

Neutropènia Febril

David Blancas Altabella

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A stylized silhouette of a mountain range in a teal color, located in the bottom right corner of the slide.

Bibliografia

- ◆ Management of febrile neutropenia: ESMO Clinical Practice Guidelines (2010).
- ◆ Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America (2011).
- ◆ ASCO Guidelines 2013.
- ◆ Uptodate (febrer 2014).

Definició

- ◆ Temperatura oral $>38.5^{\circ}\text{C}$ ó $>38^{\circ}\text{C}$ sostinguda > 1 hora.
- ◆ < 500 cel/ml o esperable que baixi <500 en les pròximes 48 hores.

... a la vida real temperatura axilar.

Síndromes de neutropènia febril

- ◆ Infecció documentada microbiològicament: focus clínic i patogen associat.
- ◆ Infecció documentada clínicament: focus clínic sense patogen.
- ◆ Febre no explicada: sense focus clínic ni patogen.

Patogènesi

- ◆ Efecte directe de la quimioteràpia en les mucoses i el sistema immune.
- ◆ Alteracions de la defensa de l'hoste secundàries a la malaltia neoplàsica (infeccions associades al tipus de tumor).

Epidemiologia

- ◆ 10-50% tumors sòlids i > 80% neoplàsies hematològiques de pacients amb neutropènia febril.
- ◆ Es documenta infecció en 20-30% dels casos.
- ◆ Bacterièmia en 10- 25% dels casos (neutropènia profunda i perllongada).
- ◆ Mortalitat 1- 36%.

Etiologia

- ◆ 1960- 1970: BGN.
- ◆ 1980- 1990: CGP més freqüents (catèters venosos, profilaxis per BGN), però menys greus.
- ◆ Actualment: SCN, enterobactèries, S. aureus, estreptococs, BGN no fermentadors, anaerobis.
- ◆ Multirresistents.
- ◆ Fongs (en alt risc, profilaxi).
- ◆ Virus (en alt risc, profilaxi i virus epidèmics).

HISTÒRIA CLÍNICA I EXPLORACIÓ FÍSICA

- ◆ Moltes vegades només febre.
- ◆ Altres vegades no hi ha febre però hi ha criteris de sepsis.
- ◆ Especial èmfasi a la pell, cavitat oral, orofaringe, pulmons, abdomen i regió perianal (no tacte rectal), catèters.

PROVES COMPLEMENTÀRIES

- ◆ Analítica: hemograma, funció renal, hepàtica i ionograma. PCR.
- ◆ Com a mínim dos "SETS" d'hemocultius perifèrics (i un de la via central, si porta).
- ◆ Altres cultius segons símptomes?.
- ◆ Rx tòrax.
- ◆ TAC segons símptomes.

...i ANTIBIÒTIC TAN RÀPID COM SIGUI
POSIBLE!!!!!!!!!!!!!!!!!!!!!!!!!!!!

