death
BCR-ABL inhibitor - Chronic Myeloid Leukemia

Lapatinib (Tykerb®)
HER2/EGFR inhibitor - HER2+ Breast Cancer

Ribociclib (Kisqali®)
CDK4/6 inhibitor - HR+/HER2- Breast Cancer

Pazopanib (Votrient®)
VEGF inhibitor - Renal Cell Carcinoma

Crizotinib (Xalkori®)
ALK inhibitor - ALKm+ Non-Small Cell Lung Cancer

Vemurafenib (Zelboraf®)
BRAF inhibitor - BRAFm+ Melanoma

Trombosis: Anticoagulants/Antiplatelets & Immunomodulatory Agents (IMiDs)

- High VTE risk with IMiD therapy, which will antagonize anticoagulant or antiplatelet therapy
- SAVED Score: risk stratification for thrombosis on IMiD therapy
- VTE prophylaxis with IMiDs recommended for SAVED Score ≥ 2:
  - Enoxaparin 40 mg subcutaneously daily
  - Rivaroxaban 10 mg daily
  - Apixaban 2.5 mg orally daily
  - Fondaparinux 2.5 mg subcutaneously daily
  - Warfarin (target INR 2.0-3.0)

Immunomodulatory Agents (IMiDs)
Lenalidomide (Revlimid®)
Thalidomide (Thalomid®)
Pomalidomide (Pomalyst®)

"SAVED" Variable	Points
Surgery within 90 days	+2
Asian race	-3
VTE history	+3
Age ≥ 80 years	+1
Dexamethasone 120-160 mg/cycle	+1
Dexamethasone > 160 mg/cycle	+2

3. Perlas en Oncología

❑Interacciones farmacocinéticas

CYP3A4: Anticoagulants/Antiplatelets + Apalutamide (Erleada®) or Enzalutamide (Xtandi®)

- **Antiplatelet interactions**:
  - SIGNIFICANT reduction in antiplatelet effect of **ticagrelor**: **AVOID**
  - *Can* cautiously consider **clopidogrel** or **prasugrel**
- **Anticoagulant interactions**:
  - SIGNIFICANT reduction in anticoagulant effect of **rivaroxaban** or **apixaban**: **CONSIDER ALTERNATE THERAPY**
  - *Can* consider **edoxaban** or **dabigatran**
  - Expect **warfarin** dosing requirements to increase by 50%
- Darolutamide (Nubeqa®) does not inhibit CYP3A4

CYP3A4: HMG-CoA Reductase Inhibitors + ALK Inhibitors

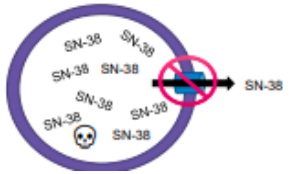
- ALK inhibitors have variable effects on CYP3A4:
  - Ceritinib (Zykadia®) and crizotinib (Xalkori®) are CYP3A4 inhibitors
  - Brigatinib (Alunbrig®) and lorlatinib (Lorbrena®) are CYP3A4 inducers
  - Alectinib (Alcensa®) does not affect CYP3A4 metabolism

AVOID CYP3A4 Statins:	Prefer Non-CYP3A4 Statins:
Atorvastatin	Pravastatin
Lovastatin	Rosuvastatin
Simvastatin	Fluvastatin

ALK: anaplastic lymphoma kinase

Glicoproteína-P Calcium Channel Blockers + Irinotecan (Camptosar®, Onivyde®) or Sacituzumab govitecan (Trodelvy®)

- Verapamil, diltiazem, and nicardipine inhibit P-glycoprotein
- SN-38 active metabolite accumulates; severe neutropenia and diarrhea result
- Consider alternate cardiovascular therapy (avoiding carvedilol and amiodarone, which also inhibit P-gp)



3. Perlas en Oncología

STEWARSHIP EN ONCOLOGIA

- Improve quality of care
- Improve patient access to care
- Improve patient safety
- Cost minimization

Chung C, et al. *Am J Health-Syst Pharm.* 2019; 76:617-621.

- *"Measures to use and preserve resources for the benefits of healthcare organizations to effectively, efficiently, and holistically address the needs of patients with cancer."*
- *"Set of coordinated strategies to improve the use of antineoplastic agents with the goal of enhancing patient outcomes while reducing financial toxicity."*

Chung C, et al. *Am J Health-Syst Pharm.* 2019; 76:617-621.; Ochs MA, et al. *Ann Hematol.* 2022; 101:1627-1644.

