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EN CONTROL DE SÍNTOMAS Y TERAPIAS DE SOPORTE

VALENCIA

8, 9 Y 10 DE MARZO 2023

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Tratamiento antitumoral en pacientes con insuficiencia orgánica y/o criterio de fragilidad

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Disclosure Information

- Consultant or Advisory Role: Boehringer-Ingelheim, Astra Zeneca, Roche and Brystol Myers Squibb
- Speaking: Roche, Astra Zeneca, Brystol Myers Squibb, Merck Serono, Ipsen Pharma, Lilly and Amgen, Angelini, Grunenthal, Kyowa Kirin, Mudipharma, Pfizer, Roche, Rovi, Leo Pharma and Boehringer Ingelheim

ÍNDICE

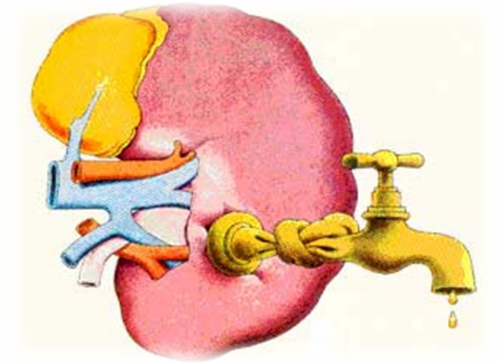
- INSUFICIENCIA DE ÓRGANO
  - Hepática
  - Renal
- FRAGILIDAD

INSUFICIENCIA ORGÁNICA

¿¿¿Y sólo 20 minutos???

Esta gente me quiere matar….

Insuficiencia renal



Insuficiencia Hepática

INSUFICIENCIA RENAL

FUNCION RENAL PACIENTES ONCOLÓGICOS

60%
daño renal[1,2]

DIRECTOS
T.Urológicos
Mieloma
GMN

INDIRECTOS
Deshidratacion
Derrame/ascitis
Infecciones
ICC

1. *Sahni V. Nat Rev Nephrol .2009*
2. *Perazella MA. Semin Nephrol 2010*
3. *Malyszko J. Lancet. 2020*

GLOMERULONEFRITIS

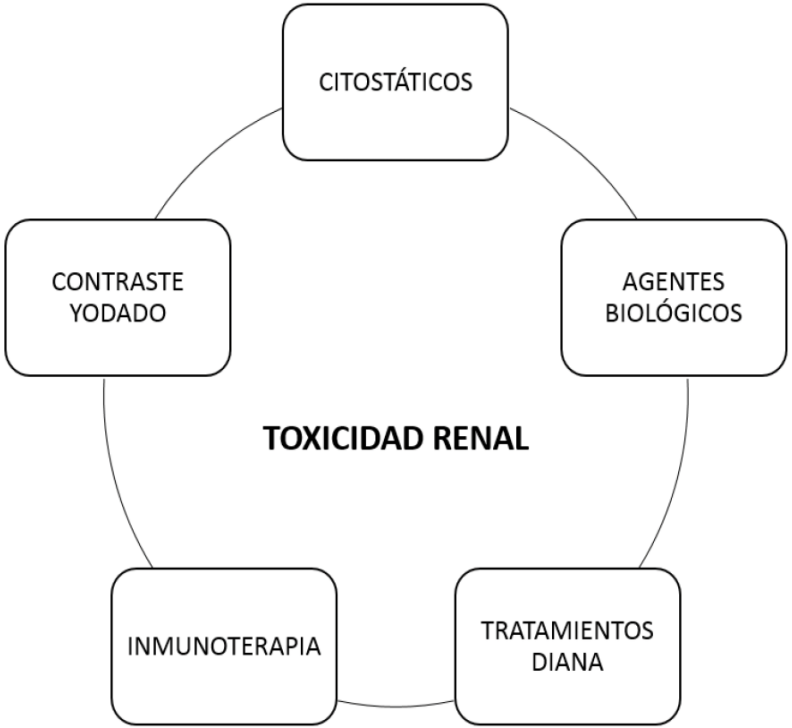
	Indication
Minimal change disease	Lung cancer, colon cancer, pancreatic cancer, bladder cancer, renal cell carcinoma, ovarian cancer, mesothelioma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, and myeloma
Membranoproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, gastric cancer, Wilms tumour, melanoma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, monoclonal gammopathy of undetermined significance, and myeloma
Mesangioproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, non-melanoma skin cancer, gastric cancer, pancreatic cancer, liver cancer, and myeloma
IgA nephropathy	Lung cancer, pancreatic cancer, renal cell carcinoma, head and neck cancer, tongue cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma
Focal segmental glomerulosclerosis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, T-cell leukaemia, and myeloma
Membranous nephropathy	Lung cancer, colon cancer, pancreatic cancer, stomach cancer, prostate cancer, breast cancer, head and neck cancer, Wilms tumour, teratoma, ovarian cancer, cervical cancer, endometrial cancer, melanoma, non-melanoma skin cancer, pheochromocytoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic lymphocytic leukaemia
Crescentic glomerulonephritis	Lung cancer, colon cancer, renal cell carcinoma, prostate cancer, gastric cancer, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, and chronic lymphocytic leukaemia
Thrombotic microangiopathy	Lung cancer, breast cancer, and gastric cancer
Amyloid A amyloidosis	Renal cell carcinoma, gastrointestinal stromal tumour, spleen sarcoma, and Hodgkin lymphoma
Anti-glomerular basement membrane glomerulonephritis	Hodgkin lymphoma
ANCA-associated vasculitis	Prostate cancer, bladder cancer, non-Hodgkin lymphoma, leukaemia, non-melanoma skin cancer, and lung cancer

ANCA=antineutrophil cytoplasmic antibody.

Table 1: **Paraneoplastic glomerulopathies in cancer patients**

Malyszko J, et al. Lancet. 2020

TOXICIDAD 2ª FÁRMACOS



TOXICIDAD FARMACOLÓGICA

- ✓ La toxicidad del agente antitumoral utilizado determina de manera importante tanto el desarrollo como el tipo de lesión renal sufrida.

- ✓ Aumentan el riesgo de lesión renal, independientemente de otros factores de riesgo:
  - Las dosis altas y la terapia prolongada [1-3].
  - La exposición combinada de fármacos[4,5].

1. Lameire NH. Ann Med 2005
2. de Jonge MJA. Semin Oncol 2006
3. Humphreys BD. J Am Soc Nephrol 2005
4. Evenepoel P. Best Pract Res Clin Anaesthesiol 2004
5. Singh NP. J Assoc Physicians India. 2003

TOXICIDAD FARMACOLÓGICA

✓ Factores de riesgo:

- Relacionados con el fármaco
- Relacionados con el tumor
  - Directos por infiltración (GU, MM, etc)
  - Indirectos (N/V, diarrea, ascitis, d.pleural, ICC…)
- Relacionados con el paciente:
  - Edad, ERC de base, CYP450, etc.

