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Antifungal chemotherapy: advances and perspectives

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Summary

Invasive fungal infections have emerged as important causes of morbidity and mortality in immunocompromised patients. In response to this challenge, the field of antifungal chemotherapy has considerably expanded. Fluconazole and itraconazole, introduced in the late 1980s, were the first durably useful alternatives to amphotericin B deoxycholate. The clinical development of the lipid formulations of amphotericin B, and, more recently, that of novel echinocandin derivatives and improved antifungal triazoles each represent milestones in antifungal drug research that have further amplified our therapeutic options. Major progress has been made in harmonising disease definitions, in defining the paradigms of antifungal intervention, and in designing and implementing clinical trials. Standardised methods for in vitro susceptibility testing of yeasts and filamentous fungi have become available, and pharmacodynamic concepts have entered preclinical and clinical drug development. This article reviews the evolution of therapeutic options over the past decade, advances in chemoprevention and empirical antifungal therapy, progress in early diagnosis and pre-emptive therapy, the promise of the new echinocandins and second generation triazoles, as well as perspectives for combination therapies and adjuvant immunoreconstitution. Invasive fungal infections will remain a frequent and important complication of modern medicine; the current momentum in the field of laboratory and clinical antifungal drug research provides hope for substantial progress in prevention and management of these life-threatening infections in the near future.

Key words: mycoses; antifungal agents; treatment; prevention

Introduction

Invasive opportunistic fungal infections have become important causes of morbidity and mortality in immunocompromised patients. While *Aspergillus*- and *Candida* species account for the majority of documented infections, recent epidemiological trends indicate a shift towards infections by *Aspergillus* spp., non-albicans *Candida* spp., and previously uncommon fungi that often have diminished susceptibility to current antifungal agents [1–4].

For decades, the treatment of invasive fungal infections consisted of amphotericin B deoxycholate (DAMB) with or without 5-fluorocytosine (5-FC). The first durably useful alternatives only emerged in the late 1980's with the advent of fluconazole and itraconazole. The past 10 years, however, have witnessed a major expansion in antifungal drug research, reflected by the introduction of the lipid formulations of amphotericin B and the development of novel echinocandin derivatives and improved antifungal triazoles [5, 6]. An increased awareness of the fungal pandemic, improved blood culture techniques and high-resolution imaging techniques have had considerable impact on improving the earlier diagnosis of invasive fungal infections, and major progress has been made in harmonising disease definitions, in defining paradigms for antifungal intervention, and in designing and implementing clinical trials [7, 8]. A standardised method for testing the in vitro susceptibility of yeasts to current antifungal agents has become available [9], and a similar method has been proposed for filamentous fungi [10]. However, mainly due to the pivotal role of host- and disease-related factors for outcome, prediction of antifungal efficacy or failure from in vitro susceptibility data remains difficult and has not been incorporated in routine clinical practice [11].

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Expansion of existing therapeutic options

Amphotericin B deoxycholate (DAMB) possesses a broad spectrum of antifungal activity *in vitro* and has been the standard treatment of most invasive fungal infections in immunocompromised patients. Recommended dosages range from 0.5 mg/kg/day for candidaemia to 1.0 to 1.5 mg/kg for acute disseminated candidiasis and suspected or proven invasive mould infections [5]. In addition to infusion-related reactions that occur in approximately 75% of patients [12], however, treatment with high dosages of DAMB is associated with significant nephrotoxicity: A recent multicentre retrospective analysis of more than 200 immunocompromised patients receiving the drug for suspected or proven aspergillosis showed that the serum creatinine level doubled in 53% of patients and exceeded 2.5 mg/dL in 29%; 14.5% of the patients underwent dialysis. The use of haemodialysis, duration of therapy with DAMB, and use of nephrotoxic agents such as ciclosporine A were associated with greater risk of death [13].

