Table 1 Summary of evidence of interaction and effects of combination antifungal therapy against Candida spp investigated by in vitro, animal and clinical studies

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| --- | --- | --- | --- | --- |
| **Authors, date** | **N** | **Combination/ comparator** | **Species** | **Major findings** |
| **In vitro** | | | | |
| *Flucytosine combinations* | | | | |
| **Flucytosine and Amphotericin B** | | | | |
| Dupont 19791 | 27 | Flucytosine + amphotericin B | *C. albicans* (26),  *C. parapsilosis* (1) | Indifference (26 – *C. albicans*)  Synergy (1 – *C. parapsilosis*) |
| Chen 19822 | 10 | Flucytosine + amphotericin B | *C. albicans* | Synergy (10) |
| Odds 19823 | 6 | Flucytosine + amphotericin B | *C. albicans* (3),  *C. kefyr* (1),  *C. tropicalis* (1),  *C. krusei* (1) | Synergy (1)  Indifference (5) |
| Scalarone 19924 | 10 | Flucytosine + amphotericin B | *C. albicans* (10) | Synergy (1)  Indifference (9) |
| Lewis 20025 | 6 | Flucytosine + amphotericin B | *C. albicans* (3*),*  *C. glabrata* (1),  *C. krusei* (1*),*  *C. tropicalis* (1) | Synergy (4 - 2 *C. albicans*, 1 *C. glabrata*, 1 *C. tropicalis*)  Indifference (2 - 1 *C. albicans*, 1 *C. krusei*) |
| Te Dorsthorst 20026 | 27 | Flucytosine + amphotericin B | *C. albicans* (9),  *C. glabrata* (9),  *C. krusei* (9) | Synergy (1 *C. krusei*)  Indifference (26 - 9 *C. albicans*, 9 *C. glabrata*, 8 *C. krusei*) |
| Alves 20127 | 68 | Flucytosine + amphotericin B | *C. glabrata* (34 FLZ-S, 34 FLZ-R) | FLZ-S:  - Synergy (21)  - Indifference (13)  FLZ-R:  - Synergy (26)  - Indifference (8) |
| Bidaud 20198 | 15 | Flucytosine + amphotericin B | *C. auris* | Synergy (1)  Indifference (14) |
| Chassot 20199 | 60 | Flucytosine + amphotericin B | *C. parapsilosis*  (30 ECH-S, 10 ANF-R, 10 CSF-R, 10 MCF-R) | ECH-S:  - Synergy (9)  -Indifference (21)  ANF-R:  - Synergy (2)  - Indifference (6)  - Antagonism (2)  CSF-R:  - Indifference (7)  - Antagonism (3)  MCF-R:  - Synergy (1)  - Indifference (1)  - Antagonism (8) |
| O’Brien 202010 | 13 | Flucytosine + amphotericin B | *C. auris*  (4 AmB-R, 1 5FC-R) | Indifference (13) |
| O’Brien 2020a11 | 4 | Flucytosine + amphotericin B | *C. auris* (AmB-R, ECH-R, AZ-R) | Indifference (3)  Antagonism (1) |
| Khalifa 202112 | 17 | Flucytosine + amphotericin B | *C. glabrata* | Indifference (17) |
| John 202313 | 11 | Flucytosine + amphotericin B | *C. auris* | Indifference (11) |
| **Flucytosine and Echinocandins** | | | | |
| Karlowsky 200514 | 18 | Flucytosine + anidulafungin | *C. albicans (4),*  *C. glabrata (4),*  *C. krusei (2),*  *C. tropicalis (4),*  *C. parapsilosis (4)* | Indifference (18) |
| Alves 20127 | 68 | Flucytosine + caspofungin | *C. glabrata*  (34 FLZ-S, 34 FLZ-R) | FLZ-S:  - Synergy (10)  - Indifference (23)  - Antagonistic (1)  FLZ-R:  - Synergy (16)  - Indifference (18) |
| Rosato 201215 | 13 | Flucytosine + anidulafungin | 13 *Candida* spp | Synergy (10)  Indifference (3) |
| Bidaud 20198 | 15 | Flucytosine + micafungin | *C. auris* | Synergy (1)  Indifference (14) |
| O’Brien 202010 | 42 | Flucytosine + anidulafungin/ micafungin/ caspofungin | *C. auris*  (6 ECH-R, 2 5FC-R. | Synergy (4)  Indifference (38) |
