Temporal Trends And Treatment Patterns Of Systemic Antifungal Therapy In Hospitals In England: An Analysis Of The Hospital Treatment Insights Database

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Objectives

The study aims to:

- Describe the temporal trends of antifungal (Intravenous (IV) or oral) exposure in the Hospital Treatment Insights (HTI) database from 2011 to 2016
- Describe the treatment patterns and indications for systemic antifungal therapy in a large linked database of pharmacy and hospital discharge data in England (The Hospital Treatment Insights (HTI) database) broken down by primary and secondary diagnoses.

Background

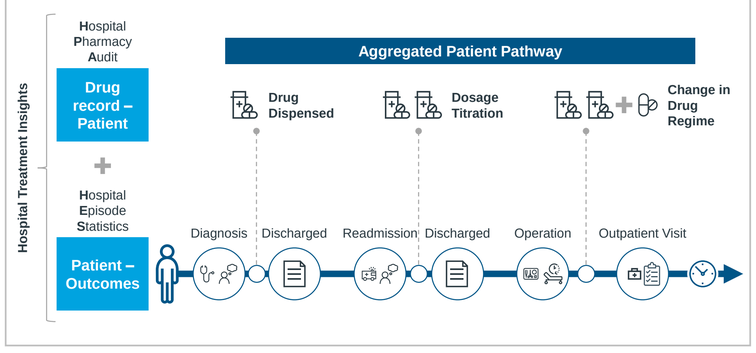
Systemic fungal infections are a growing public health challenge because they are a major cause of morbidity and mortality in hospitalised or immunosuppressed patients and are increasingly recognised as an important cause of healthcare associated infection. In the UK, the number of cases of fungal bloodstream infection reported to national surveillance systems increased 24% between 2013 and 2017 [1].

The increasing threat of drug resistance makes infections harder to treat and antifungals are vulnerable to this global concern. Thus, it is important to understand trends of antifungal use over time and this study aims to describe changes in antifungal exposure and reasons for antifungal use in the Hospital Treatment Insights (HTI) database.

Real world data have been used to inform a variety of public health decisions including drug safety since the 1990s. However, while a number of research data resources based on GP records are available, there is a lack of information on hospital medications in UK electronic healthcare data. IQVIA has been working to change this by combining data from hospital dispensing records with the Hospital Episode Statistics (HES) database, see figure 1.

The HTI database combines patient level dispensing data from hospital pharmacies with information on diagnoses and procedures in the Hospital Episode Statistics (HES) database and covers ≈ 28% of English trusts. All linkage is carried out by NHS Digital and researchers only access pseudonymised data.

Figure 1. Depiction of the HTI database



Methods

- This was a descriptive, retrospective cohort study in secondary care patients in England. The study population consisted of hospitalisations in HTI where an oral or IV administered antifungal treatment was dispensed. Data on exposure were defined by molecule name and included: Amphotericin B, Anidulafungin, Caspofungin, Fluconazole, Flucytosine, Griseofulvin, Isavuconazole, Itraconazole, Ketoconazole, Micafungin, Miconazole, Posaconazole, Voriconazole.
- For the temporal trends analysis, the first antifungal treatment for each patient within the study period (2010 to 2016 as these were the full years captured in HTI) was defined as the study exposure. Additional variables included: age at drug exposure, gender, length of hospital stay, antifungal administration route (oral or IV), and death in hospital within 1 year of drug exposure. Exposure over time was stratified by patient demographics and analysed with Chi-Squared tests for trend.
- For the treatment patterns analysis, all antifungal treatments dispensed to hospitalised patients within the study period (January 2010 and 2017, all data available for analysis in HTI) was defined as the study exposure. Indications were inferred using diagnostic codes (ICD-10) recorded in Hospital Episode Statistics and analysed using descriptive statistics.

Acknowledgements

The Hospital Episode Statistics (HES) data used for this study are collected and maintained by NHS Digital (formerly the Health and Social Care Information Centre).