Triage

All patients receiving systemic anti-cancer therapy within the previous 6 weeks*

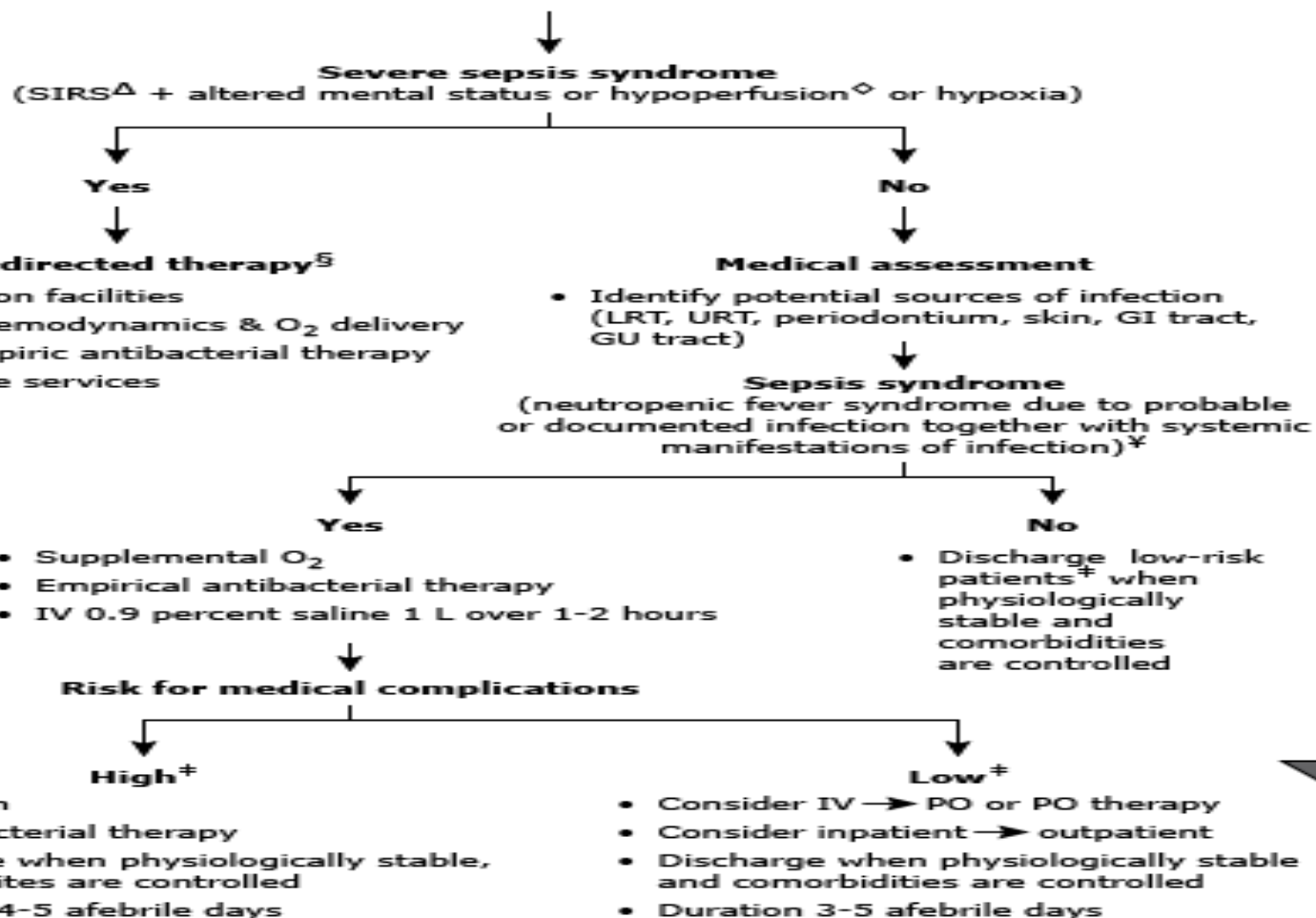
Assumption: Neutropenic fever/sepsis syndrome

Initial assessment

Temperature, pulse, respiratory rate, blood pressure, arterial O₂ saturation

Initial intervention

1. IV access (CVAD, if in situ, or peripheral line, 18G) plus normal saline
2. Blood work: complete blood count & leukocyte differential, blood cultures (CVAD + peripheral site, or two separate peripheral sites), electrolytes (Na, K, Cl, TCO₂), blood urea nitrogen & serum creatinine, blood glucose, serum lactate



0'

15'

30'

60'

AVALUACIÓ DE RISC: MASCC

Alt risc < 21 (criteri ingrés)

Table 3. The Multinational Association for Supportive Care in Cancer Risk-Index Score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms ^a	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease ^b	4
Solid tumor or hematologic malignancy with no previous fungal infection ^c	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms ^a	3
Outpatient status	3
Age <60 years	2

NOTE. The maximum value of the score is 26. Adapted from [43]. Reproduced with permission of the American Society for Clinical Oncology.

^a Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

^b Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

^c Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

ALTRES CRITERIS ALT RISC

- ◆ Neutropènia <100 i > 7 dies.
- ◆ Comorbilitats de tipus:
 - Inestabilitat hemodinàmica.
 - Patologia gastrointestinal.
 - Clínica neurològica.
 - Infecció de catèter.
 - Infiltrat pulmonar/ hipoxèmia / malaltia pulmonar crònica.
- ◆ Insuficiència hepàtica (AST $\times 5$) o renal (clearance de creatinina <30 ml/min).

ANTIBIÒTIC EMPÍRIC (baix risc)

- ◆ Tractament oral /domiciliari? (valorar segons primera dosi ev. i 24 hores d'observació).
- ◆ Ciprofloxacino més amoxicilina- clavulànic (levofloxacino (750 mg/dia)?, ciprofloxacino +/- clindamicina).
- ◆ No donar quinolones si fan profilaxis amb aquestes.
- ◆ Si febre persistent o empitjorament: reingrés / continuar a hospital.