| O’Brien 2020a11 | 12 | Flucytosine + micafungin/ caspofungin/ anidulafungin | *C. auris* (AmB-R, ECH-R, AZ-R) | Indifference (8)  Antagonism (4) |
| Khalifa 202112 | 17 | Flucytosine + caspofungin | *C. glabrata* (6 ECH-R) | Indifference |
| John 202313 | 11 | Flucytosine + anidulafungin | *C. auris* | Synergy (2)  Indifference (9) |
| **Flucytosine and Azoles** | | | | |
| Dupont 19791 | 26 | Flucytosine + econazole/miconazole | *C. albicans* | Synergy (22)  Indifference (4) |
| Odds 19823 | 12 | Flucytosine + ketoconazole/miconazole | *C. albicans (3),*  *C. kefyr (1),*  *C. tropicalis (1),*  *C. krusei (1)* | Synergy (1)  Indifference (11) |
| Lewis 20025 | 6 | Flucytosine + fluconazole | *C. albicans* (3),  *C. glabrata* (1),  *C. krusei* (1),  *C. tropicalis* (1) | Synergy (3 - 1 *C. albicans*, 1 *C. glabrata*, 1 *C. tropicalis*)  Indifference (3 - 2 *C. albicans*, 1 *C. krusei*) |
| Te Dorsthorst 20026 | 27 | Flucytosine + fluconazole | *C. albicans* (9),  *C. glabrata* (9),  *C. krusei* (9) | Synergy (6 - 5 *C. albicans*, 1 *C. krusei*)  Indifference (13 - 3 *C. albicans*, 2 *C. glabrata*, 8 *C. krusei*)  Antagonism (8 - 1 *C. albicans*, 7 *C. glabrata*) |
| Barchiesi, 200416 | 20 | Flucytosine + voriconazole | *C. glabrata* | Synergy (1)  Indifference (19) |
| Alves 20127 | 136 | Flucytosine + voriconazole/ itraconazole | *C. glabrata*  (34 FLZ-S and 34 FLZ-R) | FLZ-S:  - Synergy (16)  - Indifference (38)  - Antagonistic (14)  FLZ-R:  - Synergy (31)  - Indifference (36)  - Antagonistic (1) |
| Steier 201317 | 17 | Flucytosine + fluconazole/ posaconazole/ voriconazole/ itraconazole | *C. glabrata* (up to 8) | Antagonism (17) |
| Bidaud 20198 | 15 | Flucytosine + voriconazole | *C. auris* | Indifference (15) |
| Chassot 201918 | 120 | Flucytosine + fluconazole/ voriconazole | *C. parapsilosis*  (30 ECH-S, 10 ANF-R, 10 CSF-R, 10 MCF-R) | ECH-S:  - Synergy (9)  - Indifference (47)  - Antagonism (4)  ANF-R:  - Synergy (3)  - Indifference (13)  - Antagonism (4)  CSF-R:  - Indifference (15)  - Synergy (5)  MCF-R:  - Synergy (2)  - Indifference (2)  - Antagonism (16) |
| O’Brien 202010 | 57 | Flucytosine + isavuconazole/ itraconazole/ posaconazole/ voriconazole | *C. auris*  (14 FLZ-R, 2 5FC-R) | Synergy (1)  Indifference (56) |
| O’Brien 2020a11 | 16 | Flucytosine + isavuconazole/ posaconazole/ voriconazole | *C. auris*  (all AmB-R, ECH-R, AZ-R) | Indifference (13)  Antagonism (3) |
| Khalifa 202112 | 68 | Flucytosine + fluconazole/ itraconazole/ voriconazole/ posaconazole | *C. glabrata* | Indifference (68) |
| John 202313 | 11 | Flucytosine + voriconazole | *C. auris* | Indifference (8)  Antagonistic (3) |
| **Triple drug combinations – Flucytosine + Amphotericin B + Azoles** | | | | |
| Odds 19823 | 18 | Flucytosine + amphotericin B + ketoconazole/ miconazole | *C. albicans (3),*  *C. kefyr (1),*  *C. tropicalis (1),*  *C. krusei (1)* | Synergy (3)  Indifference (9)  + KCZ + MCZ:  - Synergy (3)  - Indifference (3) |
| *Amphotericin combinations* | | | | |
| **Amphotericin B and Echinocandins** | | | | |
