ORAL CANDIDOSIS IN INTENSIVE CARE UNIT PATIENTS

A COMPREHENSIVE REVIEW (2005–2025)

By

Junhi Zidan
ID: 21226043

A thesis submitted to the Department of Microbiology in partial fulfillment of the requirements
for the degree of
Bachelor's in Microbiology

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Junhi Zidan
ID: 21226043

Approval

The thesis/project titled “ORAL CANDIDOSIS IN INTENSIVE CARE UNIT PATIENTS: A COMPREHENSIVE REVIEW (2005–2025)” submitted by Junhi Zidan (21226043) of Fall 2025, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor’s in Microbiology on 29 January 2026.

Examining Committee:

Supervisor:

_____

Fahim Kabir Monjurul Haque, PhD
Associate Professor, Department of Microbiology
BRAC University

Chairperson:

_____

Nadia Sultana Deen, PhD
Associate Professor, Department of Microbiology
BRAC University

Ethics Statement

This narrative review consolidates open-access peer-reviewed literature (2005–2025) from PubMed (National Library of Medicine), Google Scholar, Frontiers, PMC, Europe PMC, BMC (BioMed Central), and MDPI studies that do not include information on human subjects or animals used within experiments, clinical trials or original data. No institutional Review Board (IRB) approval and informed consent was needed. The synthesis is in accordance with ethical standards of the responsible conduct of research, accurate reporting and plagiarism, contributing to transparency and reproducibility while summarizing oral candidosis as occurring in ICU patients.

Abstract/ Executive Summary

Oral candidosis is a common opportunistic mycotic infection in intensive care (ICU) with colonization rates quoted between 27% and 53% depending on when sampling occurs, the method of collection and the critical illness severity. It has been traditionally considered a focal mucosal infection, but increasing epidemiological data indicate oral candidosis represents a clinically relevant source of lower respiratory tract colonization and invasive candidemia, especially in mechanically ventilated adults (Nascimento et al., 2024; Noppè et al., 2024). The profound immune dysregulation of critical illness, broad-spectrum antibiotic exposure, invasive medical devices and impaired oral hygiene provide a conducive environment for such *Candida* overgrowth. This narrative review of literature accumulated over a period of 2 decades (2005-2025) sought to summarize the evidence on the epidemiology, microbiology, pathogenesis, risk factors for development, methods and tests employed in diagnosis, patterns of antifungal resistance as well as therapy and clinical outcomes related to oral candidosis among critically ill patients. Oral candidosis is considered as a marker for risk to systemic infection and its treatment. There is a clear need for improved epidemiological monitoring, standardized diagnostic pathways, integrated approaches to oral-care informed by specialist assessment and antifungal stewardship that are based on a secure evidence-base in order to reduce morbidity and mortality from this frequently overlooked complication of critical illness.

Keywords: oral candidosis, intensive care unit, *Candida albicans*, colonization, ventilator-associated pneumonia, mechanical ventilation, candidemia, antifungal resistance, oral care bundles, diagnostics

Dedication

I would like to dedicate this work to my family and my one & only well-wisher for all their love and support during my time as a student. Their faith in me has been a tremendous source of inspiration.

I would also like to pay tribute in this paper to my professors and mentors whose guidance and inspiration formed the framework of my own research and helped me face these challenges. Their devotion in the search for truth has served as an inspiration to us.

Finally, I would like to dedicate this study to all who work to promote the advancement of knowledge whose scientific contributions exerted significant influence on human scientific thought and continue to inspire posterity.

Acknowledgement

Alhamdulillah, the most gracious and merciful to Allah (S.W.T.) who gives me power, strength, patience and knowledge for completing this research. As per His wishes this work was done.

I acknowledge with thanks the support, guidance and co-operation received from my supervisor Dr. Fahim Kabir Monjurul Haque, PhD, Associate Professor, BRAC University in the completion of this thesis. I'd like to acknowledge sir, Akash Ahmed, Senior Lecturer, BRAC University for his help and support.

I would like to thank my family and my special one for their constant love, patience, and unwavering encouragement. May Allah bless them all.

