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Chronic mucocutaneous candidiasis, from bench to bedside

Chronic mucocutaneous candidiasis (CMC) defines a heterogeneous group of orphan and inherited syndromes characterised by chronic and recurrent infections of the skin and mucosa with the yeast *Candida*. Increasing evidence suggests that this inefficient defence against *Candida* species is reflected by a DC/T cell defect which results in an impaired Th17 and Th1 immune response and, consecutively, a failed immune instruction of tissue cells. Little is known about the incidence and prognosis of CMC. Clinically, the main complications are debilitating hands (*Candida granuloma*) and oesophageal stricture with potential mal-digestion/-absorption. Furthermore, the chronic infections are likely a risk factor for the development of squamous cell carcinoma. Since resistance to anti-mycotic drugs evolves rapidly, efficient and flexible therapeutic management is essential for CMC patients.

Key words: Candida, Chronic mucocutaneous candidiasis, APECED, T cell, IL-17, IL-22, Th17

Candida albicans is a ubiquitous, opportunistic yeast, colonizing membranes of human skin and mucosal surfaces. The yeast causes infections (candidiasis) only if the homeostasis between the virulence of the microbe and the resistance of the host immune system is disturbed. Chronic mucocutaneous candidiasis (CMC) is the collective term for a complex group of disorders characterised by persistent or recurrent infections of the skin, nails and mucosal tissues with species of *Candida*, mostly with *Candida albicans*. Patients with CMC rarely develop disseminated or systemic infections with *Candida* [1]. The first case of CMC was described by Thorpe and Handley in 1929 [2], followed by other reports in the 1950s [3, 4]. The term "chronic mucocutaneous candidiasis" was introduced in the late 1960s [5]. Today, CMC still is diagnosed clinically and by *in vitro* isolation and cultivation of *Candida* from smear tests. Additionally, diagnosis can be confirmed by mutational analysis in subgroups with known underlying genetic defects.

Heterogeneity and prevalence of CMC

The complex group of CMC syndromes can be subclassified according to distribution (local candidiasis versus generalized mucocutaneous candidiasis) and by the underlying pathomechanism (primary versus secondary syndromes) *(table 1)*.

Notably, inherited CMC syndromes are often associated with autoimmune diseases of the endocrine glands. This is the case in the autosomal-recessive "autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome" (APECED or APS-1) [6, 7], with monogenic defects in the autoimmune regulator gene (AIRE) [7-9]. Furthermore, distinct syndromes of dominantly inherited CMC [10] with endocrinopathies have been described, where the underlying genetic defect has been mapped on chromosome 2p [11]. Also, associations with a variant in the lymphoid protein tyrosine phosphatase have been reported [12]. For other primary forms of CMC the genetic basis is unknown. For most known mutations, however, the link between the mutation and immune defect(s) remains unclear. In contrast, secondary CMC syndromes are usually the consequence of local or systemic immune-suppression due to infections (especially AIDS, where candidiasis has a prognostic value [13]), reduced micro-perfusion in diabetes or immune-suppressive long-term medication. Another predisposing factor for secondary *Candida* infections is a disturbed microenvironment, *e.g.* after long-term antibiotic treatment or around dentures *(table 1)*.

Concerning the prevalence of CMC syndromes, only data on APECED exist. APECED is most common in the small populations with high consanguinity of Iranian Jews (about 1:9,000) [14], Sardinian (1:14,400) [15] and Finnish populations (1:25,000) [16] with men and women equally affected. In both the Jewish and the Finnish populations old founder mutations were detected, responsible for almost all cases [17]. Prevalence in Norway is estimated as around 1:90,000 [18]. In other parts of the world only sporadic cases of APECED have been reported. Similarly, no systematic studies have assessed how frequent (or, rather orphan) non-APECED CMC syndromes are and whether there is a gender predisposition. It is worth noticing, though, that most studies report more affected women than men [19-21].

Table 1. Clinical syndromes underlying chronic mucocutaneous Candidiasis

Name	Pathomechanism
Primary immunodeficiencies	
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED, also APS1)	Mutation in AIRE gene; associated with dysfunctions of endocrine glands
Autosomal-recessive CMC	Mutation in PTPN22 gene; associated with autoimmune endocrinopathies and antibody deficiency
Autosomal-recessive CMC	Mutation in CARD9 gene
Autosomal-recessive CMC	Unknown mutation(s)
Autosomal-dominant CMC	Mutation mapped on chromosome 2p; associated with thyroid gland malfunction
Autosomal-dominant CMC	Unknown mutation(s)
Autosomal-dominant hyper-IgE syndrome	Mutation in STAT3 gene; CMC associated with atopic dermatitis and susceptibility to infections with extracellular bacteria
Secondary CMC	
Chronic infection (HIV)	Immune-suppression
Metabolic disease (Diabetes, obesity)	
Long-term medication (corticosteroids, immunosuppressive drugs)	
Long-term antibiotic treatment	Alteration of local microenvironment
Denture	

Pathogenesis of CMC

Defence against *Candida* requires an orchestrated immune response involving both innate and adaptive mechanisms. Though the pathogenesis of CMC is complex and may be heterogeneous, increasing evidence suggests that an altered T cell cytokine secretion is a central event.