In view of this background of toxicity, the development of the lipid formulations of amphotericin B (AMB colloidal dispersion, ABCD; AMB lipid complex, ABLC; and liposomal AMB, LAMB) represented an important advance in the management of life-threatening invasive opportunistic mycoses, particularly in the setting of allogeneic stem cell transplantation. Open label clinical trials have demonstrated that these agents are significantly less nephrotoxic but at least as effective as DAMB [14–16]. The lipid formulations are thus indicated when pre-existing or arising nephrotoxicity do not allow for the delivery of therapeutically effective dosages of DAMB, or when treatment with DAMB fails to induce a clinical response. Of note, the frequency of infusion-related reactions varies among the different compounds [12, 17, 18]; indeed, in the case of ABCD, frequency and severity of infusion related reactions may exceed those associated with DAMB [17]. While the optimal dosages of the lipid formulations remain to be defined for most indications, there is a tendency among institutions to cut dosages to compensate for their high cost of acquisition. However, based on the concentration- and dosage-dependent activity of amphotericin B in vitro and in vivo [19] and the few studies that have used DAMB for comparison [20–22], we strongly advocate the use of the highest approved dosages of the lipid formulations for treatment of life-threatening infections. This may apply in particular to infections of the central nervous system (CNS), where animal data demonstrated enhanced CNS-penetration of LAMB in comparison to DAMB and enhanced penetration and antifungal efficacy of LAMB in comparison to ABCD and ABLC [23].

Largely due to its exceptionally favourable pharmacokinetic and toxicological profile, the advent of fluconazole has clearly had a major impact on the management of fungal infections. This antifungal triazolee drug is active against most pathogenic *Candida* spp. and several other yeast-like fungi [5]. Apart from the non-neutropenic setting [24], data from at least two clinical studies [25, 26] support the usefulness of fluconazole (400–800 mg/kg/day IV) for treatment of uncomplicated candidaemia also in neutropenic patients who are haemodynamically stable. In contrast, the use of fluconazole in neutropenic patients with acute disseminated candidiasis is controversial and warrants further investigation. In settings where fluconazole is given as antifungal prophylaxis, however, its role as a therapeutic agent is very limited. Breakthrough infections in this situation are highly likely to be caused by fluconazole-resistant *Candida* species, including *C. glabrata*, *C. krusei* and fluconazole-resistant *C. albicans* isolates [5]. Therefore, amphotericin B remains the current agent of choice for patients receiving fluconazole as prophylaxis that present with positive blood cultures for a yeast-like organism. Of note, the echinocandins hold great promise as a valid alternative to treatment of invasive candidiasis with amphotericin B [6].

Itraconazole has evolved into an important therapeutic option for the treatment of invasive fungal infections caused by *Aspergillus* spp, *Ps. boydii* and many dematiaceous moulds. Although itraconazole has potent activity against *Candida* spp. *in vitro*, no clinical data exist on its efficacy for treatment of invasive *Candida* infections [5]. Besides a number of potential, clinically relevant drug-drug interactions, the therapeutic usefulness of itraconazole was limited owing to the absence of an intravenous formulation and its erratic absorption from the gastrointestinal tract. Oral bioavailability has been considerably improved with the novel suspension in cyclodextrin [27], and an intravenous formulation that uses the same carrier has recently been approved. Nevertheless, despite response rates that are overall similar to those of DAMB, the reported clinical experience with itraconazole in either formulation for induction therapy of suspected or proven invasive aspergillosis in profoundly neutropenic patients is scant [28–30]. Irrespective of these considerations, itraconazole has an important role in this specific setting as therapeutic alternative for patients who cannot be treated with standard therapy, as consolidation therapy of patients who have recovered from neutropenia [5] and for therapy of infections caused by certain dematiaceous moulds [4].

Terbinafine is a member of another class of compounds known as allylamines, which inhibit squalene epoxidase in the ergosterol biosynthetic pathway. Although terbinafine has broad in vitro

activity, its pharmacokinetic profile limits its use to treatment of dermatophytosis, where it has been found to active against tinea capitis, onychomycosis, and tinea corporis.

Advances in chemoprevention and empirical therapy

The extraordinary morbidity and mortality from invasive opportunistic fungal infections provide the rationale for preventative approaches in patient populations with infection rates that exceed 10%. These include patients with acute leukaemias, allogeneic haematopoietic stem cell transplantation and liver transplantation, but also critically ill surgical patients and premature neonates with a birth weight of less than 1000 g. Apart from standardised infection control measures, current paradigms for prevention include primary chemoprophylaxis, empirical antifungal therapy, and secondary chemoprophylaxis for patients with a pre-existing deep-seated fungal infection that need further intensive anti-cancer chemotherapy or immunosuppression.