And lastly, I owe much gratitude to all other contributors in this field and further researchers. May Allah recompense them for all their toil.

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List of Acronyms

Acronym	Full Form
ICU	Intensive Care Unit
VAP	Ventilator-Associated Pneumonia
NAC	Non-Albicans Candida
CFU	Colony Forming Units
CI	Colonization Index
PCR	Polymerase Chain Reaction
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight
BDG	1,3-β-D-Glucan
MIC	Minimum Inhibitory Concentration
CLSI	Clinical and Laboratory Standards Institute
OR	Odds Ratio
RCT	Randomized Controlled Trial
NET	Neutrophil Extracellular Trap
PPV	Positive Predictive Value
NPV	Negative Predictive Value
ANC	Absolute Neutrophil Count

Glossary

Term	Definition
Oral Candidosis	Candidosis of the mouth and throat Fungal infection of oral mucosa due to *candida*.
Colonization Index (CI)	Quantitative *Candida* loads in multiple sites of the body as a predictor of risk for invasive candidosis.
Biofilm	Engineered microbiome with biofilm provides antigrowth as well as antifungal resistance.
Mechanically Ventilated	Empiric antifungal therapy when pre-transplant risk factors are present and pathogen is unidentified.
Empirical Therapy	Pre-emptive antifungal therapy based on risk factors prior to the identification of the pathogen.
De-escalation	Change to a narrower-spectrum antibiotic when susceptibilities available.
Antifungal Stewardship	Optimization of antifungal therapy to prevent resistance and improve outcomes.
Candidemia/ Candidaemia	*Candida* in the bloodstream (US spelling: candidemia).
Aspiration	Candida colonization/aspiration and development of VAP/dissemination.
Azole Resistance	Low susceptibility to fluconazole/azole antifungals frequently occurs in NAC species.
Candidemia	Systemic bloodstream *Candida* infection

Drug Efflux Pump (DEP)	Pump and pushing out antifungals and allowing resistance.
Invasive Candidiasis	Disseminated *Candida* infection with high ICU mortality (40–50%).
Minimum Inhibitory Concentration (MIC)	minimal inhibitory concentration of drug.
Multifocal Colonization	Establishing colonies at various locations within the body
Non-Albicans Candida (NAC)	Non-C. albicans isolates with more-resistant profiles.
Oropharyngeal Candidosis (OPC)	Oral mucosal *Candida* infection, as sign of HIV infection Oral Candidosis.
Ventilator-Associated Pneumonia (VAP)	Lung infection is potentially *Candida*-seeded from oral source. Ventilator-Associated Pneumonia (VAP) is a serious lung infection developing in patients on mechanical ventilation for over 48 hours, common in ICUs
Virulence Factor (VF)	Virulence factors allow microbial infections to spread, escape or inhibit the immune response, get nutrients from the host, and sense environmental changes.
Xerostomia	Dry mouth impairing clearance/ promoting *Candida* overgrowth.
95% CI	Statistical estimates (OR, prevalence) were expressed with 95% CI.

ORAL CANDIDOSIS IN INTENSIVE CARE UNIT PATIENTS: A COMPREHENSIVE REVIEW (2005-2025)

Abstract

Oral candidosis is a common opportunistic mycotic infection in intensive care (ICU) with colonization rates quoted between 27% and 53% depending on when sampling occurs, the method of collection and the critical illness severity. It has been traditionally considered a focal mucosal infection, but increasing epidemiological data indicate oral candidosis represents a clinically relevant source of lower respiratory tract colonization and invasive candidemia, especially in mechanically ventilated adults (Nascimento et al., 2024; Noppè et al., 2024). The profound immune dysregulation of critical illness, broad-spectrum antibiotic exposure, invasive medical devices and impaired oral hygiene provide a conducive environment for such *Candida* overgrowth. This narrative review of literature accumulated over a period of 2 decades (2005-2025) sought to summarize the evidence on the epidemiology, microbiology, pathogenesis, risk factors for development, methods and tests employed in diagnosis, patterns of antifungal resistance as well as therapy and clinical outcomes related to oral candidosis among critically ill patients. Oral candidosis is considered as a marker for risk to systemic infection and its treatment. There is a clear need for improved epidemiological monitoring, standardized diagnostic pathways, integrated approaches to oral-care informed by specialist assessment and antifungal stewardship that are based on a secure evidence-base in order to reduce morbidity and mortality from this frequently overlooked complication of critical illness.

