Bibliometric analysis of literature on antifungal triazole resistance: 1980 – 2015

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Abstract

Background **Triazole antifungal agents play an important role in the treatment of a wide range of fungal infections. Little is known about antifungal triazole drug resistance when compared to antibiotic resistance. Therefore, this study was carried out to give a bibliometric overview of literature on triazole antifungal drug resistance.**

Methods **Keywords related to triazole drug class and resistance were used in a search query in the Scopus search engine. The time span was set from 1980 to 2015. Data pertaining to growth of publications, the most active countries and institutions, the most cited articles, and mapping of molecular mechanisms of resistance were analyzed.**

Results **A total of 1648 journal articles were retrieved with an average of 20.46 citations per article. Annual growth of triazole resistance showed an increasing pattern during the study period. The United States of America (n=446; 27.06%) ranked first in productivity followed by the United Kingdom (UK) (n=176; 10.68%), and China (n=133; 8.07%). *Radboud University Nijmegen Medical Centre* (n=69, 4.19%) in the Netherlands ranked first in productivity, while the journal *Antimicrobial Agents and Chemotherapy* ranked first (n=255; 15.47%) in publishing articles on triazole resistance. Mapping mechanisms of resistance showed that efflux pump and mutations in target enzyme are major mechanisms described in resistance to triazoles.**

Conclusion **There was a growth of publications on triazole resistance in the past two decades with the bulk of publications on triazole resistance in *Candida* species. The data presented here will serve as baseline information for future comparative purposes.**

Keywords **Bibliometric, *Candida*, fungal infections, *Aspergillus*, triazole, resistance, prevention**

Introduction

It is estimated that more than one million deaths occur annually due to serious fungal infections.[1] Triazole antifungal agents play an important role in the treatment of a wide range of fungal infections and can save lives when used in treatment of systemic invasive fungal infections in severely ill patients.[2,3] Triazoles belong to a larger group of antifungals called azoles which were first introduced in the early 1980s.[4] The azole group includes mainly triazoles and imidazoles. The imidazoles and triazoles act by inhibiting synthesis of fungal cell membrane. However, triazoles and imidazoles differ in chemistry, therapeutic use, and pharmacokinetics. Imidazoles are predominantly used topically while triazoles are used for systemic administration.

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The widespread phenomenon of drug resistance is not unique to antibiotics, it can also be present in fungi and antifungal drug resistance is actually an emerging serious health problem.[5] Antibiotic resistance has been identified as a global health threat and efforts from governmental and non-governmental agencies have been directed towards facing this challenge through rationalization of antibiotic use. However, much less is known about the prevalence and mechanisms of antifungal drug resistance and the subsequent clinical and economic consequences. Therefore, understanding mechanisms involved in such resistance, as well as the prevalence of the problem are important aspects to researchers and clinicians in order to implement preventive measures to confront and minimize such a problem.

The emergence of antifungal resistance can be deduced from the volume and impact of literature on this topic. Bibliometrics is a statistical tool used to assess the growth of publications, highly cited articles in the field, active countries and institutions, as well as research collaboration in any particular topic. Literature review that included PubMed and Google Scholar showed that few Chinese studies were carried out on global research on mycology in general, but none was published about the emerging phenomenon of triazole resistance.[6,7] Therefore, this study was carried out to implement a bibliometric analysis on literature on triazole antifungal drug resistance. This study may enrich the literature with baseline data concerning antifungal triazole resistance. Furthermore, tracking publications on antifungal drug resistance will help health agencies implement appropriate preventive measures accordingly.

Methods

This study was carried out to retrieve data pertaining to triazole resistance using the Scopus search engine. The choice of Scopus as a search engine rather than PubMed or Web of Science was based on the advantages offered by Scopus when compared with other databases. Such advantages are beyond the scope of this article. However, details of the comparison between Scopus and other databases are available through several publications.[8]

In this study, the selected keywords to be used in the Scopus search engine were those related to the triazole drug group, particularly the marketed and clinically used ones. Such keywords include: “itraconazole or fluconazole or voriconazole or posaconazole”. The previous keywords were followed by conditional keywords to minimize error and maximize accuracy. The final search query built looked like this in Scopus:

((TITLE(resist*) AND TITLE-ABS (itraconazole OR fluconazole OR voriconazole OR posaconazole OR Albaconazole)) OR TITLE-ABS ("azole resist*" OR "triazole resist")) AND NOT TITLE (echinocandin OR amphoter* OR 5-fluorocyt* OR flucyt* OR nystatin OR leishman* OR Antileishm* OR "breast cancer")

Few false positive articles were found to contain the keywords “breast cancer” and “leishmanial” and therefore, such keywords were added in the search query using “AND NOT” phrase. The keyword “resist*” was used in title search while names of triazole agents were used in title/ abstract to maximize accuracy of retrieved articles. The above strategy was tested in Scopus and a total of a sample of 300 documents was reviewed manually to confirm validity of retrieved articles. The time span for the search was set from year 1980 to year 2015. To restrict the analysis to literature coming from peer reviewed journals, the obtained data were refined by excluding books, book chapters and errata.