Unfortunately, effective chemoprophylaxis against infections by *Aspergillus* spp. has not been demonstrated thus far [31]. Effective primary chemoprophylaxis of invasive *Candida* infections has been demonstrated most convincingly in the setting of marrow transplantation [32, 33]. A randomised, double-blind placebo-controlled trial in mostly allogeneic marrow recipients has shown that fluconazole, given at 400 mg QD from the start of the conditioning regimen until day 75, can reduce the frequency of invasive *Candida* infections, and lower mortality at day 110 [33]. Moreover, 8 years after completion of the study, there was persistent protection against invasive candidiasis and *Candida*-related death, a decreased frequency of severe, gut-related GVHD, and an overall survival benefit of 17% in fluconazole-treated patients [34]. In less risk-selected patients with haematological malignancies undergoing remission-induction chemotherapy, both fluconazole (400 mg QD) and itraconazole cyclodextrin (2.5 mg/kg BID orally) have been shown to be effective in preventing systemic infection and death due to *Candida* spp. [35, 36]. In liver transplant patients, prophylactic fluconazole (400 mg QD) reduced the incidence of invasive *Candida* infections and deaths from fungal infection, but did not improve overall survival [37]. A reduction in the frequency of invasive *Candida* infections following liver transplantation has also been demonstrated for liposomal amphotericin B (1 mg/kg/d) [38]. Prophylaxis with fluconazole reduced the incidence of invasive *Candida* infections [39] and intra-abdominal candidiasis [40] in high-risk surgical patients and invasive *Candida* infections in premature very low birth weight (VLBW) infants [41], but had no impact on infection-related and overall mortality in these settings.

A potential drawback of prophylaxis with antifungal triazoles may be the selection of azole-resistant *Candida* species: Emergence of fluconazole-resistant *C. glabrata* and *C. krusei* infections has been reported from individual centers [42, 43], and in a large European multicentre survey, antifungal prophylaxis with fluconazole in patients with haematological malignancies was significantly associated with infections by non-albicans *Candida* species [2]. However, a recently published study from Seattle on 585 patients receiving fluconazole prophylaxis showed a low incidence of breakthrough candidaemia and a low attributable mortality despite frequent colonisation with fluconazole-resistant *Candida* spp. [44].

Cancer patients with profound and prolonged neutropenia (ANC <500/µL for >10 days) who have persistent or recurrent fever despite treatment with broad-spectrum antibacterial agents are considered to be at high risk for developing invasive fungal infections. In this setting, broad spectrum empirical antifungal therapy provides effective antifungal prophylaxis and early therapy for clinically occult infections [45–47] that may arise despite prophylaxis. Agents approved for this indication include amphotericin B deoxycholate (DAMB; 0.6 mg/kg/day) and liposomal amphotericin B (LAMB; 1–3 mg/kg/d). Two large randomised multicentre trials, one of which included patients after allogeneic haematopoietic stem cell transplantation, have shown that LAMB is as effective as DAMB but associated with less infusion-related toxicity, less nephrotoxicity [12, 48] and fewer proven breakthrough fungal infections [12]. Efficacy equivalent to DAMB has also been demonstrated for itraconazole (administered IV for a minimum of 6 and a maximum of 14 days, followed by oral suspension) [49] and IV fluconazole [50] in patients with haematological malignancies not receiving allogeneic grafts. However, since the latter is not active against filamentous fungi, its use in patients at high risk for invasive mould infections is controversial. Very recently, a large randomised, multicentre trial has been completed that compared the second generation striazole voriconazole with LAMB for empirical antifungal therapy [51]. The results of this study showed comparable composite success rates, but fewer documented breakthrough infections, severe infusion-related toxicity and nephrotoxicity in patients receiving voriconazole. However, patients receiving voriconazole had significantly more frequent episodes of transient visual disturbances and hallucination. Currently, clinical trials are under way that investigate the role of other novel triazoles and of the antifungal echinocandins for this indication.

Progress in early diagnosis and pre-emptive therapy

Early diagnosis and rapid initiation of effective chemotherapy is paramount to the successful management of invasive mycoses. Current blood culture detection techniques such as the lysis-centrifugation and the BacTec Alert system may detect candidaemia earlier and more frequently than conventional systems [52]. However, candidaemia is only one of several facets of invasive candidiasis, and single organ or early disseminated candidiasis are often not associated with detectable fungaemia and may therefore require more invasive diagnostic procedures [53]. For such tissue-invasive *Candida*-infections, ultrasound, modern computed tomography techniques and magnetic resonance imaging have become indispensable tools for detection and monitoring, as well as for guidance of diagnostic procedures [54, 55]. Nucleic acid amplification based systems may complement existing blood culture systems in the future not only for early detection purposes but also for rapid determination of resistance patterns to antifungal agents [52].

