**Supplementary material**

**Table S1. Drugs available for antifungal therapy in hospitals during 2016.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antifungal acquired by hospital or patient\*** | **HRAEO**  **(PRICE PER UNIT)** | **INCAN**  **(PRICE PER UNIT)** | **HRAEB**  **(PRICE PER UNIT)** | **HUNL**  **(PRICE PER UNIT)** | **Patient**  **(PRICE PER UNIT) +** | **NGO’s** |
| **Amphotericin B deoxycholate**  **(Generic)** | X  ($5-25) | X  ($8.9) | X  ($14) | X  ($13.5) | X\*\* | X\*\*  ($14) |
| **Liposomal amphotericin B** | -- | -- | X  ($190) | -- | X  ($154-230) | X  ($175) |
| **Generic fluconazole**  **(oral, IV)** | X  ($0·8) | X  ($1·2) | X  ($0·7) | X  ($0·4) | -- | -- |
| **Itraconazole**  **(generic)** | -- | X  ($1·8) | -- | X  ($0·3) | X  ($5-14) | X  ($5-14) |
| **Voriconazole++ (IV solution)** | X  ($36·4) | X  ($36·4) | X  ($36·4) | X  ($38·63) | -- | -- |
| **Voriconazole++(oral formulation)** | -- | X  ($118) | -- | -- | X  ($150) | -- |
| **Posaconazole (Oral solution)** | X  ($558) | X  ($558) | X\*\*\*  ($766) | -- | -- | -- |
| **Posaconazole (Tablets)** | -- | -- | -- | -- | X  ($1,258) | -- |
| **Caspofungin** | X  ($110) | X  ($104) | X  ($102-104) | X | -- | -- |
| **Anidulafungin** | -- | -- | X  ($87·5) | -- | -- | -- |

\* Antifungals bought by hospital after public tenders for antifungal therapy, the cost is refunded to the hospital, or not, by patients depending on their socioeconomic conditions and public health insurance.

\*\*During 2016 and part of 2017, there was an out of stock situation, most of the hospitals in Mexico did not have AmBD available and patients had to sometimes buy the drug externally.

\*\*\* Only offered for prophylaxis in hematopoietic stem cells transplants.

Prices in US dollars

+ Public price. Prices variates depending on the public tenders for hospitals.

UNITS: Amphotericin B (both types) 50 mg per vial, fluconazole IV 100 mg per vial, itraconazole oral formulation 100 mg with 15 tablets, voriconazole IV 200 mg per vial, voriconazole oral formulation 14 tablets 200 mg each, posaconazole solution 40mg/ml, posaconazole tablets 100 mg with 24 tablets, caspofungin and anidulafungin 50mg and 100 mg respectively per vial. ++Costs for voriconazole and fluconazole were adjusted depending on the formulation used during treatment.

**Table S2. Characteristics by proven vs possible IFIs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Proven/**  **probable IFI**  **n= 98 (%)** | **NF-possible IFI n= 39 (%)** | **non-NF possible IFI**  **n= 101 (%)** | ***p* value** |
| **Age, yrs (median, IQR)** | 40 (22-58) | 16 (12-32) | 48 (27-60) | <0·0001 |
| **Sex (Female)** | 40 (41) | 21 (54) | 44 (44) | 0·37 |
| **Comorbidities**  Haematological malignancy  Solid neoplasia  Diabetes mellitus  HIV infection  Renal transplant  Other\*\* | 40 (41)  8 (8)  10 (10)  19 (19)  0  21 (21) | 29 (74)  8 (20)  0  0  2 (5)  0 | 11 (11)  22 (22)  15 (15)  1 (1)  11 (11)  41 (41) | <0·0001 |
| **First antifungal used**  Fluconazole  Caspofungin  AMBD  Anidulafungin  Voriconazole  Lipid formulation of AMB  Itraconazole | 11 (11)  18(19)  26 (27)  6 (6)  15 (15)  8 (8)  10 (9) | 23 (59)  4 (10)  10 (26)  1 (3)  1 (2.5)  0  0 | 51 (50)  20 (20)  2 (2)  19 (19)  3 (3)  5 (5)  1 (1) | <0·0001 |
| **Second antifungal used (N=80/242, 33%)**  Fluconazole  Voriconazole  Caspofungin  Lipid formulation of AMB  AMBD | **N=47**  15 (32)  12 (25)  2 (4)  2 (4)  7 (15) | **N=9**  1 (11)  2 (22)  4 (44)  0  1 (11) | **N=24**  7 (29)  1 (4)  4 (17)  6 (25)  0 | 0·002 |
| **Time of antifungal treatment (days, median, IQR)** | 16 (10-51) | 9 (5-15) | 7 (4-11) | <0·0001 |
| **Total cost of antifungal drug (US dollars, median, IQR)** | 651 (107-1847) | 84 (7-216) | 87 (7-699) | <0·0001 |
| **Hospital length of stay (days, median, IQR)** | 19 (14-33) | 17 (13-27) | 21 (12-30) | 0·76 |
| **Hospitalization cost (US dollars, median, IQR)** | 455 (172-1,258) | 184 (101-437) | 498 (141-1,163) | 0·01 |
| **Acute kidney injury** | 26 (27) | 4 (10) | 9 (9) | 0·002 |
| **Liver damage during antifungal treatment** | 33 (34) | 10 (26) | 15 (15) | 0·006 |
| **ICU stay** | 29 (30) | 6 (15) | 48 (47) | 0·001 |
| **ICU length of stay (days, median, IQR)** | 8 (4-13) | 8 (5-26) | 14 (8-20) | 0·01 |
| **Mortality rate\*** | 29 (32) | 6 (16) | 19 (19) | 0·05 |