Retrieved data were analyzed to present various bibliometric indicators while maps were visualized using the VOSviewer technique.[9] The Hirsch (*h*) index[10] and the impact factor (IF) of the publishing journal were used as indicators of impact of publications. The IF was retrieved from the latest Journal Citation Report (2015) published by Thomson Reuters.

Results

The applied strategy yielded a total of 1648 journal articles. The majority of the retrieved

articles were research articles (n=1393; 84.53%) followed by review articles (n=141; 8.56%), letters (n=52; 3.16%), conference papers (n=26; 1.58%), notes (n=13; 0.79%), short surveys (n=12; 0.73%), articles in press (n=7; 0.42%), and editorials (4; 0.24%). Retrieved articles were written in 16 different languages, mainly English (n=1489; 90.35%) followed by Chinese (n=49; 2.97%), Spanish (n=25; 1.52%), and Japanese (n=22; 1.33%). Retrieved articles received a total number of citations of 33,719, an average of 35.49 citations per article. The *h*-index of the retrieved articles was 110. A total of 1493 (90.59%) were cited at least once while the remaining 155 (9.41%) articles were not cited at all. A total of 339 (20.57%) articles were cited at least 50 times. The top five cited articles on triazole resistance were published in *Antimicrobial Agents and Chemotherapy* (737, 591, and 414 citations, respectively), *American Journal of Medicine* (568 citations), and *Journal of Hospital Infection* (463 citations).

Growth of publications

Annual growth of triazole resistance showed an increasing pattern in the 1990s followed by a fluctuating steady state for almost one decade, and then a dramatic increase was observed in the last few years. Figure 1 shows the annual growth pattern of publications on triazole resistance. The highest number of publications was seen in 2015, totaling 163 publications. The oldest article on triazole resistance was published in 1984, with the following title "Azole resistance in *Candida albicans*" in the journal *Medical Mycology*.

Resistance-related publication on *Candida* versus *Aspergillus* species

The annual growth of publications on triazole resistance in *Candida* species was almost parallel to the growth of total publications (Figure 1). However, growth of publications on triazole resistance in *Aspergillus* species started after 2008 and showed an increasing pattern similar to that in *Candida* species in the last few years of the study. The sum of publications on *Candida* and *Aspergillus* is almost equal to the

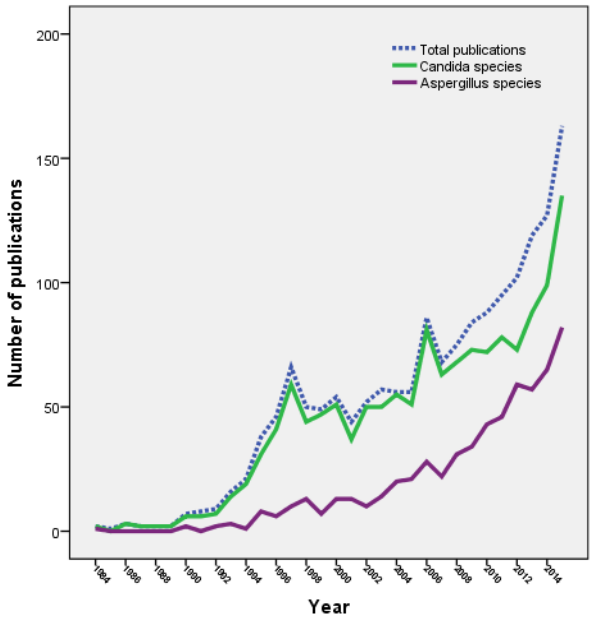


Figure 1. Annual growth of publications on triazole resistance in general and in *Candida* and *Aspergillus* species in particular

total publications across the study span. The difference between the sum of publications on either *Candida* or *Aspergillus* species on the one hand and total publications on the other hand is due to publications not related to either *Candida* or *Aspergillus* species.