| Barchiesi 200519 | 2 | Amphotericin B + caspofungin | *C. glabrata* (2) | Indifference (2) |
| Barchiesi 200720 | 3 | Amphotericin B + caspofungin | *C. parapsilosis* (3) | Indifference (3) |
| Karlowsky 200514 | 18 | Amphotericin B + anidulafungin | *C. albicans (4),*  *C. glabrata (4),*  *C. krusei (2),*  *C. tropicalis (4),*  *C. parapsilosis (4)* | Indifference (18) |
| Serena 200821 | 145 | Amphotericin B + micafungin | *C. krusei* (35),  *C. albicans* (35),  *C. parapsilosis* (15), *C. tropicalis* (15),  *C. dubliniensis* (20), *C. glabrata* (15),  *C. lusitaniae* (10) | Synergy (32)  Indifference (113) |
| Tobudic 201022 | 22 | Amphotericin B + caspofungin | *C. albicans* (planktonic (11) & biofilms (11)) | Synergy (4 – all planktonic)  Indifference (18) |
| Chaturvedi 201123 | 15 | Amphotericin B + anidulafungin/ caspofungin/ micafungin | *C. parapsilosis* (2), *C. albicans* (2),  *C. glabrata* (1) | Synergy (5 - 1 *C. albicans*, 4 *C. parapsilosis*)  Indifference (10) |
| Alves 20127 | 68 | Amphotericin B + caspofungin | *C. glabrata*  (34 FLZ-S, 34 FLZ-R | FLZ-S:  - Synergy (2)  - Indifference (27)  - Antagonism (5)  FLZ-R:  - Synergy (16)  - Indifference (18) |
| Rosato 201215 | 13 | Amphotericin B + anidulafungin | 13 *Candida* spp | Synergy (9)  Indifference (4) |
| Denardi 201724 | 60 | Amphotericin B + anidulafungin/caspofungin/ micafungin | *C. glabrata* (FLZ-R + CSF-R) | Synergy (14)  Indifference (32)  Antagonism (14) |
| Jaggavarapu 202025 | 10 | Amphotericin B + micafungin | *C. auris* | Synergy (8)  Indifference (2) |
| Reginatto 202026 | 9 | Amphotericin B + anidulafungin | *C. parapsilosis* x3,  *C. albicans* x3,  *C. tropicalis* x3 | Synergy to inhibit and remove biofilms (9) |
| Khalifa 202112 | 17 | Amphotericin B + caspofungin | *C. glabrata* (6 ECH-R) | Synergy (4) – all ECH-R  Indifference (13) |
| Hernando-Ortiz 202427 | 15 | Amphotericin B + anidulafungin/ caspofungin/ micafungin | *C. auris*  (4 non-aggregative, 1 aggregative) | Synergy (14)  Indifference (1 – AMB + MFG against aggregative strain) |
| **Amphotericin B and Azoles** | | | | |
| Dupont 19791 | 26 | Amphotericin B + econazole/ miconazole | *C. albicans* (26) | Antagonism (26) |
| Odds 19823 | 18 | Amphotericin B + ketoconazole/ miconazole | *C. albicans* (3),  *C. kefyr* (1),  *C. tropicalis* (1),  *C. krusei* (1) | Synergy (5)  Indifference (7)  + KCZ + MCZ:  - Synergy (1)  - Indifference (5) |
| Petrou 199128 | 32\* | Amphotericin B + fluconazole/itraconazole/ketoconazole/miconazole | *C. albicans* (30), others (24) | Mean FICIs for species/drug combinations:  Indifference (23)  Antagonism (9) |
| Lewis 20025 | 6 | Amphotericin + fluconazole | *C. albicans* (3),  *C. glabrata* (1),  *C. krusei* (1),  *C. tropicalis* (1) | Synergy (1 – *C. glabrata*)  Indifference (5 – 3 *C. albicans*, 1 *C. krusei*, 1 *C. tropicalis*) |
| Barchiesi, 200416 | 20 | Amphotericin + voriconazole | *C. glabrata* | Synergy (2)  Indifference (18) |
| Tobudic 201022 | 22 | Amphotericin B + posaconazole | *C. albicans* Planktonic (11)  Biofilm (11) | Planktonic: indifference (11)  Biofilm: synergy (11) |