\*Only 229 out of 238 outcomes were available.

IFI: Invasive fungal infection, IQR: Interquartile range

Currency: $20 Mexican peso by $1 US dollar. AMBD= Amphotericin B deoxycholate

\*\*Other: heart disease, autoimmune, neurologic disease, gastrointestinal disease, or prior chronic kidney disease.

**Figure S1. Proven IFIs and proportion of dead individuals**

**Table S3. Analysis only in IFIs among survivors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Proven/**  **probable IFI**  **n= 62 (%)** | **NF-possible IFI n= 31 (%)** | **non-NF possible IFI**  **n= 82 (%)** | ***p* value** |
| **Age, yrs (median, IQR)** | 30 (24-49) | 21 (8-42) | 42 (22-59) | 0·001 |
| **Sex (Female)** | 27 (43) | 19 (61) | 35 (43) | 0·18 |
| **Duration of antifungal treatment (days, median, IQR)** | 24 (14-65) | 10 (6-13) | 7 (4-11) | <0·0001 |
| **Total cost of antifungal drug (US dollars, median, IQR)** | 1072 (408-2125) | 71 (6-218) | 30 (7-731) | <0·0001 |
| **Length of hospital stay (days, median, IQR)** | 19 (14-34) | 17 (13-26) | 22 (12-33) | 0·58 |
| **Hospitalization cost (dollars, median, IQR)** | 334 (123-1,330) | 172 (100-369) | 487 (123-1163) | 0·02 |
| **Acute kidney injury** | 11 (18) | 2 (6) | 3 (4) | 0·01 |
| **Liver damage during antifungal treatment** | 17 (28) | 4 (13) | 10 (12) | 0303 |
| **ICU stay** | 13 (21) | 2 (7) | 38 (46) | <0·0001 |
| **Length of ICU stay (days, median, IQR)** | 9 (3-12) | 7 (5-10) | 14 (7-20) | 0·19 |