Oral antibiotics for fever in **low-risk neutropenic patients with cancer**: a double-blind, randomized, multicenter trial comparing single daily **moxifloxacin** with twice daily **ciprofloxacin plus amoxicillin/clavulanic acid combination therapy**--EORTC infectious diseases group trial XV.

Kern WV, Marchetti O, Drgona L, Akan H, Aoun M, Akova M, de Bock R, Paesmans M, Viscoli C, Calandra T

J Clin Oncol. 2013;31(9):1149.

- ◆ **PURPOSE:** This double-blind, multicenter trial compared the efficacy and safety of a single daily oral dose of moxifloxacin with oral combination therapy in low-risk febrile neutropenic patients with cancer.
- ◆ **PATIENTS AND METHODS:** Inclusion criteria were cancer, febrile neutropenia, low risk of complications as predicted by a Multinational Association for Supportive Care in Cancer (MASCC) score >20, ability to swallow, and ≤one single intravenous dose of empiric antibiotic therapy before study drug treatment initiation. Early discharge was encouraged when a set of predefined criteria was met. Patients received either moxifloxacin (400 mg once daily) monotherapy or oral ciprofloxacin (750 mg twice daily) plus amoxicillin/clavulanic acid (1,000 mg twice daily). The trial was designed to show equivalence of the two drug regimens in terms of therapy success, defined as defervescence and improvement in clinical status during study drug treatment (<10% difference).
- ◆ **RESULTS:** Among the 333 patients evaluated in an intention-to-treat analysis, therapy success was observed in 80% of the patients administered moxifloxacin and in 82% of the patients administered combination therapy (95% CI for the difference, -10% to 8%, consistent with equivalence). Minor differences in tolerability, safety, and reasons for failure were observed. More than 50% of the patients in the two arms were discharged on protocol therapy, with 5% readmissions among those in either arm. Survival was similar (99%) in both arms.
- ◆ **CONCLUSION:** Monotherapy with once daily oral moxifloxacin is efficacious and safe in low-risk febrile neutropenic patients identified with the help of the MASCC scoring system, discharged early, and observed as outpatients

ANTIBIÒTIC EMPÍRIC (alt risc)

- ◆ Monoterapia amb betalactàmic amb activitat antipseudomona (cefepime, imipenem, piperacilina- tazobactam). Afegir aminoglicòsids, quinolones i/o vancomicina si complicacions (ex. hipotensió, pneumònia, infecció catèter, parts toves, mucositis?) o si ha resistència sospitada o provada.
- ◆ Valorar antecedent microbiològic (SARM, BLEE, carbapenemases,...) i ATB previs.

Empirical antibiotics targeting Gram-positive bacteria for the treatment of febrile neutropenic patients with cancer.