Figure 2: Antifungal exposure time trends; overall and by gender, route of administration and death in hospital recorded in the HTI database from 2011 to 2016

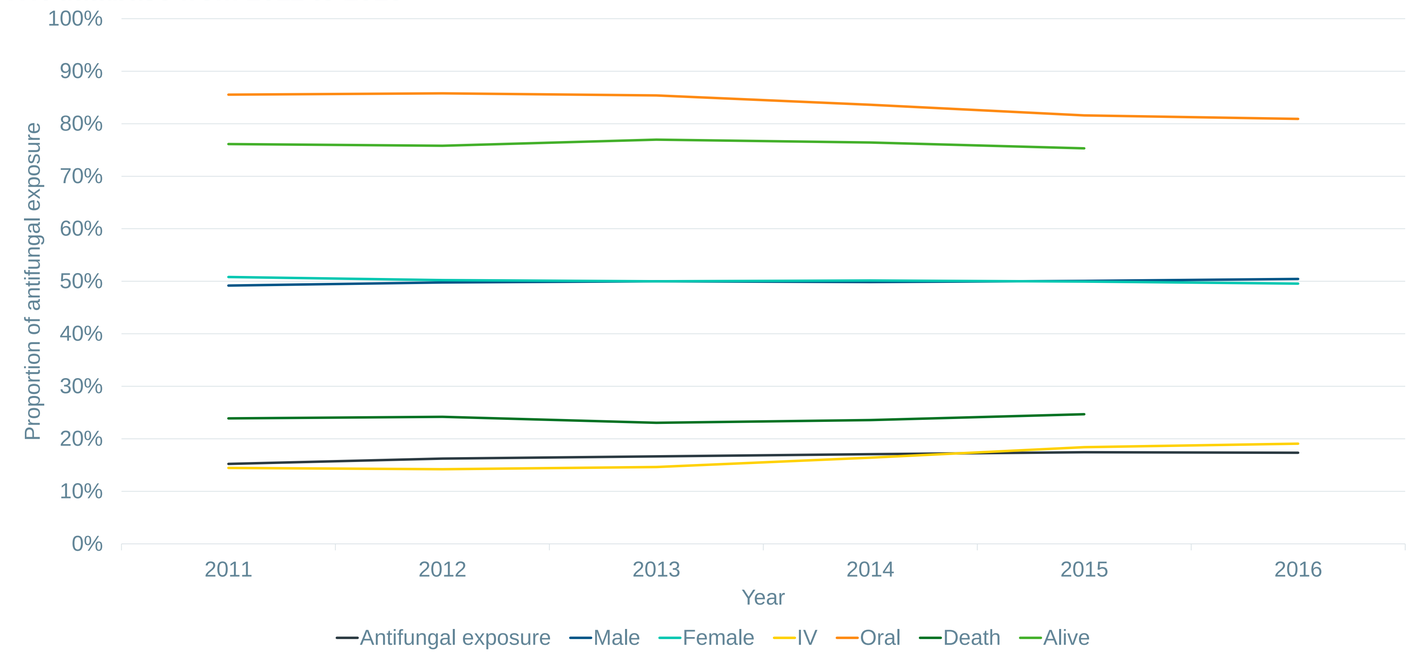


Table 1: Characteristics of antifungal exposure and longitudinal trend

	2011 (n=21,203)	2012 (n=22,616)	2013 (n=23,203)	2014 (n=23,767)	2015 (n=24,275)	2016 (n=24,139)	Total (N=139,203)	
Gender	n (%) [1]	n (%) [1]	n (%) [1]	n (%) [1]	n (%) [1]	n (%) [1]	n (%) [1]	p value [2]
Male	10,428 (49.2%)	11,260 (49.8%)	11,601 (50.0%)	11,848 (49.9%)	12,152 (50.1%)	12,177 (50.4%)	69,466 (49.9%)	p = 0.01
Female	10,775 (50.8%)	11,356 (50.2%)	11,602 (50.0%)	11,919 (50.1%)	12,123 (49.9%)	11,962 (49.6%)	69,737 (50.1%)	
Route of administration								
IV	3,065 (14.5%)	3,214 (14.2%)	3,393 (14.6%)	3,898 (16.4%)	4,470 (18.4%)	4,607 (19.1%)	22,647 (16.3%)	p < 0.01
Oral	18,138 (85.5%)	19,402 (85.8%)	19,810 (85.4%)	19,869 (83.6%)	19,805 (81.6%)	19,532 (80.9%)	116,556 (83.7%)	
Presence of death in hospital within 1 year of exposure								
Yes	5,064 (23.9%)	5,470 (24.2%)	5,347 (23.0%)	5,601 (23.6%)	5,995 (24.7%)	N/A	27,477 (23.9%)	p = 0.22
No	16,139 (76.1%)	17,146 (75.8%)	17,856 (77.0%)	18,166 (76.4%)	18,280 (75.3%)	N/A	87,587 (76.1%)	
10 year age bands								
0 to 9 years	460 (2.2%)	532 (2.4%)	494 (2.1%)	648 (2.7%)	821 (3.4%)	907 (3.8%)	3,862 (2.8%)	
10 to 19 years	384 (1.8%)	388 (1.7%)	366 (1.6%)	521 (2.2%)	537 (2.2%)	504 (2.1%)	2,700 (1.9%)	