3. Perlas en Oncología

STEWARSHIP EN ONCOLOGIA

- Redondeo o ajuste de la dosis al tamaño de vial más próximo
- Uso de biosimilares o equivalentes terapéuticos
- Minimización de la administración de medicamentos de alto coste en hospitalización

- Rounding doses to nearest vial size when difference is less than an establish percentage can be very important.
  - Minimize drug waste
  - Ensure accuracy during drug preparation
  - Reduce healthcare expenditures
- Relevant for drugs supplied in preservative-free, single-use vials

3. Perlas en Oncología

HOPA Position Statement on Dose Rounding

- Hematology/Oncology Pharmacy Association (HOPA) published position statement on dose rounding chemotherapy/biologics
  - Endorsed by National Comprehensive Cancer Network

❖ **Recomendación 1** Los anticuerpos monoclonales (Mabs)/agentes biológicos pueden redondearse al tamaño de vial más próximo dentro del **10%** de la dosis prescrita.

❖ **Recomendación 2** Para MAbs con un componente citotóxico, el redondeo de dosis se realizará en base a la recomendación de los agentes citotóxicos

❖ **Recomendación 3** Los agentes citotóxicos tradicionales pueden redondear la dosis dentro del **10%** de la dosis prescrita

Fahrenbruch R, et al. *J Oncol Pract.* 2018; 14(3):e130-136.

3. Perlas en Oncología

Automatización del proceso

DOSE BANDING

- Removes human error associated with manual dose rounding
- Dose banding example: bevacizumab

Standardized, banded dose (mg)	Standard dose lower limit (mg)	Standard dose upper limit (mg)	Lower limit rounding (%)	Upper limit rounding (%)
500	500.01	555.55	0.002	9.999
550	555.56	611.11	1.001	10.0
600	611.12	666.66	1.82	9.999
650	666.67	722.22	2.5	10.0
700	722.23	777.77	3.078	9.999
750	777.78	833.33	3.572	10.0

Gahey OG, et al. *J Oncol Pharm Pract.*

When Not to Round?

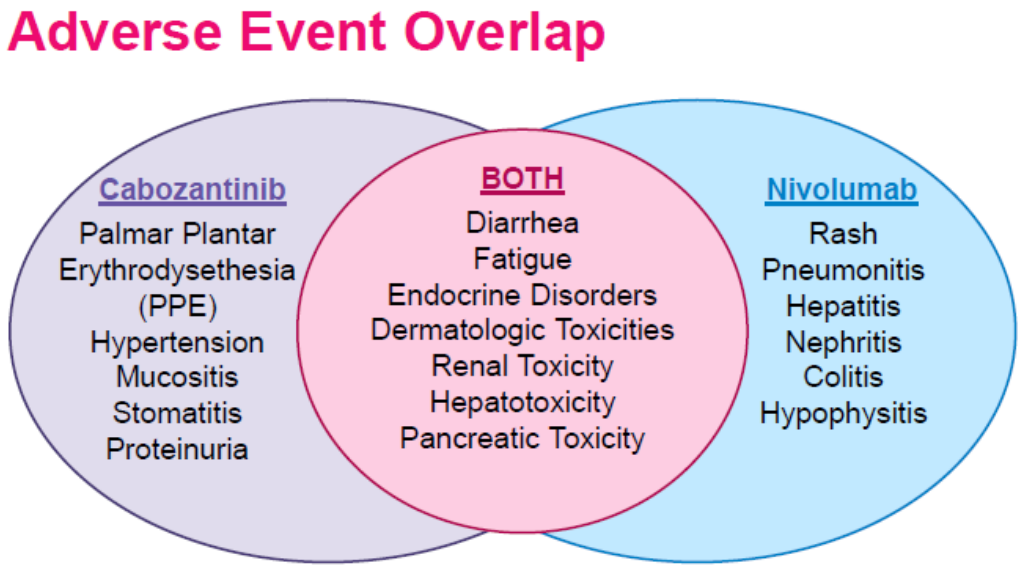
Scenario	Rationale/Example
Clinical Trial setting	May be considered a breach of study protocol
Pharmacokinetically determined dosing	Parenteral busulfan → may not be appropriate
Patient clinical factors	• Major organ dysfunction • Poor performance status • Extensive treatment history • Enzyme deficiencies/genetic polymorphisms
Dose reductions due to toxicity	Patient already has demonstrated intolerance to treatment and maybe should only be considered for rounding down dose if applicable • Ex. If dose reducing 25% for toxicity, but then dose round up to nearest vial by 10%, then patient only gets a 15% dose reduction

Fahrenbruch R, et al. *J Oncol Pract.* 2018; 14(3):e130-136.