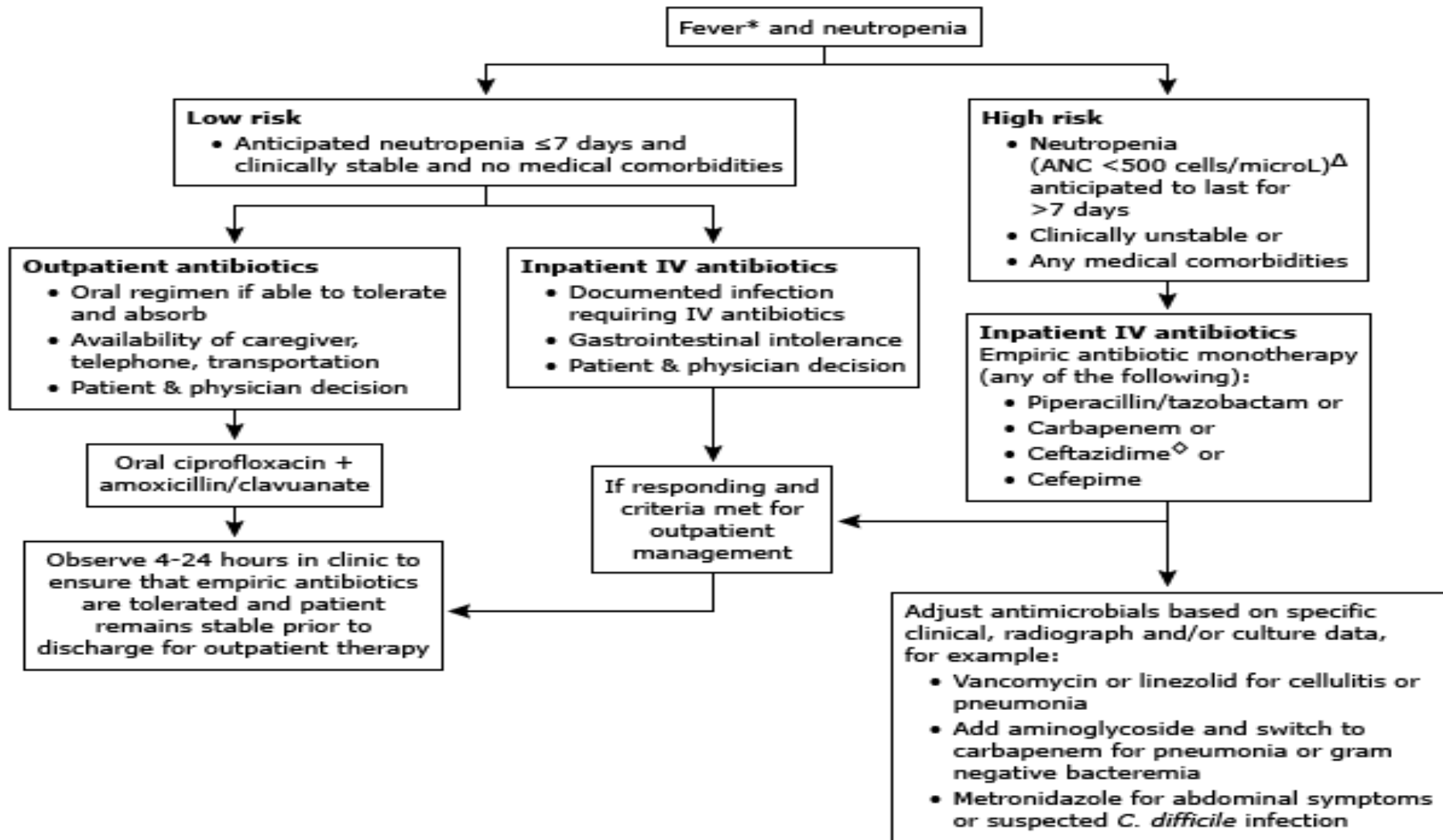
Paul M, Dickstein Y, Borok S, Vidal L, Leibovici L
Cochrane Database Syst Rev. 2014;1:CD003914.

- ◆ **BACKGROUND:** The pattern of infections among neutropenic cancer patients has shifted in the last decades to a predominance of Gram-positive infections. Some of these Gram-positive bacteria are increasingly resistant to beta-lactams and necessitate specific antibiotic treatment.
- ◆ **OBJECTIVES:** To assess the effectiveness of empirical antiGram-positive (antiGP) antibiotic treatment for febrile neutropenic cancer patients in terms of mortality and treatment failure. To assess the rate of resistance development, further infections and adverse events associated with additional antiGP treatment.
- ◆ **SEARCH METHODS:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 7), MEDLINE (1966 to 2013), EMBASE (1982 to 2013), LILACS (1982 to 2013), conference proceedings, and the references of the included studies. First authors of all included and potentially relevant trials were contacted.
- ◆ **SELECTION CRITERIA:** Randomised controlled trials (RCTs) comparing one antibiotic regimen to the same regimen with the addition of an antiGP antibiotic for the treatment of febrile neutropenic cancer patients.
- ◆ **DATA COLLECTION AND ANALYSIS:** Two review authors independently assessed trial eligibility and risk of bias, and extracted all data. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. A random-effects model was used for all comparisons showing substantial heterogeneity ($I^2 > 50\%$). Outcomes were extracted by intention to treat and the analysis was patient-based whenever possible.
- ◆ **MAIN RESULTS:** Thirteen trials and 2392 patients or episodes were included. Empirical antiGP antibiotics were tested at the onset of treatment in 11 studies, and for persistent fever in two studies. The antiGP treatment was a glycopeptide in nine trials. Seven studies were assessed in the overall mortality comparison and no significant difference was seen between the comparator arms, RR of 0.82 (95% CI 0.56 to 1.20, 852 patients). Ten trials assessed failure, including modifications as failures, while six assessed overall failure disregarding treatment modifications. Failure with modifications was significantly reduced, RR of 0.76 (95% CI 0.68 to 0.85, 1779 patients) while overall failure was the same, RR of 1.00 (95% CI 0.79 to 1.27, 943 patients). Sensitivity analysis for allocation concealment and incomplete outcome data did not change the results. Both mortality and failure did not differ significantly among patients with Gram-positive infections, but the number of studies in the comparisons was small. Data regarding other patient subgroups likely to benefit from antiGP treatment were not available. Glycopeptides did not increase fungal superinfection rates and were associated with a reduction in documented Gram-positive superinfections. Resistant colonisation was not documented in the studies.
- ◆ **AUTHORS' CONCLUSIONS:** Current evidence shows that the empirical routine addition of antiGP treatment, namely glycopeptides, does not improve the outcomes of febrile neutropenic patients with cancer.