Apart from improved detection of invasive mould infections of the paranasal sinuses [56], modern imaging techniques have facilitated early detection of pulmonary infiltrates consistent with invasive pulmonary aspergillosis permitting early pre-emptive treatment [57–59]. However, although peripheral nodules, the halo-sign and cavitation are features of pulmonary aspergillosis, these criteria are not entirely diagnostic; indeed, non-specific air space consolidation is common in early phases of the disease [60]. Therefore, a microbiological diagnosis by fibre-optic bronchoscopy with bronchoalveolar lavage or bioptic procedures should be attempted whenever feasible. Serial monitoring of galactomannan antigen and *Aspergillus*-specific nucleic acid sequences in blood [61–63] also may contribute substantially to the detection of invasive pulmonary aspergillosis, particularly in the neutropenic host. Conceptually similar to the approach to cytomegaloviral disease, these novel non-culture detection systems may permit and further refine early antifungal intervention. Carefully designed clinical trials are now needed to determine the role of these pre-emptive strategies in comparison to fever-based empirical antifungal therapy and primary chemoprevention in the high-risk population of cancer patients with profound and prolonged neutropenia.

The promise of new antifungal drugs

Systematic investigation of the structure-activity relationship of the azoles have produced a second generation of systemic antifungal triazoles: Posaconazole (Schering-Plough Inc., Kenilworth, NJ), ravuconazole (Bristol-Myers Squibb Inc., Wallingford, CT), and voriconazole (Pfizer Ltd., Sandwich, UK). The new triazoles have enhanced potency and broad-spectrum antifungal activity, including *Candida* spp., *Trichosporon beigelii*, *Cryptococcus neoformans*, *Aspergillus* spp., *Fusarium* spp., dematiaceous as well as dimorphic moulds, and perhaps, some of the zygomycetes. Whereas all three agents display non-linear plasma pharmacokinetics and undergo hepatic metabolism involving the CYP450 enzyme system, key pharmacokinetic parameters (oral bioavailability, protein binding, plasma clearance, and volume of distribution) vary. Importantly, however, no fundamental differences between the three compounds in potency, spectrum, and antifungal efficacy have been noted so far [6, 64].

Posaconazole, ravuconazole and voriconazole have demonstrated potent therapeutic efficacy in a number of immunocompromised animal models, including oropharyngeal and disseminated candidiasis and invasive pulmonary aspergillosis [6, 64]. Published data from phase II and phase III clinical trials indicate highly promising clinical efficacy of these agents against oropharyngeal and esophageal candidiasis [65–67], invasive candidiasis [68, 69], and invasive aspergillosis [68–71]. A multinational, randomised comparison of voriconazole and DAMB followed by other licensed antifungal therapy for primary therapy of invasive aspergillosis has demonstrated superior antifungal efficacy and improved survival of voriconazole-treated patients at week 12 [72]. Because toxicity was the major limiting factor for successful DAMB therapy in this trial, however, no inferences can be made as to the comparative efficacy of the lipid formulations of amphotericin. Importantly, a large randomised, multicentre trial that compared voriconazole with LAMB for empirical antifungal therapy in persistently febrile neutropenic patients showed comparable composite success rates, but fewer documented breakthrough infections, infusion-related toxicity and nephrotoxicity in patients receiving voriconazole [51]. Several reports also suggest the potential usefulness of the novel triazoles for treatment of infections by unusual hyaline and dematiaceous fungi [4, 68], and, due to its excellent CNS-penetration, of voriconazole for treatment of cerebral mould infections [68, 70],

The echinocandins are a novel class of antifungal lipopeptides. They act by inhibiting the synthesis of 1, 3-β-glucan, a homopolysacharide in the cell wall of many pathogenic fungi. Together

with chitin, the rope-like glucan fibrils are responsible for the cell wall's strength and shape and play an important role in cell division and cell growth [73, 74]. Three echinocandins are currently in clinical development: Caspofungin (Merck & Co., Inc., Rahway, NJ), micafungin (Fujisawa Inc., Deerfield, ILL), and anidulafungin (formerly LY303366; Versicor Inc, Freemont, CA). The current data suggest that these agents possess similar pharmacological properties. They have potent and broad-spectrum, potentially fungicidal *in vitro* activity against *Candida* species and cause severe structural damage to the hyphal elements of *Aspergillus* spp. They are not metabolised through the CYP450 enzyme system, and appear to be generally well-tolerated. Although at present only available in parenteral formulations, the echinocandins possess favourable pharmacokinetic properties and are targeted for once-daily dosing [75–77].