3. Perlas en Oncología

SUPERPOSICIÓN DE TOXICIDADES

Combinación: inhibidores de la tirosin-quinasa (TKIs) + inmunoterapia



Cabometyx (cabozantinib) tablet [prescribing information]. Alameda, CA: Exelixis Inc; July 2022.
Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; May 2022.

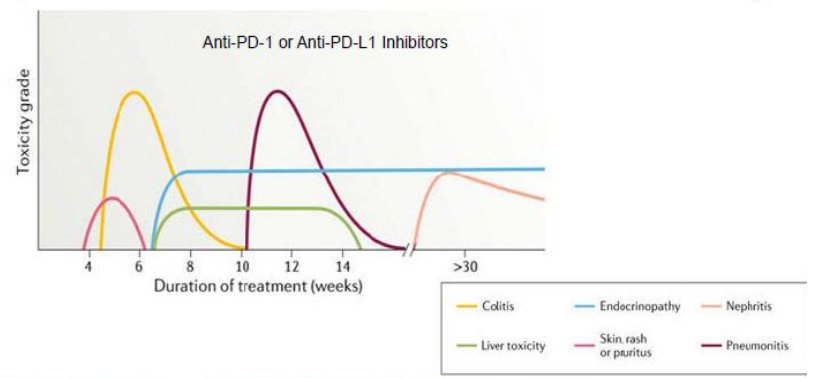
3. Perlas en Oncología

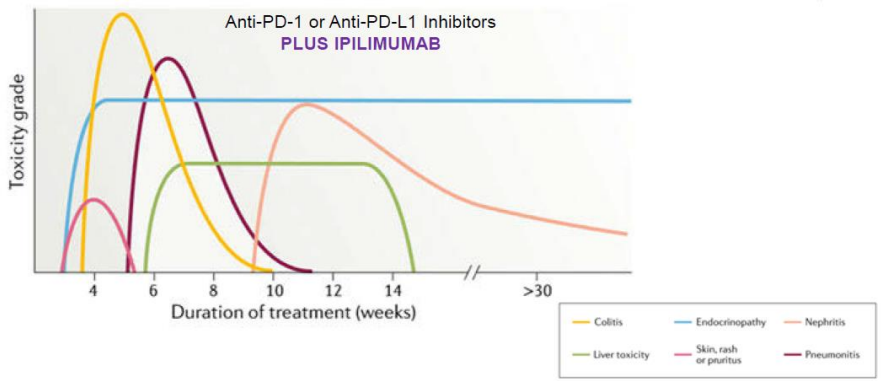
1-**Revisión** de la bibliografía

Which Came First?

ADVERSE EFFECT	CABOZANTINIB	NIVOLUMAB
✓ DIARRHEA	- Early, gradual onset (weeks) - Small frequent stools, bloating, flatulence - Resolves within a week of holding medication and anti-diarrheal use	- Can also cause colitis - Sudden onset of large volume watery stools - Associated with abdominal cramping - Can persist after holding medication and anti-diarrheals
✓ DERMATOTOXICITY	- Palmar-plantar erythrodysesthesia (PPE) - Acneiform rash - Supportive care required - Can continue therapy	- Immune-related rash, pruritus, vitiligo - Less severe rash is treated with topical steroids - Severe rash requires systemic corticosteroids
✓ NEPHROTOXICITY	- Proteinuria via VEGF inhibition - Monitor urine protein routinely - If urine protein:creatinine ratio is greater than or equal to 3.5, hold cabozantinib then resume at a lower dose	- Immune-related nephrotic syndrome - Hematuria, oliguria, increased creatinine, urine sediment - Biopsy confirmation needed - Treated with immunosuppressive therapy

Growcott S, et al. *Ox Med Case Reports*. 2018.
Choueiri TK, et al. *N Engl J Med*. 2021.
McGregor B, et al. *Cancer Treatment Reviews*. 2022.