| Chaturvedi 201123 | 10 | Amphotericin B + posaconazole/ voriconazole | *C. parapsilosis* (2), *C. albicans* (2),  *C. glabrata* (1) | Synergy (2 – 1 *C. albicans*, 1 *C. glabrata)*  Indifference (8) |
| Alves 20127 | 68 | Amphotericin + voriconazole | *C. glabrata*  (34 FLZ-S, 34 FLZ-R) | FLZ-S:  - Synergy (2)  - Indifference (22)  - Antagonism (10)  FLZ-R:  - Synergy (19)  - Indifference (15) |
| Siopi 201529 | 24 | Amphotericin B + voriconazole | *C. glabrata* (2),  *C. albicans* (2),  *C. parapsilosis* (2), *C. krusei* (2),  *C. tropicalis* (2),  *C. kefyr* (2) | Indifference, occasional antagonism (FICI range 0.69-4.5) |
| Katragkou 201730 | 18 | Amphotericin B + isavuconazole | *C. glabrata* (4),  *C. krusei* (3),  *C. albicans* (4),  *C. parapsilosis* (3), *C. tropicalis* (4) | Synergy (3 – *C. krusei*)  Indifference (11 *– C. albicans, C. parapsilosis, C. tropicalis*)  Antagonism (4 – *C. glabrata)* |
| Chassot 201918 | 120 | Amphotericin B + fluconazole/voriconazole | *C. parapsilosis*  (30 ECH-S, 10 ANF-R, 10 CSF-R, 10 MCF-R) | ECH-S:  - Indifference (29)  - Antagonism (31)  ANF-R:  - Synergy (3)  - Indifference (16)  - Antagonism (1)  CSF-R:  - Indifference (11)  - Antagonism (9)  MCF-R:  - Indifference (16)  - Antagonism (4) |
| Khalifa 202112 | 68 | Amphotericin B + fluconazole/ itraconazole/ voriconazole/ posaconazole | *C. glabrata* (17) | Synergy (11)  Indifference (57) |
| *Echinocandin combinations* | | | | |
| **Echinocandin and azoles** | | | | |
| Heyn 200531 | 98 | Micafungin + voriconazole | *C. albicans* (55),  *C. dubliniensis* (19), *C. glabrata* (12),  *C. parapsilosis* (12) | Synergy (3 - 1 *C. albicans*, 2 *C. glabrata*)  Indifference (95) |
| Karlowsky 200614 | 36 | Anidulafungin + fluconazole/ itraconazole | *C. albicans* (4),  *C. glabrata* (4),  *C. krusei* (2),  *C. tropicalis* (4),  *C. parapsilosis* (4) | Synergy (1 *C. glabrata*)  Indifference (35) |
| Chaturvedi 201123 | 30 | Anidulafungin/ caspofungin/ micafungin + posaconazole/ voriconazole | *C. parapsilosis* (2), *C. albicans* (2),  *C. glabrata* (1) | Indifference (30) |
| Alves 20127 | 68 | Caspofungin + voriconaozle | *C. glabrata* (34 FLZ-S, 34 FLZ-R) | FLZ-S:  - Indifference (29)  - Antagonism (5)  FLZ-R:  - Synergy (10)  - Indifference (24) |
| Rosato 201215 | 13 | Anidulafungin + fluconazole | 13 *Candida* spp | Synergy (10)  Indifference (3) |
| Chen 201332 | 10 | Caspofungin + posaconazole | *C. albicans* | Synergy (10, including 4 ECH-R and 1 FLZ-R) |
| Siopi 201529 | 24 | Caspofungin + voriconazole | *C. glabrata (2),*  *C. albicans (2),*  *C. parapsilosis (2), C. krusei (2),*  *C. tropicalis (2),*  *C. kefyr (2)* | Indifference, occasional synergy (FICI range 0.5-2.06) |
| Denardi 201724 | 180 | Caspofungin/ micafungin/ anidulafungin + fluconazole/ posaconazole/ voriconazole | *C. glabrata*  FLZ+CSF-R (20) | Synergy (76)  Indifference (91)  Antagonism (13) |
| Fakhim 201733 | 40 | Micafungin/ caspofungin and voriconazole/ fluconazole | *C. auris* (10 - all FLZ-R, 6 ECH-R) | Synergy (10)  Indifference (30) |