Keywords: oral candidosis, intensive care unit, *Candida albicans*, colonization, ventilator-associated pneumonia, mechanical ventilation, candidemia, antifungal resistance, oral care bundles, diagnostics

Chapter 1: Introduction

Oral candidosis is a fungal infection of the oral mucosa commonly associated with *Candida* yeasts, being *C. albicans* still the most frequently isolated species all over the world (Sobel, 2007). Previously treated as a relatively benign, localized condition restricted to immunocompromised others not in the ICU, OPC has increasingly been recognized as clinically significant in hospitalized intensive care patients (Eggimann & Pittet, 2014). In healthy individuals, *Candida* is a commensal member of the oral microbiome, but perturbations in host immune defenses or microbial ecology may lead to pathologic overgrowth and mucosal invasion by this fungus (Achkar & Fries, 2010).

The critically ill patient in the ICU is a uniquely susceptible population due to extensive immune dysregulation from severe illness, systemic inflammation, trauma and sepsis (Hotchkiss et al., 2013). ICU admission represents an independent risk factor, since it inevitably leads to exposure of patients to broad-spectrum antibiotics, steroids, invasive medical devices and prolonged mechanical ventilation that profoundly modify the oral microenvironment by creating conditions conducive for fungal outgrowth (Eggimann et al., 2015). Similarly, patients with impaired consciousness and those receiving sedation or medications seem less inclined for self-care of their oral cavity and may have an increased risk of direct colonization by microorganisms to later facilitate infection (Rautemaa & Ramage, 2011).

The epidemiological burden of opportunistic fungal infections in the ICU has escalated substantially over the past few decades, coinciding with advancements in critical care technologies which have resulted in improved survival of patients who present to ICUs with acute and complex comorbidities or profound immunosuppression (Blot et al., 2020; Méan et al., 2008). Invasive candidemia has been the object of extensive clinical and experimental research because its associated mortality rate (40-50%) is so high, but oropharyngeal candidosis is still largely underdiagnosed and undertreated despite evidence that suggests a role as the source of systemic infection by this pathogen (Nucci & Anaissie, 2001). In molecular epidemiology, genetic congruence between oral and blood isolates of Candida has been found, which confirms the pathogenetic role for endogenous dissemination from mucosa colonization (León et al., 2009).

Aspiration of colonized oral secretions is a recognized process in the development of VAP and similar processes are postulated for escape of Candida from the oral cavity to ventilated patients (Scannapieco et al., 2003). These clinical impressions, taken together, highlight the need to reconceptualize oral candidosis as more than just a local mucosal lesion but rather as a clinically meaningful and integral part of the spectrum of ICU-related fungal disease with prognostic import.

This evidence-based review aims to summarize two decades of research (2005–2025) on oral candidosis in patients admitted to ICUs. The aims are to: (1) review contemporary epidemiological trends and *Candida*-species distribution; (2) explore risk factors specific to ICU, host-related, procedural related; (3) examine pathogenesis mechanisms; (4) summarize diagnostic modalities and therapeutic options; (5) assess antifungal resistance patterns; and (6) evaluate the clinical impact of oral candidosis as a precursor for invasive disease and poor outcomes.

Chapter 2: Methods

2.1 Search Strategy and Literature Selection

This narrative review approach was conducted to search the pertinent peer-reviewed studies. The following were included in all our major biomedical databases: PubMed (National Library of Medicine), Google Scholar, Frontiers, PMC, Europe PMC, BMC (BioMed Central), and MDPI for studies published between January 2005 and December 2025. We chose to target the time frame 2005–2025 in order to synthesize current evidence and balance that with seminal manuscripts developed over two decades of clinical-scientific inquiry.