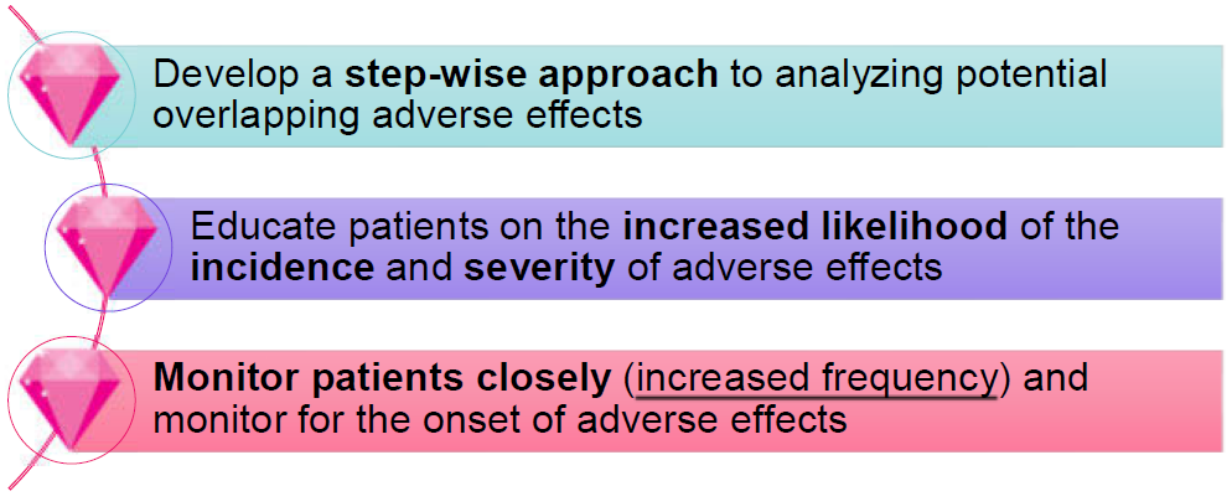




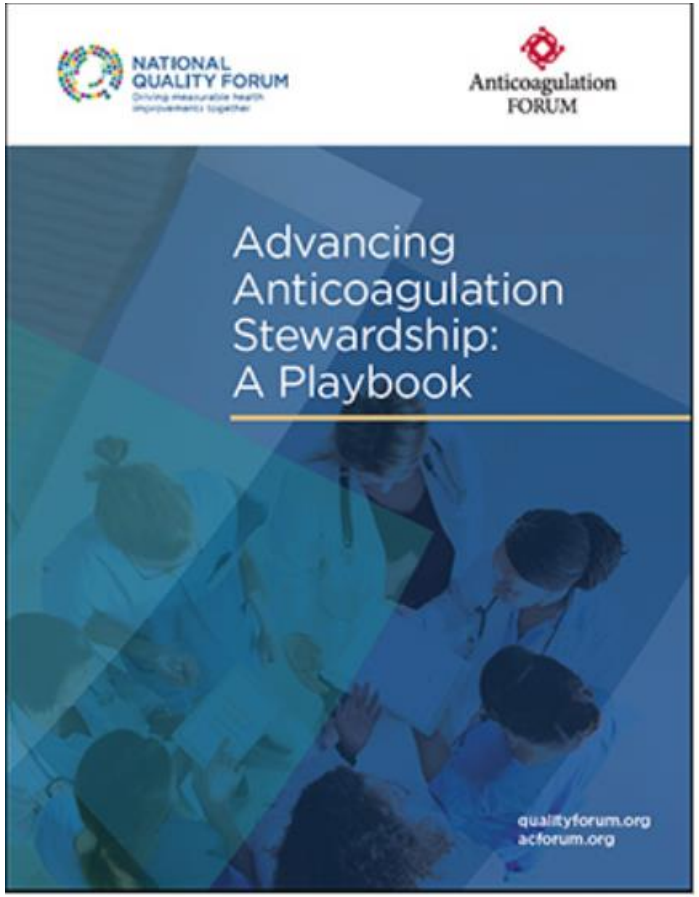
3. Perlas en Oncología

2-Puede ser necesario **reducir las dosis iniciales entre el 30% y el 50%** de los regímenes de dosificación estándar.