20 to 29 years	930 (4.4%)	1,014 (4.5%)	859 (3.7%)	919 (3.9%)	1,003 (4.1%)	983 (4.1%)	5,708 (4.1%)	
30 to 39 years	1,164 (5.5%)	1,121 (5.0%)	1,119 (4.8%)	1,146 (4.8%)	1,228 (5.1%)	1,289 (5.3%)	7,067 (5.1%)	
40 to 49 years	2,068 (9.8%)	2,297 (10.2%)	2,322 (10.0%)	2,144 (9.0%)	2,228 (9.2%)	2,207 (9.1%)	13,266 (9.5%)	
50 to 59 years	3,373 (15.9%)	3,375 (14.9%)	3,522 (15.2%)	3,677 (15.5%)	3,719 (15.3%)	3,644 (15.1%)	21,310 (15.3%)	
60 to 69 years	4,887 (23.0%)	5,328 (23.6%)	5,282 (22.8%)	5,358 (22.5%)	5,342 (22.0%)	5,198 (21.5%)	31,395 (22.6%)	
70 to 79 years	4,469 (21.1%)	4,977 (22.0%)	5,207 (22.4%)	5,344 (22.5%)	5,392 (22.2%)	5,533 (22.9%)	30,922 (22.2%)	
80+ years	3,467 (16.4%)	3,583 (15.8%)	4,032 (17.4%)	4,008 (16.9%)	4,001 (16.5%)	3,870 (16.0%)	22,961 (16.5%)	

[1] percentages based on the column totals, [2] p value based on the longitudinal trend of exposure use (Cochran–Armitage chi squared test for trend)

Table 2: Breakdown of IV and oral antifungals dispensed in HTI from 2011 to 2016

IV or oral antifungal molecule name	n (%) of total hospitalisations (N=139,203)
Amphotericin B	5,404 (3.9%)
Anidulafungin	885 (0.6%)
Caspofungin	4,809 (3.5%)
Fluconazole	104,245 (74.9%)
Flucytosine	31 (<0.1%)
Griseofulvin	47 (<0.1%)
Isavuconazole	19 (<0.1%)
Itraconazole	9,909 (7.1%)
Ketoconazole	69 (<0.1%)
Micafungin	1,873 (1.3%)
Miconazole	3,748 (2.7%)
Posaconazole	4,799 (3.4%)
Voriconazole	3,365 (2.4%)

Table 3: Primary and secondary diagnosis associated with an antifungal in HTI from 2010 to 2017