✓ Tipo de toxicidad

- *Vascular:* antiangiogénicos, GMZ, MMC, IFN y cisplatino
- *Glomerular:* IFN, bifosfonatos
- *Tubulo-intersticial:* platinos, bifosfonatos, pemetrexed, MTX..

Perazella MA. Clin J Am Soc Nephrol. 2012

PARA MUESTRA UN BOTÓN....

	Clinical kidney syndrome	Histopathology of the kidney	Prevention	Treatment
Chemotherapeutics				
Gemcitabine, mitomycin C, or cisplatin (rare)	Acute kidney injury; hypertension (new or worsened); haematuria; proteinuria	Thrombotic microangiopathy	Gemcitabine should be used with caution in patients with renal insufficiency	Drug discontinuation and supportive care; if drug-induced thrombotic microangiopathy does not improve, the use of eculizumab (C5 inhibitor) should be considered
Platins (cisplatin, carboplatin, or oxalaplatin)	Acute kidney injury; thrombotic microangiopathy; Fanconi-like syndrome; nephrogenic diabetes insipidus; syndrome of inappropriate antidiuresis; Na^+ and Mg^{2+} wasting with hypomagnesaemia	Acute tubular injury and vasoconstriction in the renal microvasculature	Intravenous fluids with K^+ and Mg^{2+}; dose adjustment; substitution of cisplatin with a less toxic carboplatin; repeat courses of cisplatin should not be given until serum creatinine is <1·5 mg per day	Discontinuation of cisplatin; treatment of hypomagnesaemia with high-dose magnesium sulfate might be required since raising the plasma Mg^{2+} increases urinary Mg^{2+} wasting
Ifosfamide	Acute kidney injury; proximal tubulopathy (hypophosphataemia, Fanconi syndrome, renal tubular acidosis type 2); distal tubulopathy (renal tubular type 1, nephrogenic diabetes insipidus); syndrome of inappropriate antidiuresis	Acute tubular injury and acute interstitial nephritis (rare)	Intravenous fluids; dose adjustment; reducing the cumulative ifosfamide dose	NA
Pemetrexed	Acute kidney injury; proximal tubulopathy; Fanconi syndrome; renal tubular acidosis type 2; nephrogenic diabetes insipidus	Acute tubular injury, interstitial edoema, and interstitial fibrosis	Intravenous fluids; CT scans with contrast should be done a few days to 1 week after pemetrexed administration	NA
Methotrexate	Acute kidney injury; syndrome of inappropriate antidiuresis	Crystalline nephropathy and acute tubular injury	Dose reduction; intravenous fluids; urinary alkalinisation; high-dose leucovorin and glucarpidase; suspending medications that interfere with methotrexate clearance	Continuing to administer alkalinised intravenous fluids with the addition of acetazolamide to keep urine pH >7; use of extracorporeal techniques have mixed results; use of glucarpidase in patients with delayed methotrexate clearance due to impaired renal function (toxic methotrexate plasma concentrations >1 μM despite adequate preventive measures)
Anti-metabolites (azacitidine, capecitabine, clofarabine, fludarabine, 5-fluorouracil, mercaptopurine, or thioguanine)	Acute kidney injury; Fanconi syndrome; nephrogenic diabetes insipidus	Acute tubular injury	Intravenous fluids; dose reduction	NA
Vincristine or cyclophosphamide	Syndrome of inappropriate antidiuresis; haemorrhagic cystitis (cyclophosphamide)	No renal histopathological lesion	Intravenous fluids; use mesna to reduce haemorrhagic cystitis with cyclophosphamide	NA
Nitrosoureas	Chronic kidney disease	Chronic interstitial nephritis	Intravenous fluids	NA

Malyszko J, et al. Lancet. 2020

PARA MUESTRA UN BOTÓN....

	Clinical kidney syndrome	Histopathology of the kidney	Prevention	Treatment
(Continued from previous page)				
Immunotherapy				
Interferons	Acute kidney injury; nephrotic proteinuria	Thrombotic microangiopathy and focal segmental glomerulosclerosis	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
IL-2 (high dose)	Capillary leak syndrome with acute kidney injury (prerenal injury or acute tubular injury)	No kidney lesions (prerenal) or acute tubular injury	Intravenous fluids; reduce NSAID exposure	NA
CTLA-4 inhibitors (ipilimumab)	Acute kidney injury; proteinuria	Acute interstitial nephritis, lupus-like glomerulonephritis, acute tubular injury, minimal change disease, and thrombotic microangiopathy	Consider low-dose steroids with drug re-exposure	Acute interstitial nephritis might respond to treatment with corticosteroids; treatment of thrombotic microangiopathy with drug discontinuation and supportive care
PD-1 inhibitors (nivolumab or pembrolizumab)	Acute kidney injury; proteinuria; electrolyte disorders	Acute interstitial nephritis, acute tubular injury, minimal change disease, immune complex glomerulonephritis, and thrombotic microangiopathy	Consider low-dose steroids with drug re-exposure	Treatment of immune-related nephrotoxicity with drug discontinuation and supportive care; use of systemic steroids (depending on the severity of symptoms)
CAR T cells	Cytokine release syndrome complicated by capillary leak syndrome with acute kidney injury (prerenal injury or acute tubular injury); electrolyte disorders	No pathology oracute tubular injury	Reduce tumour burden with chemotherapy and steroid prophylaxis prior to CAR T-cell therapy; IL-6 receptor antagonism when cytokine release syndrome is severe	NA
Other cancer drugs				
Pamidronate	Nephrotic syndrome; acute kidney injury	Focal segmental glomerulosclerosis and acute tubular injury	Dose adjustment; increase infusion time	NA
Zoledronate	Acute kidney injury; nephrotic syndrome (rare)	Acute tubular injury	Dose adjustment; increase infusion time; contraindicated when GFR is <30 mL/min	NA
Androgen deprivation therapy	Acute kidney injury	Unknown	NA	NA
Arsenic trioxide	Acute kidney injury	Acute interstitial nephritis	NA	NA
Tamoxifen	Nephrotic syndrome	Minimal change disease	NA	NA

Na^+=sodium ion. Mg^{2+}=divalent magnesium ion. K^+=potassium ion. NA=not available. NSAID=non-steroidal anti-inflammatory drugs. CAR=chimeric antigen receptor. GFR=glomerular filtration rate.