3-Empezar con un **fármaco cada vez**, si se tolera, después de una o dos semanas añadir el segundo agente.

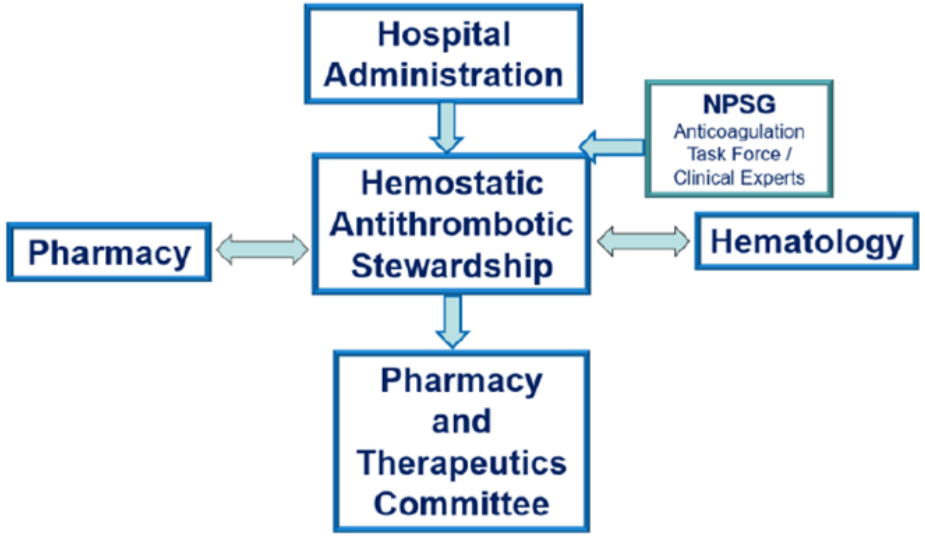


4. Anticoagulación y sangrados



Anticoagulation stewardship programs – Brigham and Women's Hospital

Hemostatic and Antithrombotic Stewardship Structure



Anticoagulation Forum: Core Elements of Anticoagulation Stewardship Programs. (Accessed August 2022, at https://acforum.org/web/downloads/ACF%20Anticoagulation%20Stewardship%20Guide.pdf).

4. Anticoagulación y sangrados

Primary Focus Areas

- Heparin Induced Thrombocytopenia
- Anticoagulation management for mechanical circulatory support patients
- Oversight of concentrated clotting factors
- Reversal agents
- Hemophilia
- Procedural use
- Patients specific consult questions and staff education

Clinical Decision Support Alerts

INR > 5	INR increase > 0.5 in 24 hours	Warfarin or other anticoagulant & drug-drug interactions	Anti-Xa laboratory monitoring
Active anticoagulation & HGB decrease ≥2 and HGB <8	Active anticoagulation & reversal agent administered	PCC administration	Fondaparinux
Rivaroxaban 2.5 mg to 15 mg	Rivaroxaban 20 mg & CrCl <50 ml/min	Dabigatran & CrCl <50 ml/min	Triple therapy

4. Anticoagulación y sangrados

Joint Commission National Patient Safety Goals

The organization uses approved protocols and evidence-based practice guidelines for the following

- Initiation and maintenance of anticoagulant therapy
- Baseline and ongoing laboratory tests to monitor and adjust doses / agents
- Perioperative Management
- Reversal of anticoagulation and management of bleeding events

Provides education to patients and families specific to the anticoagulant medication prescribed

Addresses anticoagulation safety practices

https://www.jointcommission.org/standards/national-patient-safety-goals/; Burnett AE, et al. Res Pract Thromb Haemc 2022;6:e12757.