| Katragkou 201730 | 18 | Micafungin + isavuconazole | *C. glabrata (*4),  *C. krusei* (3),  *C. albicans* (4),  *C. parapsilosis* (3), *C. tropicalis* (4) | Synergy (10, *C. albicans, C.* *parapsilosis, C. krusei)*  Indifference (8, *C. glabrata, C. tropicalis*) |
| Caballero 202134 | 18 | Anidulafungin/ caspofungin/ micafungin + isavuconazole | *C. auris* (6) | Synergy (18) |
| Khalifa 202112 | 68 | Caspofungin + fluconazole/ itraconazole/ voriconazole/ posaconazole | *C. glabrata* (17, 6 ECH-R) | Synergy (15)  Indifference (53) |
| Nagy 202135 | 23 | Caspofungin + isavuconazole | *C. auris* (23 - South Asian (9); East Asian (4); South African (5); South American (5)) | Synergy (14)  Indifference (9) |
| Pfaller 202136 | 72 | Anidulafungin + isavuconazole/ voriconazole | *C. auris* (36 - 32 FLZ-R, 9 VRC-NWT, 5 ECH-NWT) | Synergy (16)  Indifference (55)  Antagonism (1) |
| Balla 202237 | 8 | Caspofungin + posaconazole | *C. auris* (4 CSF-R) | Synergy (4)  Indifference (4) |
| **Animal models** | | | | |
| *Flucytosine combinations* | | | | |
| **Flucytosine + amphotericin B** | | | | |
| Titsworth 197338 | Mice I/S (cortisone) 8/group | Flucytosine + amphotericin B | *C. albicans* | Synergy (kidney culture sterility) for combination; reduced doses possible with combination |
| Rabinovich 197439 | Mice  44/group | Flucytosine + amphotericin B | *C. albicans* | Combination showed improved survival and reduced tissue burden |
| Polak 198240 | Mice | Flucytosine + amphotericin B | *C. albicans* (3) | Synergy, or “definitely additive” for all strains including 5FC-R strain. Increased survival, dose-dependent synergy/indifference |
| Polak 198741 | Mice | Amphotericin B + flucytosine | *C. albicans* | Synergy, increased survival. Dose-dependent synergy/indifference |
| Thaler 198842 | Rabbits (12, neutropenic (Ara-C)) | Flucytosine + amphotericin B | *C. albicans,*  *C. tropicalis* (2) | Complete fungal eradication from kidney (most refractory site) |
| Atkinson 199543 | Mice (I/S with 5FU) | Flucytosine + amphotericin B | *C. glabrata*  (4- 2 FLZ-R) | Equal kidney/spleen burden reduction to AmB monotherapy; more effective than FLZ or 5FC monotherapy |
| Hope 200544 | Mice I/S (CP) 3/group | Flucytosine + Amphotericin B | *C. albicans* | Constructed a model for in vivo interaction of amphotericin B and flucytosine in murine kidney ­- additive interaction |
| **Flucytosine + echinocandin** | | | | |
| Mariné 200645 | Mice (I/S with CP/5FU, 10-20/group) | Flucytosine + micafungin | *C. glabrata* (1) | Reduced fungal burden compared to mono in spleen but not kidney |
| **Flucytosine + azoles** | | | | |
| Polak 198240 | Mice | Flucytosine + ketoconazole | *C. albicans* (3) | Indifference (3) |
| Polak 198741 | Mice | Flucytosine + itraconazole/ fluconazole | *C. albicans* | Synergy, increased survival. Dose-dependent synergy/indifference |
| Thaler 198842 | Rabbits (12, neutropenic (Ara-C)) | Flucytosine + ketoconazole | *C. albicans,*  *C. tropicalis* (2) | Less effective at fungal eradication than KTZ monotherapy |
| Atkinson 199543 | Mice (I/S with 5FU) | Flucytosine + fluconazole | *C. glabrata* (4- 2 FLZ-R) | Additive effect for 1 isolate, no reduction in fungal burden for other 3 isolates |
| *Amphotericin combinations* | | | | |