**Table S4.** **Characteristics management by proven infection among survivors**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Invasive candidiasis**  **N=22** | **Aspergillosis**  **N=13** | **Endemic**  **(Histo/Cocci)**  **N=12** | **Other\***  **N=15** | ***p* value** |
| **Age, yrs (median, IQR)** | 42 (24-59) | 27 (18-30) | 43 (31-50) | 28 (23-36) | 0·02 |
| **Sex (Female)** | 11 (50) | 7 (54) | 2 (17) | 7 (47) | 0·21 |
| **First antifungal used** |  | | | | |
| Fluconazole | 4 (18) | 0 | 1(8) | 1(7) | <0·0001 |
| Caspofungin | 12(54) | 0 | 0 | 1(7) |
| AMBD | 0 | 3(23) | 8(67) | 7(46) |
| Anidulafungin | 5(23) | 0 | 0 | 0 |
| AMB Lipid formulation | 0 | 0 | 0 | 5(33) |
| Voriconazole | 1(4) | 8(62) | 0 | 1(7) |
| Itraconazole | 0 | 1(8) | 3(25) | 0 |
| **AKI** | 2 (9) | 1 (8) | 2 (17) | 6 (40) | 0·07 |
| **Liver damage** | 7 (33) | 5 (38) | 1 (8) | 4 (28) | 0·35 |
| **Time of antifungal treatment (days, median, IQR)** | 14 (11-22) | 56 (33-74) | 91 (14-259) | 54 (24-68) | <0·0001 |
| **Length of hospital stay (days, median, IQR)** | 21 (15-34) | 33 (14-37) | 17 (1-26) | 17 (15-25) | 0·54 |
| **ICU stay** | 7 (32) | 1 (8) | 1 (8) | 4 (27) | 0·22 |
| **Length of ICU stay (days, median, IQR)** | 11 (5-16) | -- | -- | 2 (2-8) | -- |
| **Total cost of antifungal drug (USD, median, IQR)** | 1072 (528-1461) | 1382 (645-2924) | 266 (163-546) | 1843 (567-46543) | 0·015 |
| **Total cost associated with hospital stay (USD, median, IQR)** | 316 (97-1258) | 126 (92-201) | 348 (108-1471) | 819 (368-2041) | 0·02 |

\*Cryptococcosis, mucormycosis, fusariosis

**Table S5. Multivariate analysis of factors associated with death.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Factor** | **Survived**  **N=175 (%)** | **Died**  **N=54 (%)** | **OR** | **CI95%** | ***p* value** |
| **Sex (Female)** | 81 (46) | 22 (41) | 0·97 | 0·49-1·9 | 0·94 |
| **Age** | 40 ± 21 | 36 ± 21 | 0·99 | 0·98-1·01 | 0·56 |
| **ICU stay** | 53 (30) | 29 (54) | 1·6 | 0·79-3·2 | 0·19 |
| **Liver damage** | 31 (18) | 24 (44) | 2·34 | 1·13-4·86 | 0·02 |
| **AKI** | 16 (9) | 21 (39) | 4·29 | 1·8-10·02 | 0·001 |

Adjusted for Sex and age

X2=32·49, DF=5, p<0·0001, Sensitivity of the model 80%.

**Table S6. Antifungal therapy cost of proven/probable IFIs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Invasive candidiasis**  **N=32** | **Aspergillosis**  **N=22** | **Histoplasmosis / coccidioidomycosis**  **N=22** | **Other \***  **N=22** |
| Cost antifungal per day (USD)  Mean, 95%CI value | 84, 59-109 | 89, 29-148 | 24, 4-43 | 320, 67-572 |
| Cost per day in hospital (USD)  Mean, 95%CI value | 25 (19-31) | 25 (19-31) | 25 (19-31) | 25 (19-31) |
| Cost per day in ICU  (USD)  Mean, 95%CI value | 90 (67-112) | 90 (67-112) | 90 (67-112) | 90 (67-112) |
| Estimates of IFIs in 2016 in Mexico \* | 12,103  (3,621 to 20,584) | 7,851  (-5918 to 21,621) | 9598  (-21034 to 40265) | 2065  (475-3656)\*\* |
| Rate of AKI, 95%CI | 22%, 7-37 | 18%, 1-36 | 32%, 11-53 | 38%, 15-61 |
| Rate of LD, 95%CI | 39%, 21-57 | 50%, 27-73 | 23%, 4-42 | 24%, 4-44 |
| Rate of ICU stay,  95%CI | 53%, 35-71 | 9%, 0-22 | 27%, 7-47 | 18%, 1-36 |
| Time of treatment (days, Mean, 95%CI) | 15, 11-19 | 36, 22-49 | 90, 25-154 | 69, 20-118 |
| Proportion of increasing antifungal cost due to AKI | \*\*\* | 4 times | \*\*\* | 3 times |
| Proportion of increasing antifungal cost due to LD | \*\*\* | \*\*\* | \*\*\* | 5 times |
| Proportion of increasing antifungal cost due to ICU stay | \*\*\* | \*\*\* | \*\*\* | 7 times |

\*Cryptococcosis, mucormycosis, fusariosis. \*\* Mucormycosis

\*\*\* No significant increasing cost was seen.