Active countries, institutions, and journals

The top ten active countries in publishing about triazole resistance are shown in Table 1. The United States of America (n=446; 27.06%) ranked first in productivity followed by the United Kingdom (UK) (n=176; 10.68%), and China (n=133; 8.07%). The list of active countries represents four different world regions: northern and southern America, Europe, and Asia. International collaboration analysis for active countries using the VOSviewer technique showed that there were three clusters of international collaboration: (1) the red cluster which included the USA, Netherlands, India, China, Canada, Japan, and Brazil; (2) the green cluster which included UK, France, Belgium, Italy, Poland, and Switzerland; (3) the blue cluster which included Germany, Spain and Austria (Figure 2).

Table 1. List of top ten active countries in publishing documents on triazole resistance

SCR	Country	Frequency	Percentage of total publications (n=1648)
1st	United States of America	446	27.06
2nd	United Kingdom	176	10.68
3rd	China	133	8.07
4th	India	113	6.86
5th	Germany	109	6.61
6th	The Netherlands	99	6.01
7th	France	98	5.95
8th	Japan	95	5.76
9th	Spain	88	5.34
10th	Italy	85	5.16
10th	Switzerland	85	5.16

SCR – standard competition ranking.
Equal countries were given the same ranking number.

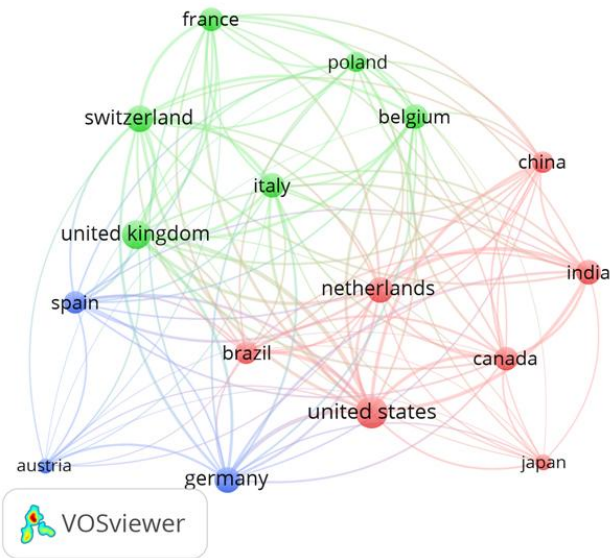


Figure 2. Network visualization map of international collaboration among countries with a minimum of 20 publications on triazole resistance. Lines connecting countries are indicative of collaboration. Thicker lines indicate stronger collaborations. Countries represented with larger circle size or font size had relatively more international collaboration.

Top ten active institutions are shown in Table 2. *Radboud University Nijmegen Medical Centre* (n=69, 4.19%) ranked first in productivity followed by *Centre Hospitalier Universitaire Vaudois* (n=51, 3.09%) and *University of Manchester* (n=45, 2.73%). However, when these institutions were re-ranked based on the percentage of publications with high citations (i.e., > 50 citations per article), *University of Texas Health Science Center at San Antonio* ranked first with more than of 60% of its publications being highly cited followed by *Centre Hospitalier Universitaire Vaudois*.

The top ten preferred source titles for publishing documents on triazole resistance are shown in Table 3. *Antimicrobial Agents and Chemotherapy* journal ranked first (n=225; 15.47%) followed distantly by *Journal of Antimicrobial Chemotherapy* (n=76; 4.61%). The IF of journals in the active list ranges from 1.63 to 5.39. Of the active journals in the list, two were in the specific field of mycology.

Molecular mechanisms of resistance

A search for articles on mechanisms of resistance retrieved a total of 410 articles. Mapping related keywords in title/abstract of the 410 articles yielded a network visualization map presented as Figure 3. The map shows three clusters of keywords. Keywords such as CDR1, CDR2, MDR1, and ERG11 were closely and strongly clustered with *Candida albicans* keyword while keywords such as CDR1, efflux, MDR, drug efflux, transporter, efflux, abc, accumulation, *Candida glabrata*, and fluconazole are associated with each other. The following keywords: cyp51a, voriconazole, itraconazole, *Aspergillus* species, and *Aspergillus fumigatus* were clustered together and appeared in blue color.