| **Amphotericin B + echinocandin** | | | | |
| Hossain 200346 | 7 mice/ group | Amphotericin B + caspofungin | *C. albicans* (AZ-R) single clinical isolate | Combination has no significant increase in survival; significantly reduced kidney CFU vs monotherapy CSF and brain CFU vs monotherapy AmB |
| Barchiesi 200519 | 7-10 mice/group (neutropenic – CP) | Amphotericin B + caspofungin | *C. albicans* | Kidney tissue burden CSF+AmB < AmB or CSF |
| Olson 200547 | 7 mice/ group (I/S – CP) | Amphotericin B ± caspofungin/ micafungin (given sequentially and in combination) | *C. glabrata* | AmB+CSF/MCF significantly enhanced fungal clearance in kidneys / was sterilising in some cases |
| Mariné 200645 | Mice (I/S with CP/5FU, 10-20/group) | Amphotericin B + micafungin | *C. glabrata* (1) | More effective than monotherapy on survival and tissue fungal burden |
| Barchiesi 200720 | 8 mice/group (I/S - CP) | Amphotericin B + caspofungin | *C. parapsilosis* (3) | Kidney tissue burden CSF+AmB < AmB or CSF |
| **Amphotericin B + azole** | | | | |
| Polak 198240 | Mice | Amphotericin B + ketoconazole | *C. albicans* (3) | Synergy (1)  Antagonism (2) |
| Polak 198741 | Mice | Amphotericin B + itraconazole | *C. albicans* | Mainly indifference and antagonism. Decreased survival |
| Thaler 198842 | Rabbits (12, neutropenic (Ara-C)) | Amphotericin B + ketoconazole | *C. albicans,*  *C. tropicalis* (2) | Reduction in fungal burden in kidney, eradication in other organs (as does AmB monotherapy) |
| Atkinson 199543 | Mice (I/S with 5FU) | Amphotericin B + fluconazole | *C. glabrata* (4- 2 FLZ-R) | Ineffective, possible antagonism |
| Sugar 199548 | Mice- I/S and non-I/S | Amphotericin B ± fluconazole | *C. albicans* | Survival and tissue burden  combination no better than AmB monotherapy |
| Sanati 199749 | Mice neutropenic (CP)  Rabbit endocarditis | Amphotericin B ± fluconazole | *C. albicans* | Mice - survival similar in all arms  - kidney tissue burden AmB±FLZ= AMB >FLZ  - brain burden FLZ±AmB = FLZ >AmB  Rabbit endocarditis – AMB >AmB±FLZ>FLZ |
| Sugar 199850 | Mice | Amphotericin B ± itraconazole | *C. albicans* | Combination has negative interaction on survival and kidney burden v AmB |
| Louie 199951 | Rabbit endocarditis, endophthalmitis and pyelonephritis (20-30/group) | Amphotericin B + fluconazole | *C. albicans* | Eye (vitreous) fungal burden: faster clearance but equivalent d14 efficacy to monotherapies  Kidney/heart valve fungal burden: more active than FLZ monotherapy at reducing but less effective than AmB monotherapy.  Similar d14/21 efficacy to monotherapies. |
| Louie 199952 | Mice | Amphotericin B ± fluconazole | *C. albicans* FLZ-S (1) and FLZ-R (3) | AmB>AmB+FLZ>FLZ for survival  Tissue burden kidney AmB=AmB+FLZ  Concludes that AmB+FLZ antagonistic (FLZ-S), or additive (FLZ-R) |
| Louie 200153 | Rabbit endocarditis and pyelonephritis | Amphotericin B ± fluconazole | *C. albicans* | Pre-exposure of *C. albicans* to FLZ reduces fungal susceptibility to AmB.  AmB+FLZ most rapidly sterilised kidneys and cardiac vegetations |