Malyszko J, et al. Lancet. 2020

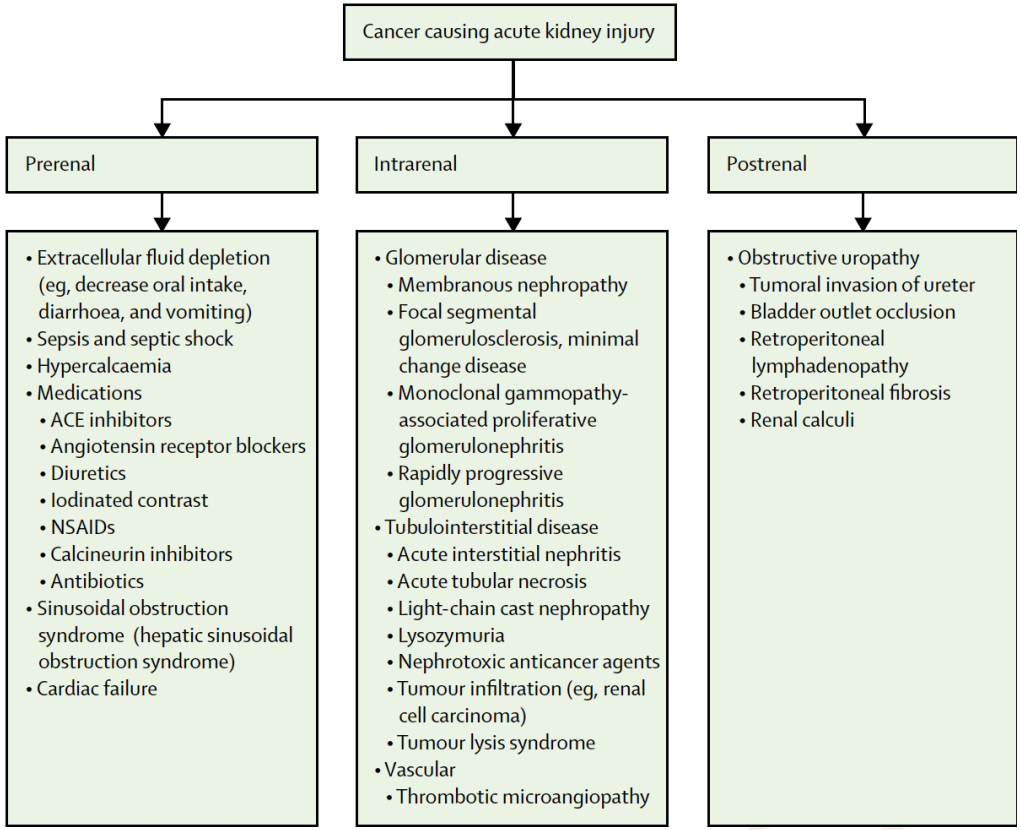
PARA MUESTRA UN BOTÓN....

Targeted cancer drugs				
Anti-VEGF drugs (bevacizumab or aflibercept)	Acute kidney injury; proteinuria (might be nephrotic); hypertension	Thrombotic microangiopathy	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
Tyrosine kinase and multikinase inhibitors (sunitinib, sorafenib, pazopanib, or imatinib)	Acute kidney injury; proteinuria; hypertension	Thrombotic microangiopathy, focal segmental glomerulosclerosi, acute interstitial nephritis, and acute tubular injury (all these histopathologies have been seen with imatinib)	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
EGFR inhibitors (cetuximab, panitumumab, gefitinib, or erlotinib)	Hypomagnesaemia; other electrolyte disorders	No renal histopathologic lesion	NA	NA
BRAF inhibitors (vemurafenib or dabrafenib)	Acute kidney injury; electrolyte disorders	Acute tubular injury, allergic acute, and interstitial nephritis	NA	NA
ALK inhibitors (crizotinib)	Acute kidney injury; electrolyte disorders; hypophosphataemia; proteinuria; haematuria; renal microcysts on ultrasound	Acute tubular injury and acute interstitial nephritis	NA	NA
Rituximab	Acute kidney injury (in tumour lysis syndrome); electrolyte distrubances	Crystalline (uric acid) nephropathy and acute tubular injury	Intravenous fluids	NA

Malyszko J, et al. Lancet. 2020

CAUSAS DE DAÑO RENAL AGUDO

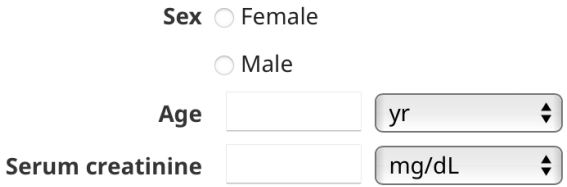
↓Volumen
Fármacos
Obstructiva



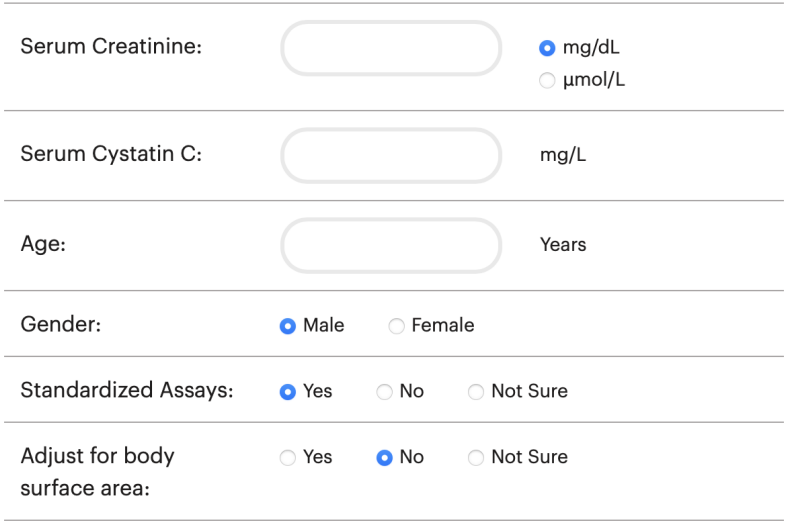
Malyszko J, et al. Lancet. 2020

FORMA DE CALCULAR AL FUNCIÓN RENAL

1. The Modification of Diet in Renal Disease (MDRD) equation
2. The Cockcroft-Gault equation
3. **2021 chronic kidney disease epidemiology (CKD-EPI) creatinine equation**
4. 2021 CKD-EPI creatinine-cystatin C equation

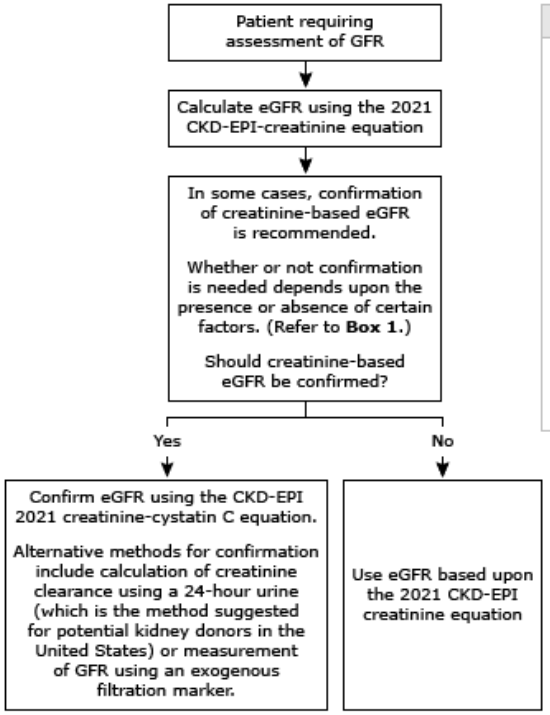


iDoctus
Medicina en la palma de la mano



https://www.kidney.org/professionals/kdoqi/gfr_calculator
https://public.idoctus.com