AL-LÈRGIA PENICILINA

- ◆ La majoria toleren cefalosporines i carbapenems.
- ◆ Si història d'anafilàxia evitar-los: ciprofloxacino més clindamicina o aztreonam més vancomicina.

Initial management of fever and neutropenia



G-CSF (Factor estimulator de colònies)

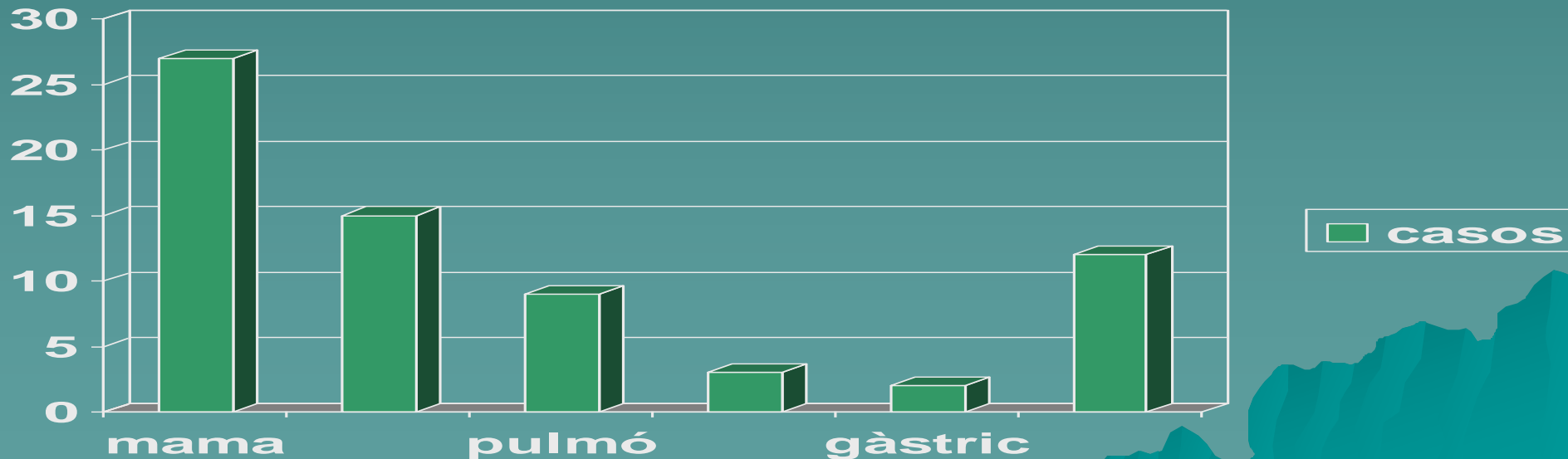
- ◆ No recomanat (IDSA) perquè no millora la supervivència, alt cost i efectes secundaris.
- ◆ Redueix els dies de neutropènia, la durada de la febre i estada hospitalària.
- ◆ ASCO i ESMO: No però SI (< 100 cel., neutropènia esperable > 10 dies, edat > 65 anys, neoplàsia no controlada, pneumònia, hipotensió, sepsis, infecció fúngica o febre intrahospitalària)

MANEIG AMBIENTAL

- ◆ Higiene de mans (mesura més eficaç per prevenir infeccions).
- ◆ No aïllament ni barreres de protecció ni ventilació específiques (excepte trasplantament hematopiètic).
- ◆ Dieta neutropènica?.
- ◆ Cures de la pell, cavitat oral i periné.
- ◆ No plantes ni animals.
- ◆ Evitar treballadors i visitants no vacunats i malalts.