Concerning the functioning of the innate immunity, contradicting reports exist [22]. Single reports demonstrate defects in innate immunity. This is true for phagocytic cells such as neutrophil granulocytes, where a serum-dependent functional defect has been published [23]. A subtle impairment in activation and migration of other phagocytic cells such as macrophages or monocytes [24] has also been reported in single CMC patients [1, 25], though these might be secondary effects due to an altered cytokine production. Furthermore, some studies suggest a defect in natural killer (NK) cells in CMC, either stating they were decreased [26] or functionally impaired [27]. However, recent studies indicate a normal candidicidal capacity and migratory behaviour of neutrophils in CMC patients [28, 29], and most studies agree that CMC patients do not suffer from a generally impaired innate immunity.

There seems to be no general defect in humoral immunity either, as most CMC patients show normal serum concentrations of immunoglobulins and high titres of specific antibodies against *Candida* species [1, 30]. Again, within the heterogeneous group of CMC patients, a small subgroup seems to suffer from recurrent respiratory infections accompanied by deficiencies of the IgG subclasses 2 and 4 [31].

Protection against mucocutaneous *Candida* infections seems to rely mainly on cell-mediated immunity, in particular on T cells. Evidence for that hypothesis is given by the fact that patients lacking T cells due to a severe combined immunodeficiency or DiGeorge syndrome often suffer from oral candidiasis and *Candida* infections of skin and nails, but very rarely from systemic candidiasis [32].

The ability of T cells to proliferate to *Candida* antigen is controversial: some studies describe a diminished proliferation both to *Candida* and to mitogens [33], others state a specific defect in the proliferation to *Candida* or a normal T cell proliferation [27, 28].

Cytokine secretion of T cell subtypes rather than proliferation seems a more critical parameter in the pathogenesis of CMC. An impaired Th1 immune response leads to an increased susceptibility to severe *Candida* infections [34] while a reduction of IL-10 increases resistance to these infections [35]. Furthermore, the T helper subset Th17 was recently described to be essential in *Candida* resistance in mice and humans [36-38]. In fact, numerous studies show that CMC patients suffer from a deregulated T cell cytokine production, with a diminished production of type 1-cytokines [28, 39-41], such as IFN-γ, IL-12 and IL-2 and an increased secretion of IL-10 or IL-4 [42]. The most striking defect in CMC patients, however, is the drastically reduced or completely absent production of IL-17 and IL-22 [19]. In one family with autosomal-recessive CMC, this absence of Th17-associated cytokines was shown to be due to a homozygous point mutation in the caspase-associated recruitment domain 9 (Card9) gene, which results in impaired innate signaling from the antifungal pattern-recognition receptor dectin-1 [43]. Whether deregulated T cell cytokine production is due to a direct T cell defect or a disturbed interaction with APC remains to be elucidated, as evidence exists that dendritic cells of CMC patients show an abnormal maturation [20] while having a normal distribution of pattern recognition receptors [21]. Decreased levels of the tissue-instructing cytokines IL-17, IL-22, and IFN-γ on the one hand and increased counteracting type-2 cytokines [44, 45] on the other, result in a diminished production of antimicrobial peptides [46, 47], and failed recruitment of phagocytic cells such as neutrophil granulocytes [48, 49], by epithelial