- Plasma fresco congelado
- Fibrinógeno
- Factor VII recombinante activado
- Concentrado de complejo protrombínico
- Idarucizumab
- Andexant alfa

Why Anticoagulation Stewardship for Reversal and Bleeding Management?*

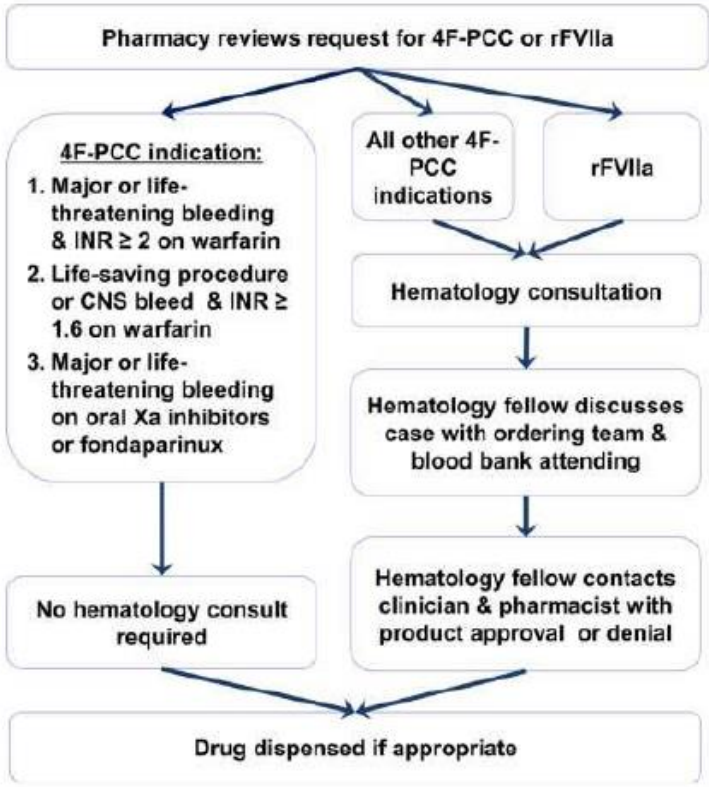
High Cost and / or Limited Resources	High Risk / Narrow Therapeutic Index	Complex - Off Label Use / Unclear Guideline Recommendations
• Concentrated clotting factors and reversal agents come at a steep cost • Drug shortages and/or decreases in blood bank supplies may limit resources available	• Reversal strategies come with a risk of thrombosis from the agent itself, the bleeding event, and the underlying disease requiring anticoagulation	• Many of these products are used for off-label indications and/or off-label dosing • Lack of prospective RCT data, studies may have conflicting results, or not address specific populations / clinical scenarios • Guidelines are not always clear or in agreement and require patient specific evaluation

* May also be referred to as Thrombosis and Hemostasis Stewardship with a broader scope

Dane KE, et al. Hematol Oncol Clinc N Am. 2019; 33:887-901, Dane KE, et al. J Am Coll Clin Pharm. 2022;5:622-631.

4. Anticoagulación y sangrados

Tufts Medical Center approved indications for 4FPCC and rVIIa



Hemostatic Stewardship at John's Hopkins A Toolkit for program implementation

Factor VII Dose Minimization

- Identify areas of off-label use at the institution
  - Post-op bleeding in cardiac surgery
- Balance benefit vs Risk
  - Lowest effective dose (17-30 mcg/kg) vs dose seen in hemophilia population (45-90 units/kg)
  - Lower risk of thrombosis
- Rapid access for approved indications; restrict inappropriate use
- Ensure optimal efficacy
  - Surgical management of bleeding 1st
  - Optimize PH and core body temperature

Inappropriate Antithrombin Use

- Repletion for low ATIII levels
  - If ACT / PTT / Anti-Xa is therapeutic don't need to replete
- Management of "heparin resistance"
  - Consider additional UFH bolus (s)
  - If getting PTTs, check anti-Xa
- If intra-operative:
  - Additional heparin
  - Consider FFP
  - Evaluate ACT goal

Fixed dose 4FPCC Warfarin Reversal

- FDA approved dosing based on INR and weight based on factor IX content since formulated for hemophilia B
- Waiting for INR delays time to administration
- Several studies have shown
  - Acceptable INR reversal in most pts
  - Decreased cost
  - Less thromboembolic events
  - Decreased time to administration
- Ability to re-dose as needed
- Considerations
  - Important to know INR turn around time at your institution
  - Patients with presenting INR >7 and weight >120kg may require additional dosing pending repeat INR

Dane KE, et al. Hematol Oncol Clinc N Am. 2019; 33:887-901, Dane KE, et al. J Am Coll Clin Pharm. 2022;5:622-631, Ciolek A, et al. Clin Appl Thromb Hemost. 2018 Jan;24(1):186-191.