CALCULO FILTRADO GLOMERULAR



Box 1

Settings in which creatinine-based eGFR should be confirmed:

- Factors present that affect endogenous sources of creatinine:
  - Very high muscle mass
  - Very low muscle mass (eg, chronic heart failure, amputations, neuromuscular disease)
  - Advanced liver disease
- Factors present that affect exogenous sources of creatinine:
  - Very high animal protein diet
  - Very low-protein diet (eg, vegetarian, vegan)
- In patients with creatinine based-eGFR 45 to 59 mL/min/1.73 m^2 and no other evidence of kidney disease (eg, no albuminuria or radiologic abnormality)
- In settings where accuracy of the GFR estimate is more important:
  - Potential kidney donors
  - When treatment is planned with a medication that is renally cleared, has significant toxicity, and a narrow therapeutic range (eg, some chemotherapy agents)

- ✓ Fórmula 2021 CKD-EPI creatinine-cystatin C
- ✓ Aclaramiento de Cr en orina de 24h

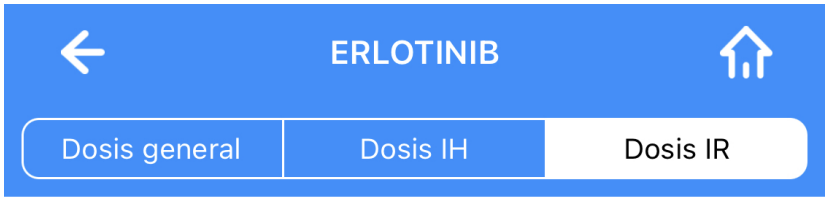
- ➢ Alta o baja masa muscular, dieta alta en proteínas, suplementos de creatina, dieta vegetariana, enfermedad hepática y fragilidad extrema.
- ➢ Recomendado si CDDP dosis altas

GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

UpToDate®

AJUSTAR DOSIS A FUNCIÓN RENAL…

¡¡¡¡¡NO SÓLO DE LOS FÁRMACOS ANTITUMORALES!!!!

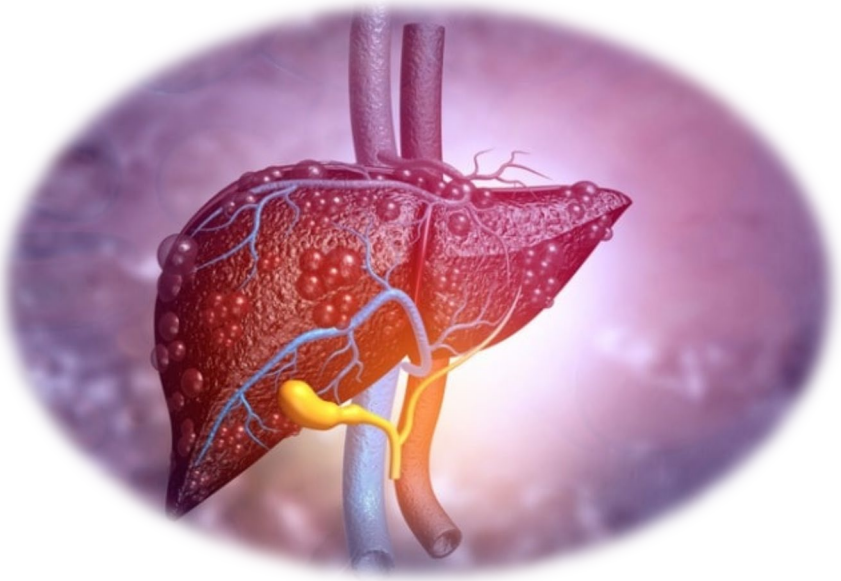


Posología en insuficiencia renal

* Leve o moderada: No es necesario ajustar la dosis.
* Grave: La seguridad y eficacia no ha sido estudiada en pacientes con concentración sérica de creatinina > 1,5 veces el límite superior normal. Uso no recomendado.

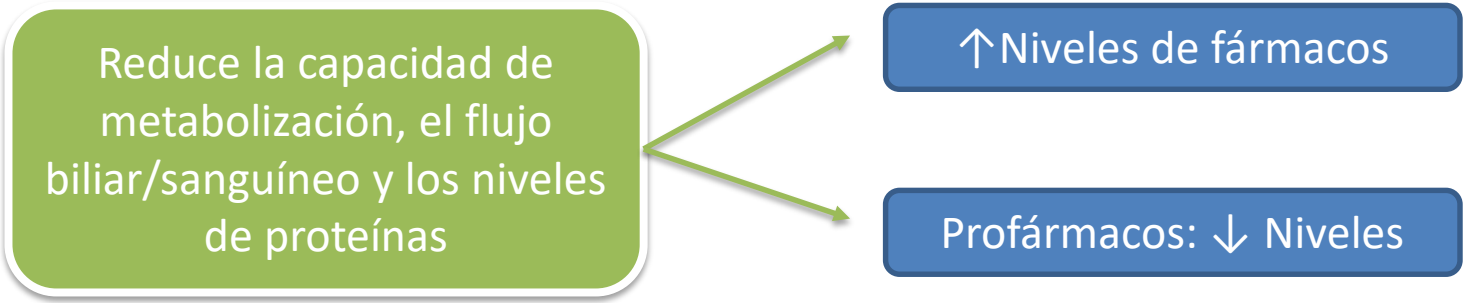
iDoctus
Medicina en la palma de la mano

INSUFICIENCIA HEPÁTICA



IMPORTANCIA DE LA FUNCIÓN HEPÁTICA

- ✓ La insuficiencia hepática:



Comprender la ruta metabólica del fármaco y su farmacocinética son esenciales para tomar decisiones sobre la dosis.

Krens SD. Lancet Oncol. 2019

IMPORTANCIA DE LA FUNCIÓN HEPÁTICA

- ✓ Las causas más comunes de deterioro de la función hepática en el paciente oncológico son las **metástasis hepáticas**, si bien pueden deberse a; hepatotoxicidad farmacológica, cirrosis o hepatitis[1].

- ✓ La incidencia de daño hepático secundario a la **quimioterapia oscila entre el 2-4%,** si bien es tremendamente variable[1].

- ✓ La función hepática anormal puede alterar el metabolismo de los fármacos y aumentar el riesgo de toxicidad extrahepática.

1. Krens SD. Lancet Oncol. 2019

EVALUACIÓN FUNCIÓN HEPÁTICA

- ✓ Para la función hepática, no existe una fórmula comparable a la tasa de filtración glomerular estimada para la función renal.
- ✓ La FDA y la EMA recomiendan el sistema de puntuación **Child-Pugh** para evaluar la insuficiencia hepática [1,2].