2.2 Search Terms and Keyword Strategy

The following keywords and combinations were utilized, with Boolean operators employed to optimize retrieval:

Primary search terms:

- ("oral candidiasis" OR "oral candidosis" OR "oropharyngeal candidiasis") AND ("intensive care unit" OR "ICU" OR "critical care" OR "critically ill")
- ("*Candida*" OR "candidiasis") AND ("mechanically ventilated" OR "mechanical ventilation" OR "endotracheal intubation").
- ("ventilator-associated pneumonia" OR "VAP") AND ("*Candida*" OR "candidiasis" OR "fungal")
- (“candidemia” OR “candidaemia”) AND (“oral colonization” OR “respiratory colonization” OR “source”)
- (“antifungal resistance” OR “azole resistance” OR “fluconazole resistance”) AND (“*Candida*” OR ”ICU” OR “critically ill”)
- ("biofilm" OR "biofilms") AND ("*Candida*" OR " candidosis ") AND ("intensive care")
- ("*Candida auris*" OR "multidrug-resistant *Candida*") AND ("ICU" OR "healthcare-associated")

Secondary search terms for specific topics:

- "Colonization index" AND ("*Candida*" OR "candidosis")
- “Oral care guidelines" AND ("oral care OR "VAP prevention") OR("Ventilator associated pneumonia protocols").

- "Chlorhexidine" AND ("candidosis" OR "candidiasis" OR "oral decontamination")
- "Species distribution" AND ("*Candida*" OR "candidosis") AND ("temporal trends" OR "epidemiology")

2.3 Inclusion and Exclusion Criteria

Inclusion criteria:

- Studies (original research, systematic reviews, meta-analyses, clinical guidelines) focused on oral oropharyngeal *Candida* infections in adult (≥18 years) ICU patients.
- Published in English-language peer-reviewed journals
- Original data studies on epidemiology, prevalence, incidence, risk factors, pathogenesis, diagnosis, treatment outcomes or prevention for oral candidosis in ICUs.
- Studies reporting the presence of *Candida* colonization in oral or respiratory sites in mechanically ventilated patients
- Prospective clinical trials or observational studies focusing on oral care interventions (chlorhexidine, mechanical care) or antifungal prophylaxis/treatment in the ICU population.
- Surveillance studies documenting species distribution and antifungal susceptibility patterns in ICU populations.

Exclusion criteria:

- Studies that included only non-ICU groups (community-acquired oral candidosis, outpatient-based/ambulatory oral candidosis)
- Case series includes less than 5 reported cases.
- Studies with no apparent methodology, outcome, or results reporting
- Non-full-text studies
- Opinion, editorial, commentary without original supporting data
- Investigations of *Candida* species only involving non-oral/non-respiratory sites not referring to ICU populations
- Studies in which the relationship between oral/respiratory *Candida* colonization and VAP, invasive candidosis or mortality was investigated.

2.4 Data Extraction and Synthesis

The information extracted from each of the included studies was presented in a standard template as follows:

Study characteristics:

- Year of publication/ author/ journal/ study design (PROSPECTIVE/ RETROSPECTIVE/ RCT/ cohort).
- Country, geographic area, ICU type (medical/ surgical/ mixed)
- Size of the sample, characteristics of the patients and criteria for ICU admission

Epidemiological data:

- Occurrence and Acquirement of Oral & Respiratory Candida Colonization
- Temporal appearance of colonization (D1, D5, D8 and so on.)
- Development from colonization to clinical disease
- Regional variation in colonization rates

Microbiology:

- Distribution (percentage) of Candida species and corresponding CFU counts if available.
- Antifungal susceptibility to fluconazole, echinocandins, and amphotericin B
- Resistance rates by species and geographic region
- Results of molecular epidemiology (genotyping, concordance analyses)

Risk factors and outcomes:

- Results univariate and multivariate risk factors (odds ratios, 95% confidence intervals, p-values)
- Clinical results (mortality, length of ICU stay, VAP incidence, progression to invasive disease)
- Method of diagnosis applied and its diagnostic accuracy (sensitivity, specificity, predictive values)
- Treatment treatments, duration and response rates

Key findings and conclusions

The extracted data were organized thematically into major sections covering epidemiology, species distribution, pathogenesis, risk factors, diagnosis, antifungal resistance, treatment, prevention, and clinical outcomes. Where possible, findings from multiple studies were compared and synthesized to identify consensus findings, areas of disagreement, and evidence gaps.