4. Anticoagulación y sangrados

❑Andexanet-alfa

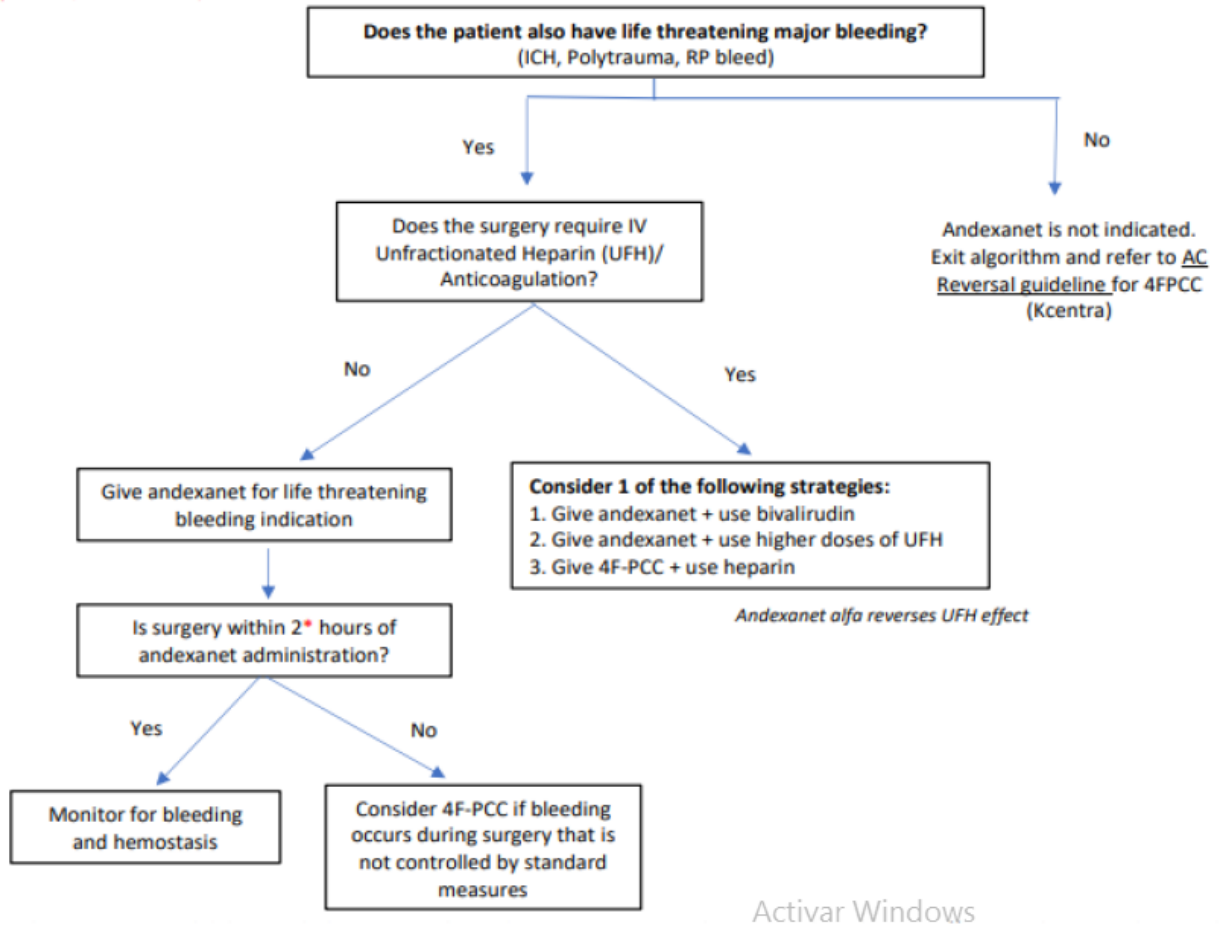
Criteria	Critical life-threatening bleeding and rivaroxaban/apixaban ingested less than 18 hours ago	Critical life-threatening bleeding	su
Indications	For critical life-threatening bleeding defined as bleeding that causes hemodynamic compromise, threatens a vital organ, or may result in disability, that does not respond to conventional measures and did not receive 4PCC prior	**AND** dose ingested more than 18 hours ago **OR** patient received alternative reversal strategies at OSH (eg: 4PCC)	See
Approval Required	No approval required for apixaban or rivaroxaban for critical life-threatening major bleeding if dose less than 18hr prior		Requires hema
Laboratory Monitoring	**Baseline CBC, Anti-Xa (Apixaban/Rivaroxaban) stat:** draw prior to administration; do not wait for results		Anti-Xa (Apixaban/Ri consideration of adm 50ng/mL,

If urgent or emergent surgery is required and there is insufficien dissipate, HAT service or hematology attending needs to be cor strategies.