	1 point	2 points	3 points
Total bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3·5	2·8–3·5	<2·8
Prothrombin time (sec prolonged) or INR	<4 or <1·7	4–6 or 1·7–2·3	>6 or >2·3
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)†	None	1 or 2	3 or 4

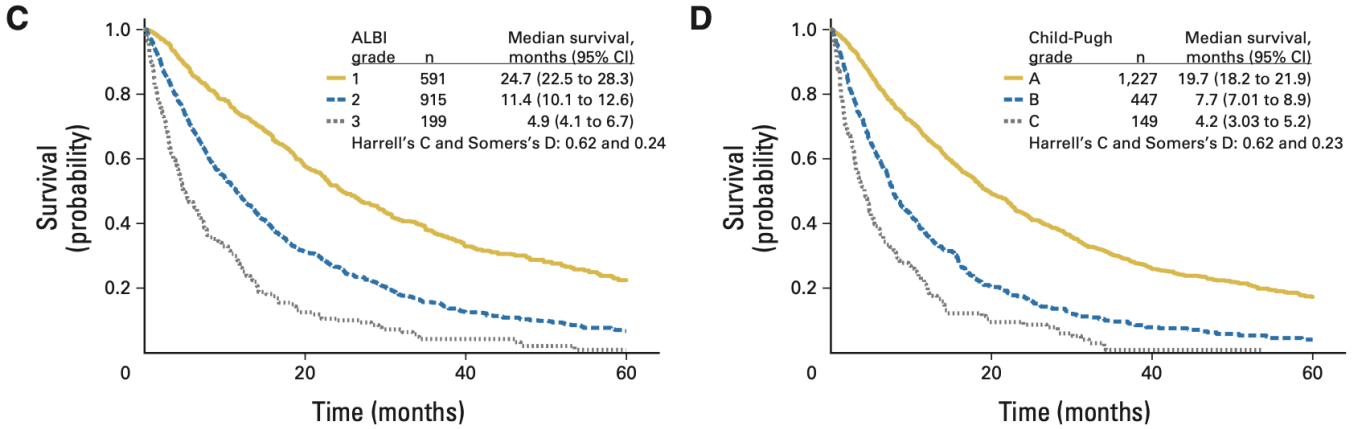
INR=international normalised ratio. *Child-Pugh classification is obtained by adding the score for each parameter. Grade A (mild)=5–6 points. Grade B (moderate)=7–9 points. Grade C (severe)=10–15 points. †Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram. Grade 1: restless, sleep disturbed, irritable or agitated, tremor, and impaired handwriting, five cycles per s (cps) waves. Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves. Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, and slower waves. Grade 4: unarousable coma, no personality or behaviour, decerebrate, and slow 2–3 cps delta activity.

1.https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokineticsmedicinal-products-patients-impaired-hepatic-function_en.pdf
2. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.
3. Krens SD. Lancet Oncol. 2019

ALTERNATIVAS A CP –> ALBI

Este modelo elimina la subjetividad de las variables como la ascitis y encefalopatía hepática.

ALBI score = (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.085)



ALBI mostró una mejor capacidad de discriminación que Child-Pugh para predecir el pronóstico (CHC)

1. Johnson PJ. J Clin Oncol. 2015
2. Peng Y. Expert Rev Gastroenterol Hepatol 2020

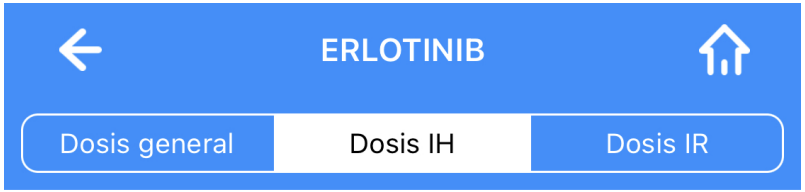
	Effect of liver impairment	Dose modification	Ref
Capecitabine	Increased aspartate aminotransferase or bilirubin: no relation to pharmacokinetics or toxic effects	No dose adjustment needed	2
Cisplatin and carboplatin	No published studies	Unlikely to need dose adjustments; mainly renal excretion	3
Cyclophosphamide	No changes in clearance	No dose adjustments needed	4
Docetaxel	Increased risk of neutropenia, mucositis, and death Increased bilirubin, with or without raised transaminases: 12–27% decreased drug clearance	Use not recommended if bilirubin is more than upper limit of normal, or if ratio of aspartate aminotransferase to alanine aminotransferase is >1·5-times upper limit of normal and alanine phosphatase is >2·5-times upper limit of normal	5,6
Doxorubicin	Myelosuppression; mucositis	Bilirubin <51 µmol/L: normal dose Bilirubin 34–51 µmol/L: decrease dose by 50% Bilirubin 51–85 µmol/L: decrease dose by 75% Bilirubin >85 µmol/L: withhold treatment	4 7 7 7
Epirubicin	Aspartate aminotransferase more sensitive marker of clearance than bilirubin	Consult dose guidelines based on levels of aspartate aminotransferase	8
Erlotinib	Increased aspartate aminotransferase or bilirubin	Aspartate aminotransferase ≥3-times upper limit of normal or bilirubin 17–120 µmol/L: 50% dose reduction	9
Etoposide	Mild to moderate impairment: no pharmacokinetic effect Severe impairment: myelosuppression; mucositis Decreased albumin increases unbound drug concentration and increases haematological toxic effects	Unclear (increased renal clearance might compensate)	10
Fluorouracil	Increased bilirubin: no relation to toxic effects	No dose adjustment needed	11
Gemcitabine	Increased aspartate aminotransferase alone: no increase in toxic effects Increased bilirubin: deterioration in liver function	Usual dose: 1000 mg/m² Increased aspartate aminotransferase: no dose change needed Increased bilirubin: reduce dose by 20% (ie, to 800mg/m²) and increase if tolerated	12
Imatinib	No notable pharmacokinetic differences or increased toxic effects	Stop treatment if hepatotoxicity develops; should probably not rechallenge	13
Irinotecan	Increased aspartate aminotransferase alone: no increase in toxic effects Increased bilirubin: neutropenia and diarrhoea	Increased aspartate aminotransferase: no dose change Increased bilirubin: reduce dose: 3-weekly irinotecan (usual dose 350 mg/m² every 3 weeks) • Bilirubin <1·5-times upper limit of normal: 350 mg/m² • Bilirubin >1·5–3-times upper limit of normal: 200 mg/m² • Bilirubin >3-times upper limit of normal: irinotecan not recommended Weekly irinotecan (usual dose 125 mg/m² for 4 of 6 weeks) • Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase <5-times upper limit of normal: 60 mg/m² • Bilirubin 3·1–5-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase <5-times upper limit of normal: 50 mg/m² • Bilirubin <1·5-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase 5·1–20-times upper limit of normal: 60 mg/m² • Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase 5·1–20-times upper limit of normal: 40 mg/m²	14–16
Oxaliplatin	Increased bilirubin, aspartate aminotransferase, or alkaline phosphatase: no effect on drug clearance or neurotoxicity	No dose adjustment	17
Paclitaxel	Increased aspartate aminotransferase or bilirubin increases myelosuppression	Reduce dose if increased aspartate aminotransferase or increased bilirubin	18
Sorafenib	Clearance does not differ between patient cohorts	Bilirubin ≤1·5-times upper limit of normal: 400 mg twice a day Bilirubin 1·5–3-times upper limit of normal: 200 mg twice a day Bilirubin 3–10-times upper limit of normal: sorafenib not recommended Albumin <25 g/L: 200 mg daily	19
Topotecan	No obvious effects	No dose adjustment needed if bilirubin 29–84 µmol/L	20
Vinorelbine	Increased bilirubin decreases drug clearance Volume of liver affected correlates with clearance	Suggested dose: Bilirubin 2·1–3-times upper limit of normal: reduce dose by 50% Bilirubin >3-times upper limit of normal: reduce dose by 75% Diffuse liver metastases: decrease dose by 50% (irrespective of bilirubin concentration)	21