Sant Camil 2008-2013

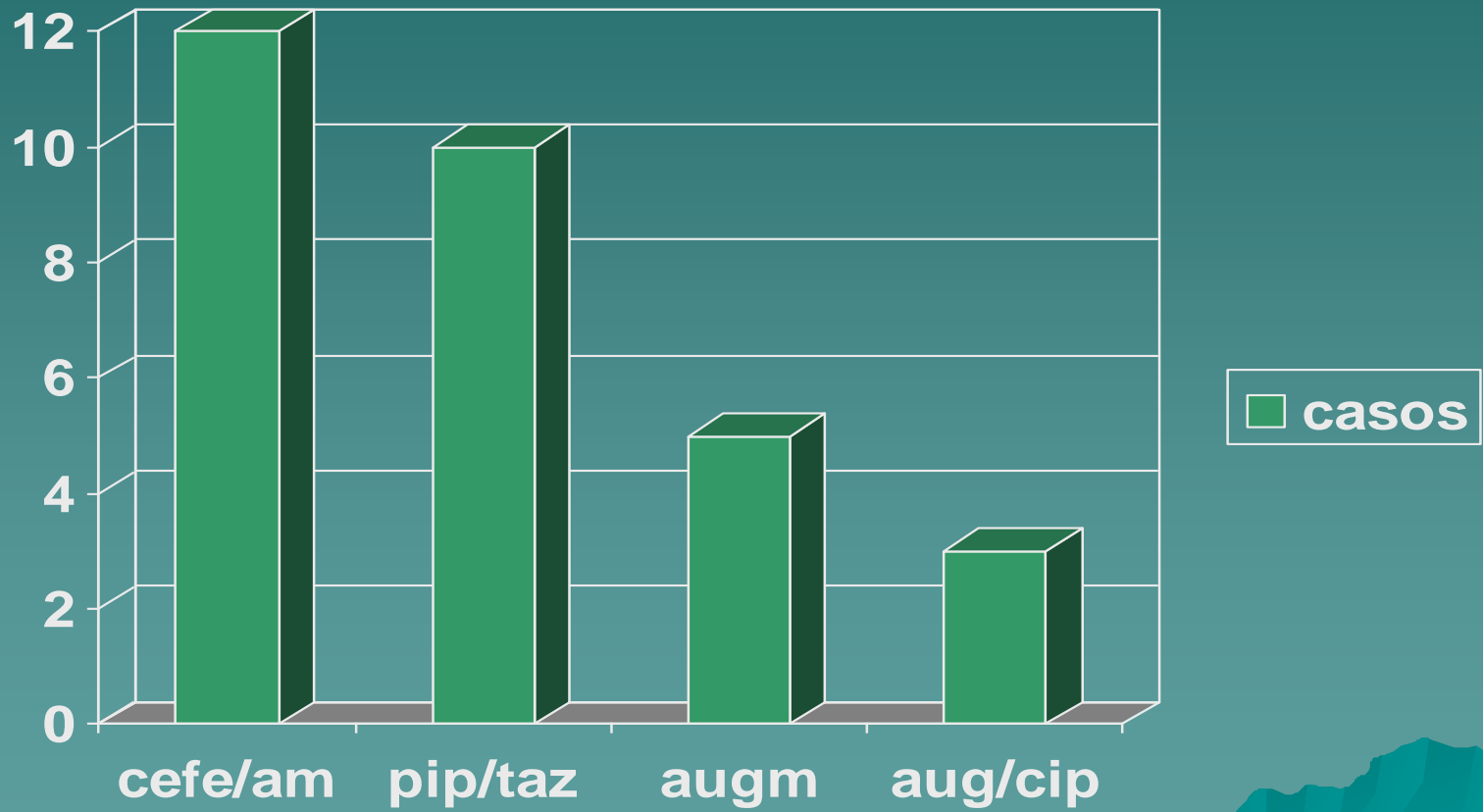
- ◆ 68 episodis.
- ◆ 67 % dones.
- ◆ Edat mitja 59 anys (28- 81).
- ◆ Neoplàsia sòlida: 76.5%.



Sant Camil 2008-2013 (II)

- ◆ Dies QTP: 10 (2- 51).
- ◆ Comorbilitat: 25%.
- ◆ Ingrés per urgències: 79.4%.
- ◆ Hemocultius: 88.2% (5% positius).
- ◆ Altres cultius: 57.4 %.
- ◆ Radiologia simple: 86.8%.
- ◆ MASCC < 21: 30.5%.
- ◆ Mortalitat: 5.9% (relacionat amb edat?, hipotensió i MASCC <21).

Antibiòtics



CONCLUSIONS

- ◆ És diferent la febre neutropènica de la sepsis neutropènica.
- ◆ Les infeccions per CGP són més freqüents però menys greus que les produïdes per BGN.
- ◆ Hi han escales de risc validades (MASCC) pronòstiques.
- ◆ Un bon i ràpid tractament antibiòtic és fonamental per la supervivència d'aquests pacients.