*If greater than 18 hours since last dose, requires STAT anti-fac assess anticoagulant concentration before approval of andexanet.

Patients Requiring Surgery on† an Oral Factor Xa Inhibitor (FXai)
(Apixaban or Rivaroxaban)
Hematology & HAT must be notified

Send Stat Anti-Xa (Apixaban/Rivaroxaban) level



4. Anticoagulación y sangrados

Guidelines for Reversal of Oral FXa Inhibitors for Major Bleeding

ACC Expert Consensus Decision Pathway 2020	Anticoagulation Forum Guidance Document 2019	AHA/ACC/HRS AF Guidelines 2019
Administer andexanet alfa* If andexanet alfa is not available, administer 4F-PCC or aPCC Consider activated charcoal for known recent ingestion (within 2-4 hr) *ANNEXA-4 full report excluded patients with DOAC levels <75 ng/ml because those patients were considered to have clinically insufficient levels for reversal agent. If drug effect/ level can be assessed without compromising urgent clinical care decisions, then assessment should be performed before andexanet alfa is administered	Rivaroxaban and apixaban major bleeding → Suggest andexanet alfa; if not available, suggest 4F-PCC 2000 units Edoxaban or betrixaban-associated major bleeding → suggest high dose andexanet alfa or 4F-PCC 2000 units	Andexanet alfa can b useful for the reversal rivaroxaban and apixal in the event of life-threatening or uncontrolled bleedin (COR IIa, B-NR)

CONSIDERACIONES FINALES DEL GC REVALMED SNS

La Dirección General de Cartera Común de Servicios del SNS y Farmacia (DGCCSSNSYF) ha emitido resolución de no financiación para el medicamento ***ONDEXXYA®*** *(andexanet alfa) para pacientes adultos tratados con un inhibidor directo del factor Xa (apixabán o rivaroxabán) cuando es necesario revertir la anticoagulación por una hemorragia potencialmente mortal o descontrolada.*

January CT et al. Heart Rhythm 2019;16(8):e66-e93, Cuker A et al. Am J Hematol 2019 Jun;94(6):697-709, Frontera JA et al. Crit Care Med 2016; 44:2251-2257. Tomaselli GF et al. J Am Coll Cardiol 2017;70(24):3042-3067. Baugh CW et al. Ann Emerg Med. 2019;S0196-0644(19)31181-3. Tomaselli GF et al. J Am Coll Cardiol 2020;76(5):594-622

4. Anticoagulación y sangrados

Programas implantados

Results

From October 1, 2018 to January 15, 2020: 121 consultations
Time from consultation to recommendation: 20 min (median)
Initial request approval rate: 28%
Recommendation acceptance rate: 98.9%
Total cost avoidance: $1,005,871.78

Status of initial request (n=92)	
Approved	30.4%
Modified	51.1%
Denied	6.5%
Direct Consult	12%

Modifications	
Andexanet alfa → FFP	30.8%
Andexanet alfa → 4FPCC	53.8%
Andexanet alfa → dose adjustment	15.4%
4FPCC → andexanet alfa	9.5%
4FPCC → FFP	47.6%
4FPCC → dose adjustment	42.9%

4 farmacéuticos (24/7)

Impact on PCC Use

Outcome	Pre-Intervention	Post-Intervention
Inappropriate orders	55.8%	2.6%
Associated additional drug cost	$104,273	$10,831
Appropriate doses given per month	7.67	6.73

Anticoagulation Stewardship Financial Impact

AC Intervention cost avoidance	$694,217
Estimated annual PCC cost savings	$385,473
Anticoagulation stewardship funding	- $280,000
Approximate net impact	$799,690

2 farmacéuticos

POSTMIDYEAR ASHP More than a meeting

sefh Sociedad Española de Farmacia Hospitalaria

Muchas gracias

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Beatriz Torroba Sanz

Servicio de Farmacia

Hospital General Universitario Gregorio Marañón

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