Field KM. Lancet Oncol. 2008

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Telithromycin ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone* ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine* ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine* ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant* ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone¶ ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack$^{\Delta}$ ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*



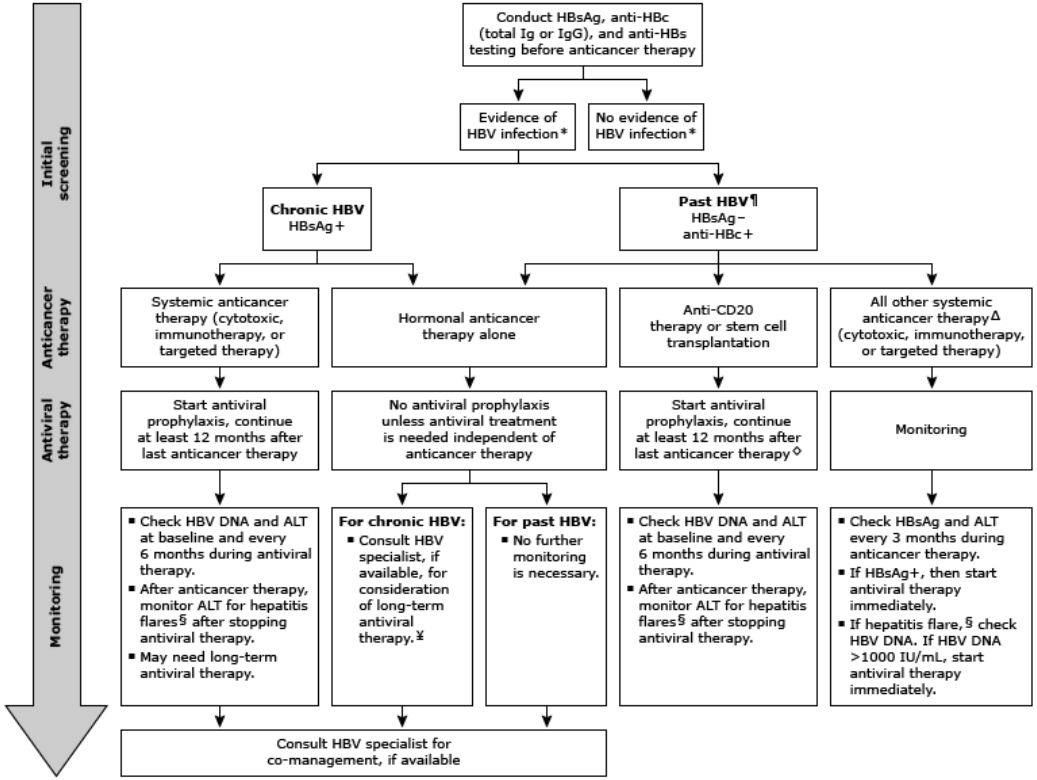
Posología en insuficiencia hepática

* Leve o moderada: Precaución. Considerar reducir la dosis o interrumpir el tratamiento si la pruebas de función hepática cambian de forma considerable.
* Grave: No ha sido estudiada su seguridad y eficacia. Uso no recomendado si transaminasas > 5 veces LSN.

iDoctus
Medicina en la palma de la mano

https://public.idoctus.com

ALGORITMO SCREENING VHB Y MANEJO INICIO TRATAMIENTO



https://www-uptodate-com

FRAGILIDAD

“Todos los oncólogos son oncólogos geriatras, sean conscientes de ello o no”

Stuart M. Lichtman, ASCO connection, January, 2015

¿ES TODO LO MISMO?

FRAGILIDAD

✓ Se define al anciano frágil como aquel que tiene una **disminución de las reservas fisiológicas y un mayor riesgo de declinar**, lo que lo sitúa en una **situación de mayor vulnerabilidad** ante perturbaciones externas y resulta en una **mayor probabilidad para presentar episodios adversos de salud** (hospitalización, institucionalización, muerte, caídas) **y pérdida de función, discapacidad o dependencia.**

✓ Detección → Anciano frágil es aquél que presenta uno o más de los siguientes factores:

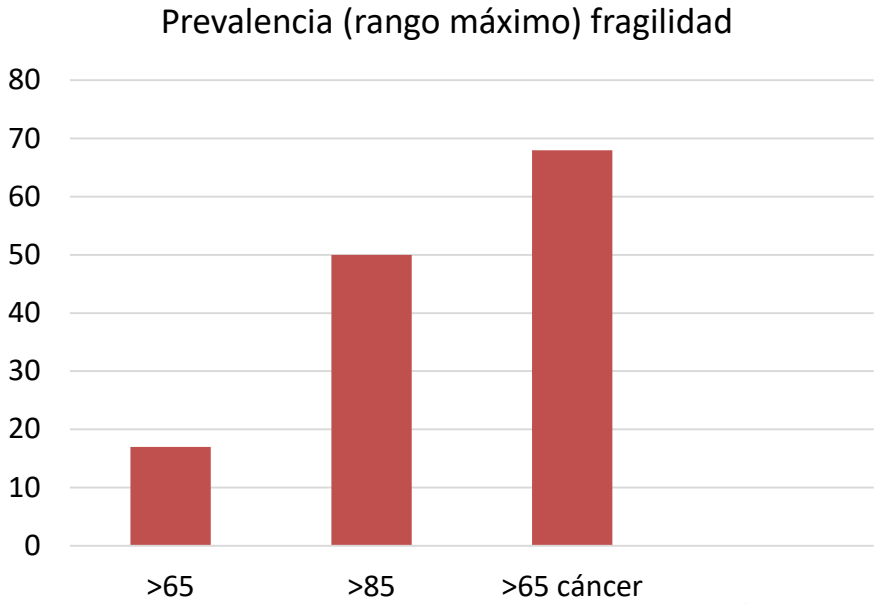
- Edad > 80 años
- Vive sólo
- Pérdida reciente de su pareja (< 1 año)
- Patología crónica invalidante
- Caídas frecuentes
- Polifarmacia
- Ingreso hospitalario en el último año
- Demencia u otro deterioro cognitivo o depresión
- Deficiencia económica
- Insuficiente soporte social.