Primary diagnosis	n (%) of total hospitalisations (N=155,194)
Acute myeloblastic leukaemia	8,806 (5.7%)
Multiple myeloma	8,758 (5.6%)
Sepsis, unspecified	7,108 (4.6%)
Lobar pneumonia, unspecified	6,302 (4.1%)
Diffuse large B-cell lymphoma	5,507 (3.5%)
Malignant neoplasm of breast, unspecified	5,227 (3.4%)
Urinary tract infection, site not specified	4,075 (2.6%)
Secondary diagnosis	
Chemotherapy session for neoplasm	20,153 (13.0%)
Agranulocytosis	7,584 (4.9%)
Sepsis, unspecified	4,183 (2.7%)
Acute renal failure, unspecified	4,138 (2.7%)
Essential (primary) hypertension	3,083 (2.0%)

Results

There were 139,203 hospitalisations in the temporal trends cohort from 2011 to 2016 with a median hospital duration of 11 (IQR: 3 to 28) days and mean age of 61 years (SD: 20.1). Additional characteristics of the cohort consist of (table 1):

- Similar gender stratifications between males (n=69,466, 49.9%) and females (n=69,737, 50.1%)
- In children, the most common age band was 0-9 years (n=3,862 (2.8%)). While in adults, older age bands had a higher frequency of antifungal exposure: 60-69 years (n=31,395 (22.6%)), and 70-79 years (n=30,922 (22.2%)).
- Antifungal exposure grew year on year from 21,203 in 2011 to 24,139 in 2016 and the most common antifungal treatment was fluconazole (n=104,245, 74.9%) (table 2)
- Overall, oral treatments (n=116,556, 83.7%) were more common than IV's (n=22,647, 16.3%); however, IV antifungal use had a large (50.3%) increase from 2011 (n=3,065, 14.5%) to 2016 (n=4,607, 19.1%) (p<0.01).
- There were 27,477 (23.9%) deaths in hospital within 1 year of antifungal exposure. The median time to death was 42 (IQR: 11 to 141) days and this proportion remained stable from 2011 to 2015 (23.9% to 24.7%, p=0.22).

There were 155,194 hospitalisations from 2010 to 2017 in the treatment patterns cohort, mean age of 58 years (SD 21.5):

- The top 5 primary diagnoses as seen in table 3 were: acute myeloblastic leukaemia (n=8,806, 5.7%), multiple myeloma (n=8,758, 5.6%), unspecified sepsis (n=7,108, 4.6%), unspecified lobar pneumonia (n=6,302, 4.1%) and diffuse large B-cell lymphoma (n=5,507, 3.6%).

Conclusion

- Our study shows increasing annual antifungal exposure, especially IV use, in English hospitals from 2011 to 2016. Furthermore, haematological malignancies are the leading diagnosis associated with dispensation of antifungals.
- An exposure cohort was defined as the first antifungal given during a hospitalisation. This was used as a proxy for an incidence cohort due to the ad hoc nature of the secondary healthcare system, which is designed to help anyone at need and removes the requirement to register at a hospital. This eliminates the ability to design a wash in period, the due diligence required to ensure true incidence.
- A limitation of this study includes the inferring of diagnostic coding. However, results are consistent with clinical practice, which recommends antifungal use for the treatment of systemic fungal infections or prophylactic treatment for patients at high risk of fungal infection (i.e. after a recent bone marrow transplant).
- Overall, HTI (linked pharmacy and hospital discharge data) can provide insights into the trends and treatment patterns of systemic antifungal use over time. HTI is a versatile database that warrants further research and monitoring especially for treatments given in secondary care settings. This is an interesting find that has clinical impact for this important cause of healthcare associated infections.

References

1. PHE (2018). Polymicrobial bacteraemia and fungaemia in England, Wales and Northern Ireland: 2017. HPR 12(10) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/691268/hpr1018_polymcrbls.pdf