Discussion

In the current study, we sought to give a bibliometric overview of literature on triazole antifungal resistance in the past four decades. To accomplish this, we used the well-known Scopus database, which has been used in previously published bibliometric studies.[11-14] Our study showed that publications on triazole resistance

Table 2. List of top ten active institutions/organizations in publishing on triazole resistance

SCR	Institution/organization	Country	Frequency	Percentage	Frequency of highly cited articles	Percentage of highly cited articles	SCR based on percentage of highly cited articles
1st	*Radboud University Nijmegen Medical Centre*	The Netherlands	69	4.19	15	21.74	7th
2nd	*Centre Hospitalier Universitaire Vaudois*	Switzerland	51	3.09	27	52.94	3rd
3rd	*University of Manchester*	UK	45	2.73	15	33.33	6th
4th	*University of Iowa*	USA	42		19	45.24	4th
5th	*Nijmegen Interdenominational Hospital Canisius-Wilhelmina*	The Netherlands	40	2.43	7	17.50	9th
6th	*Centro Nacional de Microbiologia*	Spain	37	2.25	13	35.14	6th
7th	*University of Texas Health Science Center at San Antonio*	USA	35	2.12	21	60.00	1st
8th	*Julius-Maximilians-Universität Würzburg*	Germany	34	2.06	13	38.24	5th
8th	*Jawaharlal Nehru University*	India	34	2.06	6	17.65	8th
10th	*Second Military Medical University*	China	30	1.82	2	6.67	10th

SCR – standard competition ranking; **UK** – United Kingdom; **USA** – United States of America.
Equal countries were given the same ranking number, and then a gap is left in the ranking numbers.

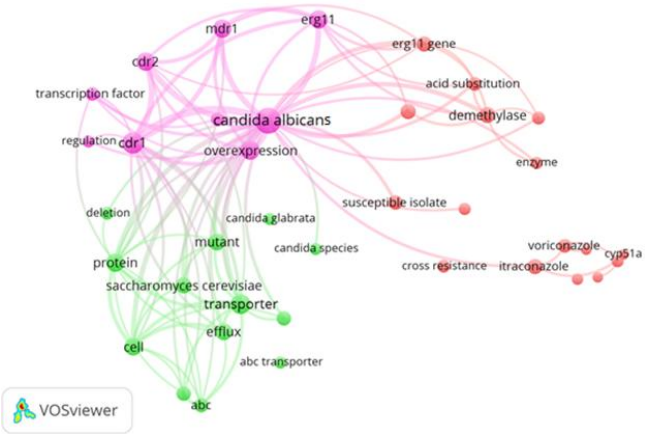
Table 3. Top ten preferred source titles for publishing documents on triazole resistance

SCR	Journal title	Frequency	Percentage N=1648	Impact factor (2015)
1st	*Antimicrobial Agents and Chemotherapy*	255	15.47	3.34
2nd	*Journal of Antimicrobial Chemotherapy*	76	4.61	4.27
3rd	*Journal of Clinical Microbiology*	66	4.00	2.44
4th	*Medical Mycology*	49	2.97	2.10
5th	*Clinical Infectious Diseases*	41	2.49	5.39
6th	*Mycoses*	38	2.31	2.33
7th	*International Journal of Antimicrobial Agents*	26	1.58	3.54
8th	*FEMS Yeast Research*	25	1.52	1.63
9th	*Diagnostic Microbiology and Infectious Disease*	23	1.40	2.45
9th	*Plos One*	23	1.40	3.54

SCR – standard competition ranking.
Equal countries were given the same ranking number, and then a gap is left in the ranking numbers.

have been increasing and growing rapidly particularly in the past decade. The high *h*-index is a strong indication of the importance of this subject to clinicians, researchers and microbiologists in general. Furthermore, the top active countries included China, Brazil, India along with the USA and European countries.

Figure 3. Network visulaization map showing common molecular mechanisms for triazole resistance



This indicates that triazole antifungal resistance is of concern to almost all world regions. These results support the findings that invasive fungal infections are a growing cause of death in severely ill patients, particularly in patients with immune dysfunction.[15] With increased incidence of invasive fungal infections and emergence of triazole resistance, patients with hematological malignancies and those exposed to stem cell transplantation will increasingly face therapeutic failure. Furthermore, clinicians will be pressured to use multiple antifungal agents or newly discovered and expensive ones, which will add burden on the patients and health system.[16]

The bulk of literature on triazole resistance focused on *Candida*. Actually, a recent study by the Centers for Disease Control and Prevention showed that *Candida* infections were the most common cause of healthcare-associated bloodstream infections in the USA.[17] Invasive fungal infections with *Candida* are not only life-threatening but also very expensive to treat.[18] Triazole resistance in *Candida* is also complicated by recent findings of resistant *Candida* species to newer antifungal agents, echinocandins.[19,20] Resistance of *Candida* species, such as *Candida glabrata*, to both fluconazole and echinocandins is a real healthcare concern.