ES UN ESTADO DE VULNERABILIDAD PREVIO A LA DISCAPACIDAD

https://www.san.gva.es/documents/246911/251004/guiasap03ancianofragil.pdf

PREVALENCIA FRAGILIDAD

- ✓ En individuos > 65 años oscila a nivel mundial entre el 7-17%[1-3]:
  - Si > 85 años, asciende al 25-50%[4,5].
  - Si ancianos oncológicos entre el 7% y el 68%.



1.Fried LP. J Gerontol A Biol Sci Med Sci. 2001
2.Bandeen-Roche K. J Gerontol A Biol Sci Med Sci. 2006
3. Collard RM. J Am Geriatr Soc. 2012
4.Song X. J Am Geriatr Soc. 2010
5.Clegg A. Lancet. 2013.
6.Handforth C. Ann Oncol. 2015

IMPLICACIONES DE LA FRAGILIDAD EN ONCOLOGÍA

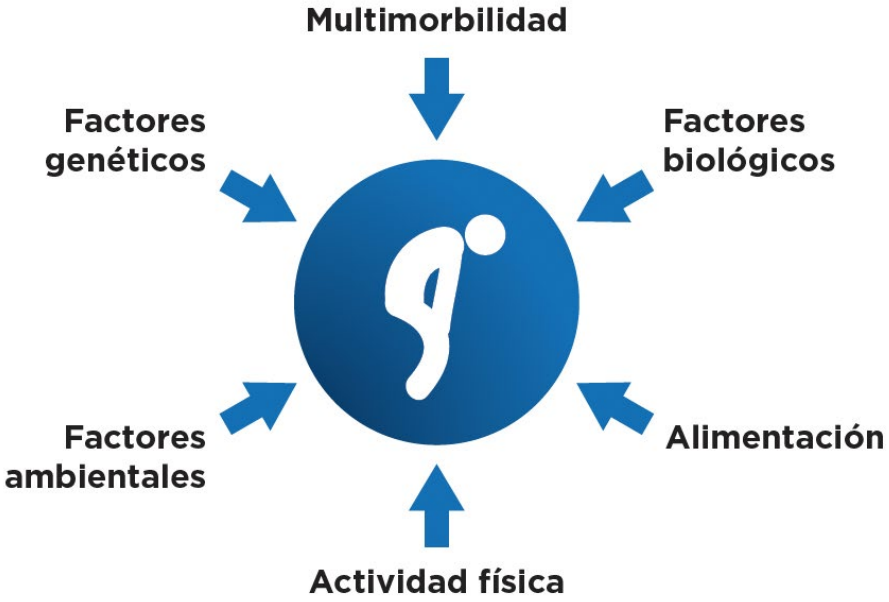
1. Menor supervivencia a corto y largo plazo tras una cirugía[1,2].

2. Peor control locorregional y a una disminución de la supervivencia con la RT (CCC)[3].

3. Mayor toxicidad/peor tolerabilidad a la quimioterapia con mayor mortalidad[4].

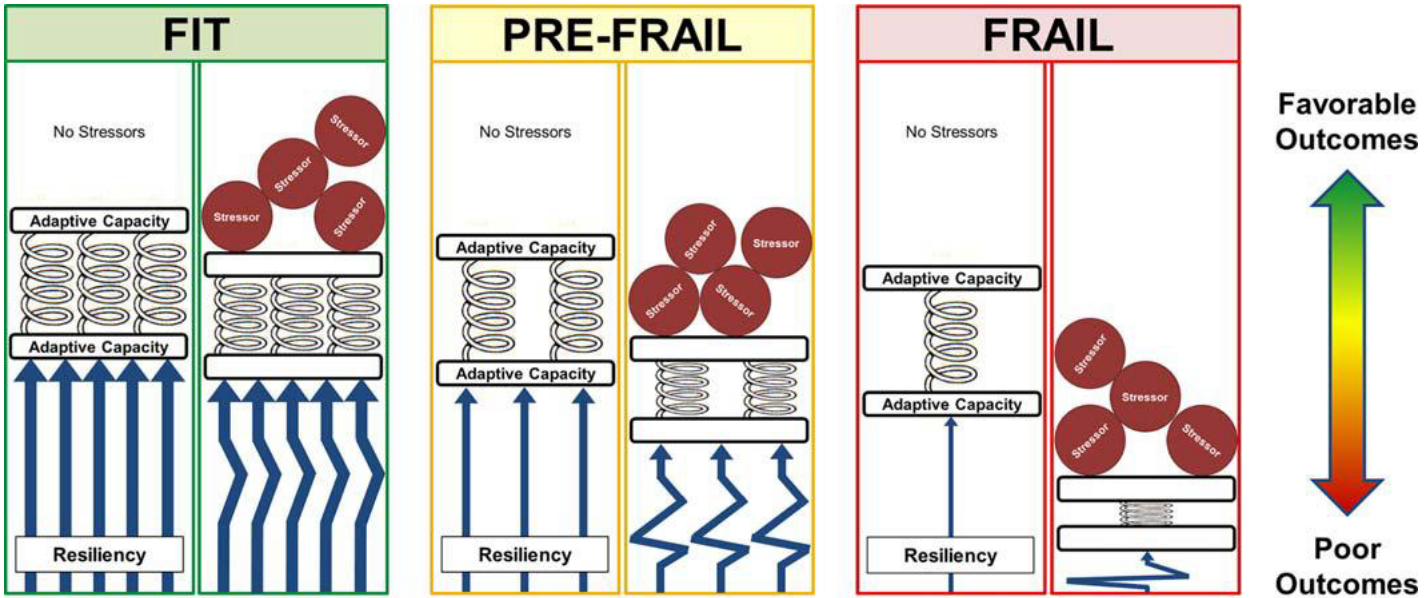
1.Ethun CG. A Cancer Journal for Clinicians. 2017
2. Noor A. The Laryngoscope. 2018.
3. Mady LJ. Clinics in Geriatric Medicine. 2018.
4. Handforth C. Annals of Oncology. 2015.