| Meletiadis 2023  54 | Neutropenic mice | Amphotericin B + posaconazole (3 different doses) | *C. albicans* | Kidney burden - synergistic (low AmB dose) and antagonistic (intermediate/high AmB doses) |
| **Echinocandin + azole** | | | | |
| Graybill 200355 | 8-12 mice/ group | Caspofungin + fluconazole | *C. albicans* | CSF>CSF±FLZ>FLZ in reducing kidney CFU |
| Mariné 200645 | Mice (I/S with CP/5FU, 10-20/group) | Micafungin + fluconazole | *C. glabrata* (1) | Less effective than monotherapy on tissue fungal burden |
| Chen 201332 | 5 mice/ group | Caspofungin + posaconazole | *C. albicans,* FLZ-R and ECH-R FKS mutant strain | Combination showed improved survival in wild type and FLZ-R isolate |
| Nagy 202135 | 8 mice/ group (I/S – CP) | Caspofungin + isavuconazole | *C. auris* | Combination showed (non-significant) reduction in kidney tissue burden compared to CSF monotherapy |
| **Clinical studies** | | | | |
| **Flucytosine + amphotericin B** | | | | |
| Kujath 199356 | Randomised trial,  n = 40  Deep-seated candidiasis in surgical patients | Fluconazole (400mg STAT, 300mg/d) (20) vs amphotericin B (0.5 mg/kg) + flucytosine (3 x 2.5 g) (20) | *C. albicans* (34),  *C. glabrata*(7),  *C. troplicalis*(3)  Some mixed infection | Earlier elimination with AmB/5FC: 5.5d vs 8.5d  Similar elimination/reduction rates: 17/20 (85%) with AmB/5FC vs 18/20 (90%) with FLZ)  Similar mortality: 5/20 (25%) with AmB/5FC, 6/20 (30%) with FLZ  Nephrotoxicity leading to 1 treatment failure with AmB/5FC. No other toxicity |
| Abele-Horn 199657 | Randomised  trial  72 Systemic  candidiasis in  ICU | Fluconazole (400mg STAT,  200mg/d) (36) vs  amphotericin B (1-1.5 mg/kg)  + flucytosine (3 x 2.5 g) (36) | *C. albicans,*  *C. glabrata,*  *C. tropicalis,*  *C. krusei,*  *C. guillermondii*  *21 x mixed*  *infection* | Successful pathogen eradication at end of treatment in 42/52 (83%) with AmB/5FC vs 22/46 (48%) with FLZ p<0.001.  Similar overall cure (61% vs 56%)  and mortality (39% vs 36%)  Nephrotoxicity: 31% in AmB/5FC vs  0% in FLZ |
| **Fluconazole + amphotericin B** | | | | |
| Rex 200358 | Randomised trial, n = 219 Candida bloodstream infection (candidaemia) | Fluconazole(800mg) ± amphotericin B | Non-*krusei Candida* spp | Combination had higher success rates (69% vs 56%, p=0.043):  - Improved blood stream clearance: 94% vs 83% (p=0.02)  - 38% lower odds of failure with combined therapy  - No antagonism  No difference in 90d mortality (39, 40%), higher nephrotoxicity in combined treatment |

Abbreviations: AmB = Amphotericin B; ECH = Echinocandin; CSF = Caspofungin; MCF = Micafungin; ANF = Anidulafungin; 5FC = Flucytosine; AZ = Azole; FLZ = Fluconazole; MCZ = Miconazole; PSZ = Posaconazole; VRC = Voriconazole; NWT = Non-Wild Type; -S, -R = sensitive, resistant; I/S = Immunosuppression.

Studies included if investigating antifungal drugs currently in use, *in vitro* studies included if used checkerboard techniques that reported fractional inhibitor concentration indices (FICI), defining synergy as FICI ≤0.5, indifferent 0.5-4.0, and antagonistic >4.

\*Mean FICIs for each *Candida* species/antifungal combination.

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