The antifungal efficacy of the current echinocandins has been documented in several immunocompromised animal models of superficial and disseminated candidiasis and invasive pulmonary aspergillosis [75–77]. Phase II and III clinical trials of all three echinocandins, performed in patients with oesophageal candidiasis, have demonstrated potent clinical efficacy in conjunction with an excellent safety profile [78–80]. Published data on the clinical efficacy of the echinocandins in the treatment of more invasive infections are currently limited to caspofungin [81, 82] and micafungin [83, 84]. Based on a complete or partial response in 41% of 63 patients enrolled on a clinical phase II trial for invasive aspergillosis and its excellent safety profile [81], caspofungin was approved in early 2001 for treatment of invasive aspergillosis refractory of or intolerant to amphotericin B formulations or antifungal triazoles. Recently, the preliminary data of a multicentre, randomised, double-blind phase III clinical trial have been presented that compared the efficacy of caspofungin (70 mg on day one, followed by 50 mg daily) in the primary treatment of invasive *Candida* infections in 224 mostly non-neutropenic patients to that of amphotericin B deoxycholate (0.6–1.0 mg/kg) [82]. Patients were treated for 14 days after the last positive blood culture, but could be switched to fluconazole after ten days of intravenous therapy. Among patients receiving at least one dose of study drug, 73% of patients in the caspofungin cohort and 61.7% of patients in the DAMB cohort had a therapeutic success at the end of intravenous therapy. Among patients who received five or more doses, the response rates were 80.7% and 64.9%, respectively. There was no difference in relapse or survival, but patients receiving caspofungin had less drug-related clinical or laboratory adverse events. At present, further phase III efficacy studies of echinocandins for treatment of invasive candidiasis, for prophylaxis in haematopoietic stem cell transplantation, and for empirical antifungal therapy in persistently febrile neutropenic patients are ongoing or have been initiated.

Perspectives for combination therapies

The availability of antifungal drugs with different molecular targets has opened new avenues for exploring combination therapies of two or even three agents. The obvious aim of this approach is foremost to enhance onset and potency of antifungal efficacy, but also to broaden the antifungal spectrum, to decrease the selection of resistant clones, and to reduce treatment associated toxicity. The subset of patients that are most likely to benefit from antifungal combination therapy are those with acute or fulminant infections or infections at anatomically privileged sites such as the brain [85, 86].

The paradigm for antifungal combination therapy is the combination of DAMB and 5-FC, that exhibited synergistic activity against *Cr. neoformans* in vitro and in animal models [87] which translated into superior outcome in patients with cryptococcal meningoencephalitis [88, 89]. Beyond the therapy for cryptococcal meningitis, however, clinical experience with combination therapies is anecdotal and there is an understandable trend, in desperately ill patients, for using whichever combination appears to have a theoretical advantage. Nevertheless, irrespective of the pressing clinical need, careful preclinical investigation of antifungal combination therapies is warranted, followed by appropriately designed randomised clinical trials. This may be exemplified by the observation of a drug- and fungus specific antagonism between DAMB and the antifungal azoles in vitro and in animal models, that has been consistently noted predominantly with the lipophilic azoles against *Candida*- and *Aspergillus* spp. [90–92]. A recently completed placebo controlled study comparing fluconazole 800 mg/d plus placebo versus fluconazole 800 mg/d plus amphotericin B (0.7 mg/kg/d) for treatment of non-neutropenic candidaemia, however, revealed no evidence of antagonism but an apparent trend toward more rapid clearance of the blood stream and improved antifungal efficacy of the combination [93]. Whereas the combination of amphotericin B and itraconazole continues to be highly controversial [85, 86], preclinical studies so far collectively indicate no antagonism of combinations of echinocandins with azoles, amphotericin B, or the chitin-synthase inhibitor nikkomycin Z against common

opportunistic fungal pathogens [75, 76]. Indeed, first reports are emerging that point to the clinical usefulness of such combination therapies in the treatment of invasive aspergillosis [94, 95]. Over the next decade, combination therapy will probably become the standard of care for fungal infections that are notoriously difficult to treat. However, how these combinations can be harnessed to improve antifungal therapy can only be evaluated in sufficiently powered, randomised clinical trials that are founded on discriminative infection models of invasive fungal diseases.