Factores que interactúan condicionando el estado de fragilidad



https://www.nutricionemocional.es/sites/default/files/infooncologia_n10.pdf

FASES DE LA FRAGILIDAD



Robust adaptive capacity and resiliency to stressors

Weak adaptive capacity and resiliency to stressors

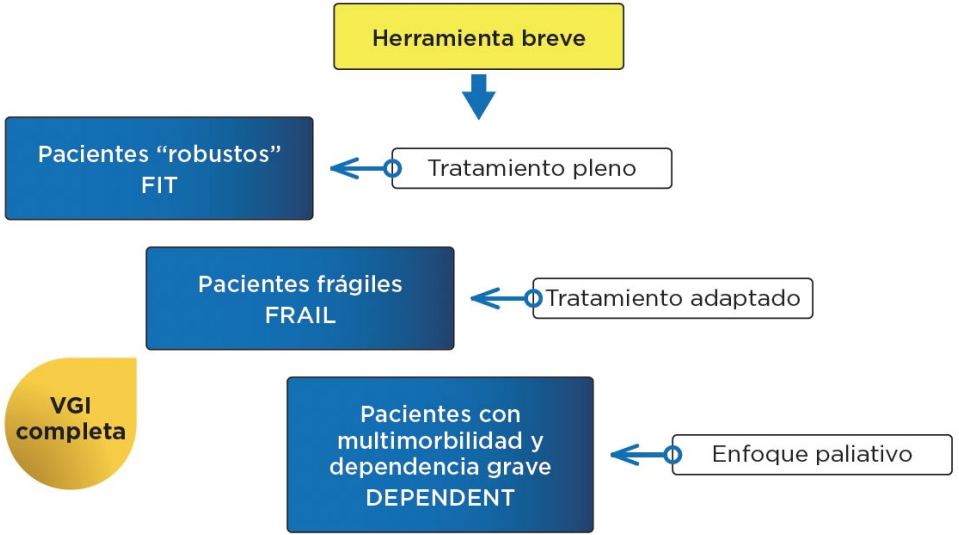
Poor adaptive capacity and resiliency to stressors

DISCAPACITADO

Adapted from: Robinson TN. J Am Coll Surg. 2015.

VALORACIÓN DE LA FRAGILIDAD

- ✓ Habitualmente, las decisiones de tratamiento se basan en la **impresión clínica** del médico del grado de fragilidad, sin ningún soporte objetivo.
- ✓ Existen varias herramientas de cribado de fragilidad
  - G8
  - VES-13
  - Modified Frailty Index (mFI)
  - Mini-Cog
  - Timed Up and Go (TUG)



https://www.nutricionemocional.es/sites/default/files/infooncologia_n10.pdf

G8 y VES-13

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: > 85
		1: 80-85
		2: < 80
	Total score	0-17

BMI = body mass index

Items	Score
Age	
– 75–85 years	1
– >85 years	3
Self-evaluation of your health	
– Excellent	0
– Very good	0
– Good	0
– Fair	1
– Poor	1
Do you have difficulty with the following activities:	
– Stopping, crouching, or kneeling?	1
– Lifting or carrying objects as heavy as 5 kg?	1
– Reaching or extending arms above shoulder level?	1
– Heavy housework such as scrubbing floors or washing windows?	1
– Writing or handling and grasping small objects?	1
– Walking 500 m?	
Because of your health or physical condition, do you need help for:	1
– Shopping for personal items?	1
– Managing money?	1
– Walking across the room (use of a cane or walker is okay)?	1
– Doing light housework?	1
– Bathing or showering?	

ALTA SENSIBLIDAD

ALTA ESPECIFICIDAD

Adapted from Bellera CA. Ann Oncol. 2012; Adapted from Saliba D. J Am Geriatr Soc. 2001

VALGER

Paciente Anciano Oncológico

HERRAMIENTA ONLINE PARA REALIZACIÓN DE VALORACIÓN GERIÁTRICA EN PACIENTES ONCOLÓGICOS.

Datos Personales | Listados | Documentación | Viernes, 10 febrero 2023

Datos Basales

Fecha: **viernes, 10 febrero 2023**
Centro: **HOSPITAL UNIVERSITARIO DE TORREJÓN**
Paciente:**0753-001**

Edad ____ años

Sexo Seleccione

Tipo tumoral Seleccione

Estadio Seleccione

Tratamiento que se propone

- Quimioterapia
- Inmunoterapia
- Biológicos (antiangiogénicos, anti-HER2, ITKs...)
- Radioterapia
- Otro, especificar

Paciente	Datos Basales	Cribado G8	Funcional	Cognitiva	Nutricional	Psicológica
Fecha	Socio-familiar	Comorbilidad	Geriátrico	Expectativa de vida	Toxicidad	Resumen
0753-001						

https://www.e-clinical.org/valger/

¿Podemos tratar la fragilidad? → Plan de atención integral

1. Abordar sistemáticamente las enfermedades y otros factores desencadenantes o agravantes:
   - ✓ Polifarmacia (la retirada de fármacos innecesarios, aporta beneficios).
   - ✓ Sarcopenia
   - ✓ Causas tratables de: pérdida de peso y de fatiga, depresión, anemia, hipotensión, hipotiroidismo y déficit de vitamina B12 y folato).
2. Ejercicio físico, principalmente de resistencia (fuerza muscular), y la adecuada ingesta de proteínas.
   - ✓ Ejercicios multicomponente (aeróbico, resistencia, equilibro y flexibilidad).
3. Ideal → atención domiciliaria diseñada de manera personalizada (centrada en la persona).

1.Dent E. The Lancet. 2019
2. Dent E. J Nutr Health Aging. 2019


PACIENTE
TUMOR
Agresivo/Indolente
TRATAMIENTO
Eficacia/Toxicidad
EXPECTATIVA DE VIDA, VALORES,PRIORIDADES

TOMA DE DECISIONES

1. ¿El paciente fallecerá por cáncer o con cáncer?

2. ¿Tolerará el paciente el tratamiento?

3. ¿El cáncer y su tratamiento van a provocar elevada morbilidad?

Balducci et al. Eur J Cancer 2001

SEGÚN ASCO ESTO ES LO MÍNIMO

Summary of a minimum data set for practical assessment of vulnerabilities in older patients with cancer

1. Predict chemotherapy toxicity (if clinically applicable): Cancer and Aging Research Group or Chemotherapy Risk Assessment Scale for High-Age Patients tools
2. Estimate (noncancer) life expectancy (if clinically applicable): ePrognosis
3. Functional assessment: Instrumental Activities of Daily Living
4. Comorbidity assessment: Medical record review or validated tool
5. Screening for falls, one question: How many falls or falls with an injury have you had in the previous 6 months (or since your last visit)?
6. Screening for depression: Geriatric Depression Scale or other validated tool
7. Screening for cognitive impairment: Mini-Cog or Blessed Orientation-Memory-Concentration test
8. Screening for malnutrition: Weight loss/body mass index

From: Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018; 36(22):2326-2347. Reprinted with permission. Copyright © 2018 American Society of Clinical Oncology. All rights reserved.

¿QUÉ HACÉIS VOSOTROS?

- ¿Solo valoráis edad?
- ¿Comorbilidad?
- ¿Fragilidad?
- ¿Escalas? ¿A ojo?

CONCLUSIONES

1. Ser oncólogo médico no es lo mismo que quimioterapeuta, va mucho más allá…

2. Es imprescindible valorar la función renal y hepática de los pacientes.

3. Optimizar la polifarmacia.

4. Control de interacciones farmacológicas/inhibidores/inductores enzimáticos

5. La fragilidad:
   - ✓ Debe ser valorada y evaluada. El ojo clínico no es suficiente.
   - ✓ Maniobras encaminadas a evitarla y revertirla

XVII CURSO SEOM PARA RESIDENTES

EN CONTROL DE SÍNTOMAS Y TERAPIAS DE SOPORTE

Gracias por vuestra atención

#mirSEOM23