FUNGI & ANTI-F. AGENTS.

- ↑ IN FUNGAL INFECTIONS LATELY. REASONS:
  - BROAD SPECTRUM ANTI-BIOTICS (OPPORTUNISTIC)
  - IMMUNOSUPPRESSIVE AGENTS
  - INDWELLING CATHETERS
  - HOSPITALIZATION.
- CANDIDA IS 4th MOST COMMON BLOODSTREAM PATHOGEN & MOST DEADLY.
- CANDIDA IS AN OPPORTUNISTIC PATHOGEN.
- OTHER FUNGI CAN BE: OPPORTUNISTIC, SYSTEMIC (ANYTHING THAT ENDS IN MYCOSIS), SUBCUTANEOUS, SUPERFICIAL (DERMATOPHYTE)
- OROPHARANGEAL CANDIDIASIS (OPC)
  - IN HIV PATIENTS
  - DEVELOP RESISTANCE TO EVEN THE NEWEST DRUGS
  - AMPS (ANTI-MICROBIAL PEPTIDES) LIKE β-DEFENSINS CAN KILL THEM
- C. ALBICANS MOST COMMON. C. GLABRATA SECOND. KRUSEI & LUSANILEAE LEAST COMMON.
  - RECENT SHIFT TOWARDS NON-ALBICANS CANDIDA.
  - RISK FACTORS — GRANULOCYTOPENIA, MUCOSAL DISRUPTION FROM CHEMO.
- FLUCONAZOLE IS ORAL DRUG OF CHOICE. GOOD FOR MOST INFECTIONS, BAD FOR GLABRATA & REALLY BAD FOR KRUSEI
- NEUTROPENIC PATIENTS: AMPHOTERICIN B + FLUCONAZOLE.
- VORICONAZOLE & CASPOFUNGIN ARE NEW AGENTS.
- WHAT YOU LOOK FOR IN AN ANTI-FUNGAL AGENT:
  - FUNGICIDAL
  - BROAD SPECTRUM
  - HIGH TISSUE CONCENTRATION.
  - LOW RISK OF TOXICITY
  - LOW RATE OF RESISTANCE.
  - ORAL & I.V. FORMULATION.
  - INEXPENSIVE.

ANTIFUNGAL TARGETS

- MEMBRANE FUNCTION (AMPHOTERICIN B, NYSTATIN) ← POLYENES
- CELL WALL SYNTHESIS (ECHINOCANDINS: CASPOFUNGIN)
- NUCLEIC ACID SYNTHESIS (5-FLUOROCYTOSINE)
- ERGOSTEROL SYNTHESIS (AZOLES: FLUCONAZOLE)
- PROTEIN SYNTHESIS (SORAARNS)
- MANNOPROTEINS (~~TER~~ RADIMICINS)

- MIC - MINIMUM INHIBITORY CONCENTRATION. — YOU WANT AS LOW A NUMBER AS POSSIBLE
- ZONE OF INHIBITION SHOULD BE ≥16 mm (MAY REQUIRE INCREASED DOSAGE).
  >19 mm — REGULAR DOSE

MIC (FLUCONAZOLE) — AMOUNT REQUIRED TO KILL.
- < 8 μg/mL — SUSCEPTIBLE
- 16-32 μg/mL — DOSE-RELATED
- >64 μg/mL — RESISTANT

FILAMENTOUS FUNGI — AMPHOTERICIN B, CASPOFUNGIN, ITRACONAZOLE

ALBICANS — FLUCONAZOLE ONLY.

ECHINOCANDINS — NEW CLASS OF DRUGS — CAN'T DETERMINE EFFECTIVENESS IN VITRO.

AZOLES — ANY AGENT THAT ENDS IN CONAZOLE. YEAST & FILAMENTOUS FUNGI (EXCEPT FLUCONAZOLE — YEAST ONLY)

ACTION — INHIBITS DIFFERENT STEPS IN SYNTHESIS OF ERGOSTEROL.

RESISTANCE — ALTERATION IN TARGET ENZYME
- ALTERATION IN STEROL BIOSYNTHESIS (ACCUMULATION OF 14-α-METHYL FECOSTEROL).
- REDUCTION IN INTRACELLULAR TARGET ENZYME CONCENTRATIONS (MORE ENZYME PUMPS)
- OVEREXPRESSION OF TARGET ENZYME.

POLYENES — AMPHOTERICIN B, NYSTATIN, LIPID-BASED POLYENES.

RESISTANCE — NO WIDESPREAD RESISTANCE (EXCEPT LUSITANEAE) DUE TO QUALITATIVE OR QUANTITATIVE CHANGE IN MEMBRANE STEROLS.

ACTION — BINDS TO ERGOSTEROL & MAKES PORES IN MEMBRANE.

5-FLUOROCYTOSINE — DOESN'T WORK AGAINS FILAMENTOUS FUNGI. USED IN COMBINATION WITH OTHER DRUGS.

ACTION — INHIBITS NUCLEIC ACID SYNTHESIS.

RESISTANCE — BLOCKED UPTAKE, BLOCKS FORMATION OF FUMP (ALTERNATE PATHWAY THAT BLOCKS N.A. SYNTHESIS).

ECHINOCANDINS - INHIBIT CELL WALL SYNTHESIS. BLOCKS β1,3-D GLUCAN SYNTHASE.

★CASPOFUNGIN

RESISTANCE - MUTATION OF TARGET GENE
- OVEREXPRESSION OF WALL SYNTHESIS TRANSPORT ENZYME.
- TRANSPORTER THAT SENDS DRUG OUT OF CELL. (ABC TRANSPORTERS)
- RESISTANCE TO ONE ECHINOCANDINS DOESN'T MEAN RESISTANCE TO ALL ECHINOCANDINS.
- NEW FORMS OF RESISTANCE ARE LIKELY TO EMERGE.

COMBINATION THERAPY

- SYNERGY — POSITIVE INTERACTION
- ANTAGONISM — NEGATIVE INTERACTION
- ADDITIVITY/INDIFFERENCE/NO INTERACTION — OBSERVED EFFECT IS SUM OF INDIVIDUAL EFFECTS.
  - ★ FLUCONAZOLE + AMPHOTERICIN B — NO ANTAGONISM.
- VORI + ANYTHING — FOR FILAMENTOUS FUNGI (EXCEPT MUCRF)
- ANYTHING ELSE - FOR CANDIDA (YEAST).

FOR TREATMENT

- START WITH MOST POTENT ANTI-FUNGAL
- INCREASE DOSE
- LOOK FOR SYNERGY WITH OTHER AGENTS
- COMBINATION FOR PATIENTS WHO ARE UNRESPONSIVE TO MONOTHERAPIES OR MIC'S OF AGENTS ARE HIGH.