Adjunctive Immunotherapies and Immunoreconstitution

Restoration or enhancement of host defences is of utmost importance for the successful management of invasive fungal infections. At present, therapeutic strategies include dose-reduction or discontinuation of corticosteroids, if feasible, the administration of recombinant cytokines, and donor elicited granulocyte transfusions for profoundly neutropenic patients [96]

The prognostic importance of corticosteroids has been emphasised by a recent retrospective study in haematopoietic stem cell transplant patients with invasive aspergillosis, that showed a direct relationship of high cumulative corticosteroid dosages prior to diagnosis with dismal outcome [97]. Of note, methylprednisolone was the major immunosuppressive drug of the combination of cyclosporine and methylprednisolone in experimental pulmonary aspergillosis. Cyclosporin A alone did not lead to the progression of pulmonary aspergillosis and did so only when used chronically with methylprednisolone [98].

Recombinant haematopoietic cytokines such as granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) shorten the duration of neutropenia and reduce the period of greatest risk for developing invasive fungal infections. While the full impact of this potentially preventive modality on the incidence of invasive fungal infections is unclear, a considerable body of preclinical in vitro and in vivo data has now accumulated that shows that recombinant cytokines (i.e., G-CSF, GM-CSF, M-CSF, interferone-γ), effector cells, and antifungal drugs can work synergistically to oppose fungal growth [99]. Beyond the direct effects of G- and GM-CSF on phagocytic effector cells, there is growing experimental evidence that Th-1 dependent immunity plays an important role in host defences against invasive candidiasis and aspergillosis. Cytokines and anti-cytokines that promote this pathway (i.e., interferon γ, IL-12 and anti-IL-4) may be protective in vivo and act in co-operation with antifungal drugs [96, 99].

G-CSF administered to healthy donors prior to leukapheresis, improvements in collection techniques and cytokine exposure to harvested and irradiated granulocytes increase dosage and function of transfused granulocytes [100] and are currently investigated as adjunctive therapy for refractory fungal infections in patients with persistent neutropenia. The co-transplantation of novel granulocyte/monocyte progenitors that give rise to granulocytes and monocytes [101], the adoptive transfer of immunocompetent T-cells [102], and perhaps, the development of T-cell vaccines [103] are further preclinical avenues toward cellular immunotherapy and prevention.

Conclusions

When extrapolating past and present epidemiological trends, it appears highly likely that invasive opportunistic fungal infections will remain a frequent and important complication of modern medicine. Improved diagnostic tools, an expanded and refined antifungal armamentarium, further elucidation of antifungal resistance, incorporation of pharmacodynamics as well as combination and immunotherapies offer hope for further substantial progress over the next decade.

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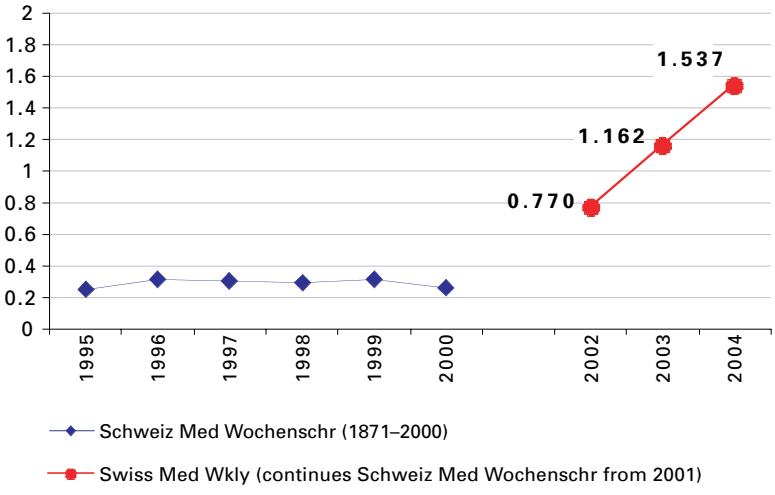

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