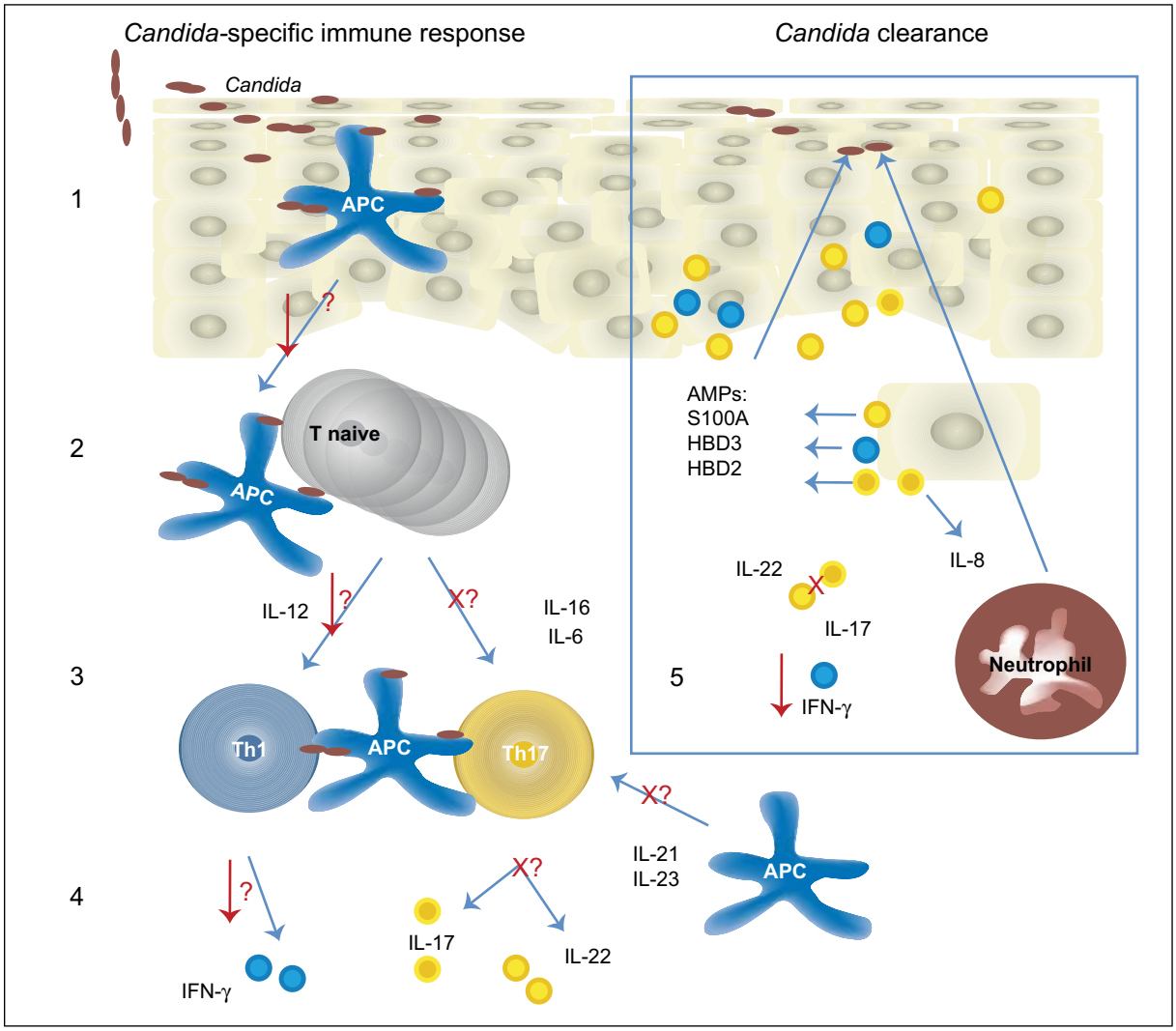

Figure 1. The pathogenesis of CMC. On encountering *Candida*, antigen presenting cells take up and process antigens (1), then migrate to regional lymph nodes and present them to specific naive T cells (2), which undergo clonal expansion and differentiation towards memory effector cells, mainly of the Th1 or Th17 phenotype (3). A second stimulation of T cells with *Candida* leads to secretion of IFN-γ or IL-17 and IL-22, respectively (4). These cytokines induce secretion of antimicrobial peptides (AMPs) and neutrophil-recruiting IL-8 in epithelial cells (5). Lack of IL-17 and IL-22 and diminished IFN-γ results in CMC. The potential defects in this cascade underlying CMC are marked with a red "X" (absent) or "↓" (reduced), however, at what level the tissue-instructing cytokine production is disturbed is unknown so far (indicated by question marks).

cells *(figure 1)*, which results in an impaired clearing of *Candida* selectively at surface barrier organs [50].

Clinical course of CMC

Impaired clearing of *Candida* is the basis for the main clinical symptoms of CMC, a chronic local inflammation, erosion/ulceration and hyperproliferation/squamation of skin and mucosal epithelia that ranges from mild angular cheilitis to severely inflamed thick plaques and crusts. Predisposed areas are the oral and oesophageal mucosa, the trunk (especially the axillary and vaginal regions) and the hands and nails (onychomycosis or candidal paronychia). Primary CMC syndromes usually show an early onset within the first years of life, while secondary CMC occurs later.