The data retrieved in this study shed light on the resistance of different *Candida* species to triazole antifungal agents. Important and commonly encountered species include *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and others. Antifungal resistance in *Candida* has been linked to misuse of antibiotics that could affect normal gut flora and creates favorable conditions for growth of various *Candida* species.[21,22] Resistance of *Candida* species to triazoles has been reported to be constant during the '90s and early 2000s.[23] This is actually in agreement with the results obtained in our study and presented in Figure 1 where the number of publications on triazole resistance remained almost stead for many years in the '90s and up until year 2007. Infections with *Candida* isolates that were resistant to both fluconazole and echinocandins were termed multidrug resistant *Candida* infections and had to be treated with compounds with potential toxicity, such as older formulations of amphotericin B, which might increase the risk of mortality.[24]

Literature on antifungal triazole resistance included not only *Candida*, but also cases of resistance in *Aspergillus* species. Resistance of *Aspergillus* to triazole antifungal agents has emerged recently as shown in the data presented. Some studies have attributed resistance in *Aspergillus* partially to use of azole antifungal agents in agriculture.[1,25] Similar to *Candida*, *Aspergillus* infections associate increased mortality and costs.[26-28] The global prevalence of triazole resistance in *Aspergillus* still remains low but an unexpected rise in resistance is a possibility.[29,30] *Aspergillus* resistance was not only seen for fluconazole but also for the newer agent voriconazole.[31,32]

The visualization map showed that multiple mechanisms can contribute to resistance in *Candida* and/or *Aspergillus*. Resistance in fungal species could be natural or acquired through exposure to antifungal agents. For example, inappropriate dosing of antifungal agents might increase the risk of resistance in *Candida* species.[33] A major mechanism of resistance in *Candida* is efflux pump leading to decreased intracellular concentration of the drug. Other mechanisms such as alteration or up-regulation of target enzyme, demethylase, have also been

suggested.[34,35] For *Aspergillus* species, mechanisms of resistance involve efflux pump and changes in target enzyme encoded by the *cyp51A* and *cyp51B* genes.[36,37] Top cited articles on triazole resistance included articles on *Candida* biofilms and its role in resistance and therapeutic failure. Some *Candida* species have the ability to form biofilms attached to biological or inert surfaces such as catheters.[38,39] Such biofilm formation enhances virulence of *Candida* and acts as a barrier that prevents antifungal agents to reach the fungal cells.[40]

Given that triazole resistance is becoming an obvious problem, particularly for *Candida,* collective efforts are needed to face and solve this problem. Research on antifungal resistance needs to be carefully followed to watch for changes in prevalence or virulence of fungal infections and their associated mortality and morbidity. Bibliometric analysis is a good tool for tracking publications on resistance from different researchers in different parts of the world. Furthermore, we can track various mutations reported to be involved in antifungal resistance through periodic bibliometric analysis of published literature from all world regions. Linking the emergence of antifungal resistance with risk factors, i.e., clinical practices such as suboptimal dosing of antifungal agents or over-prescribing, or not following treatment guidelines, will help in understanding multiple dimensions of the problem and initiating preventive policies to curtail the emergence of antifungal resistance.

Our study is the first to initiate baseline data on bibliometrics of antifungal resistance, but it has a few limitations, similar to those of previous bibliometric studies.[41-45] Despite the fact that the Scopus database is considered an excellent source for bibliometric analysis compared with PubMed or Web of Science, there are some journals that contain publications on resistance but that are not indexed in Scopus and therefore were not counted. Furthermore, even in the most validated bibliometric studies, false negative and false positive results remain an unavoidable possibility. When retrieving data from Scopus regarding countries or institutions, it should be kept in mind that sometimes different names of institutions create different profiles for the same institutions and these profiles are not always merged. Therefore, the productivity of certain institutions or countries might be under-estimated.

Conclusions

Publications on triazole resistance have been increasing in the past two decades, particularly those on *Candida* species**.** Tracking publications on triazole resistance is needed to implement proper policies wherever appropriate. The study showed that the bulk of publications on triazole resistance were contributed by the USA with a considerable share from other parts of the world. This bibliometric analysis showed that publications have studied different molecular mechanisms of resistance. The data presented in this study will serve as baseline information for future comparative purposes.

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