Clinically, CMC patients suffer from high psychological stress, dissatisfying aesthetic appearance and uncomfortable itch, burning sensations or pain. Furthermore, *Candida* plaques can cause severe clinical complications. Due to lesion expansion, local *Candida* plaques (*Candida granuloma*) can massively debilitate use of the hands. Another frequent and dangerous complication due to volume expansion and/or scarring after chronic inflammation is stricture of the oesophageus, which has to be treated with balloon dilatation or stenting [51].

A secondary consequence of chronic plaques in the gastrointestinal tract can be mal-digestion or mal-absorption with consequent iron and vitamin deficiency or even excessive loss of weight and cachexia that requires intraveneous nutrition. A third group of complications comprises metaplasia or neoplasia, such as the development of oral squamous cell carcinoma, as reported

Table 2. Recommended anti-*Candida* drugs

Class/name	Recommended dosage	Additional information
Azoles (Triazoles)		
Fluconazole (first-line drug)	100-200 mg/day; systemic infections up to 800 mg/day; pediatric 6-12 mg/kg/day	Oral administration; Candida-static activity; sometimes resistances (esp. fluconazole); liver enzymes ↑, drug-drug-interactions
Itraconazole	200 (– 400) mg/day	
Voriconazole	400 mg/day oral or 8 mg/kg/day intravenous	
Posaconazole	600-800 mg/day	
Ravuconazole	No official recommendations yet (in clinical phase I and II studies)	
Echinocandins		
Caspofungin	70 mg/first day, then 50 mg/day (dose reduction in liver dysfunction)	Intravenous administration; Candidicidal activity; low side-effects (infusion reactions, liver enzymes ↑)
Micafungin	100-150 mg/day; prophylaxis: 50 mg/day	
Anidulafungin	200 mg/first day, then 100 mg/day	
Polyenes		
Local amphotericin B	2 g/day	Local Candida infections (oral Candidiasis), safe and little resistance
Liposomal amphotericin B	3 mg/kg/day	Intravenous administration; rarely infusion-related side effects and nephrotoxicity

in several cases of severe CMC [52-54]. Potentially, neoplasia develop as a consequence of the chronic inflammation, as previously described for gastro-oesophageal reflux disease [55] and cutaneous inflammation [56].

Therapy of CMC

Historically, CMC was treated with immune-stimulating or -restoring agents such as adoptive leukocyte transfer [57] or thymus transplantation [58]. After the development of systemic anti-fungal drugs, however, long-term medication with azole antimycotics became the standard therapy of *Candida* infections [59] *(table 2)*. Azoles inhibit ergosterol synthesis, thereby acting statically against *Candida*. Today fluconazole is recommended as the first-line systemic drug at a dosage of 100-200 mg/day. However, sensitivity to fluconazole often decreases over time [60]. Regular microbial sensitivity tests (antibiogram) of isolated *Candida* strains are therefore essential in the treatment of CMC. Itraconazole, voriconazole and posaconazole [61] are newer azole-antifungals that can substitute fluconazole. Another class of systemic antifungal drugs applicable against *Candida* infections are the echinocandins [62] caspofungin [63], micafungin [64] and anidulafungin. They act against fungi by inhibition of glucan synthesis and, therefore, cell wall formation. The main disadvantage of echinocandins is the lack of oral formulation. Echinocandins and azoles are comparably efficient against *Candida* infections. Though no long-term safety analyses are available, echinocandins seem relatively safe and show potential synergism with other antimycotics. Echinocandins are now considered as the first line option in life threatening systemic candidiasis [65].

A third class of antifungal agents are polyenes, which bind to ergosterol. The only polyene currently recommended for systemic anti-*Candida* treatment is amphotericin B; however, since it has to be administered intravenously and it shows severe side effects (in particular nephrotoxicity), amphotericin B has to be considered a third-line agent, although new lipid-associated formulations show lower toxic side effects [66]. Topical amphotericin B, however, is, like Nystatin, recommended as safe for long-term treatment of local infections, as resistance is rarely observed.

Conclusion

Chronic mucocutaneous candidiasis is a highly heterogeneous group of mostly inherited syndromes. Though some genetic defects are known, the link to a specific immune dysfunction remains elusive. Recent studies show this specific immune dysfunction is based upon an impaired Th17/Th1 immune instruction of epithelial cells. Further studies and clinical trials are needed to investigate whether CMC patients could benefit from (additional) biological drugs, such as local or systemic administration of IL-17 and/or IL-22.

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