2.5 Quality Assessment

The studies included were critically appraised for their methodological quality using a set of established standards prepared in statement-based form. These standards emphasized several critical variables that impact on the credibility and trustworthiness of study results:

- **Sample size and power**: Assessing whether the sample size was big enough to identify meaningful differences.
- **Clear, pre-defined definitions of study endpoints:** The outcomes (oral candidosis, colonization or invasive disease) being well-defined beforehand the initiation of a study.
- **Sufficient statistical analysis and reporting confidence limits:** We examined whether the method of statistical analysis was sound (e.g., presence of power calculation) and the results were reported with confidence limits.
- **Prospective vs. retrospective study design:** Impact of study design on bias.
- **Transparency in the reporting of limitations:** The extent of whether limitations either were reported explicitly or, if not, addressed.
- **Relevance to ICU populations:** To have study patients be representative of current-day ICU patients.
- **Follow-up time:** If the follow up time was long enough to capture the transition from colonization to invasive disease.
- **Risk of selection bias, information bias and confounding biases**: We assessed whether the study was free from other obvious sources of bias that could affect its results.

Higher quality studies were defined as those that used a prospective design, multicenter enrollments large enough to support the primary issue (n >100), clearly defined outcomes, and multivariate analysis adjusting for significant confounders.

2.6 Narrative Synthesis Approach

A narrative synthesis is used for this review, as heterogeneity in the study designs, patients' cohort, diagnostic approach and outcome definition was found to be not conducive for quantitative pooling of data. The narrative synthesis is structured as follows: (1) description of the number and characteristics of included studies; (2) identification of patterns and groupings in study findings; (3) exploration of relationships, trends or sources of variation among the results across studies; (4) organization of the findings into coherent overviews around each major topic area; and (5) appraisal for strength and consistency across studies.

Chapter 3: Epidemiology and Prevalence of Oral *Candida* Colonization

3.1 Historical Perspective and Temporal Evolution (2005–2025)

The epidemiology of oral candidosis in the ICU population has changed very considerably during the last two decades when from being largely ignored commensal overgrowth, it has become appreciated as clinically relevant reservoir of invasive infection. Introduction Preliminary work (2005–2010) demonstrated very high levels of oral/ respiratory *Candida* colonization among ICU patients compared to non-ICU populations. Méan et al. reported in their excellent review from bench to bedside that *Candida spp*. caused 5 to 10% of all bloodstream infections in the United States, with incidence that was between 5 to 10 times higher in ICUs compared with other hospital wards.

The concept of the Colonization Index (CI) was established in the mid-2000s and has been extensively described previously (Eggimann and Pittet, 2014), offering a quantitative framework for colonization to invasive disease. These authors, in their 20-year review of data, noted that the Candida Index (CI) was a successful predictor for invasive candidosis in critical care patients with an optimum predictive value being recorded at colonization threshold levels on days 3 to 6 before documented candidemia.

3.2 Contemporary Prevalence Rates (2020–2025)

The best contemporary epidemiologic information is from the prospective multicenter study of Nascimento et al. (2024) for 675 ICU patients in three Portuguese hospitals from January 2020 to February 2022. This study observed a progressive increase in the prevalence of colonization over an ICU stays:

- **Day 1 (ICU admission)**: 27.3% prevalence (colonized patient at baseline and colonized on admission)
- **Day 5 (mid-week)**: 42.9% prevalence (progressive colonization)
- **Day 8 (second week)**: 52.7% prevalence (colonization established)

Moreover, 15.3% of patients developed new Candida colonization while in the ICU, and 29.2% (n=89) had colonization at all three time points showed persistent colonization during their stay at ICU. Temporal development of oropharyngeal Candida colonization was illustrated by 675 ICU patients in prospective multicenter data:

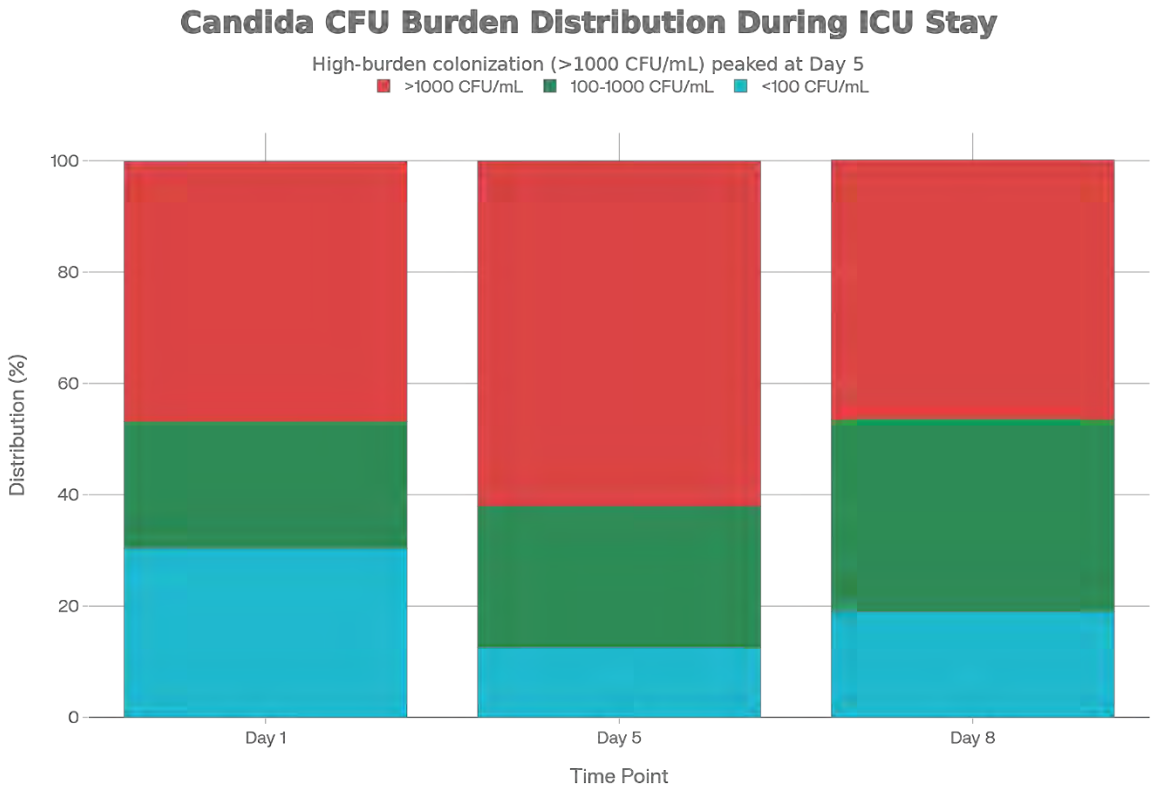

Figure 1. Temporal dynamics of oral *Candida* colonization in ICU patients.

Temporal changes in colonization while the patient is an ICU inpatient demonstrating a stepwise increase in prevalence and direction toward higher CFU loads with time.

(A) Progressive colonization prevalence during ICU run in 675 MV patients from three Portuguese hospitals (2020–2022). Colonization was evaluated at 3 time points: D1 (ICU admission, blue bar), D5 (midweek evaluation, orange bar), and D8 (confirmed ICU stay, grey bar). The frequency of SARS-CoV-2 DNA in stools was 27.3% upon admission, which increased to 42.9% on the fifth day and 52.7% on the eighth day ($p < 0.001$ for trend). (B) Change in fungal burden distribution over time with an increased number of patients having high CFU counts ($\geq 10^4$ CFU/mL) on Day 8 compared to Day 1. Values are shown as a percentage of colonized patients at indicated time point. The error bars represent 95% confidence intervals. Adapted from Nascimento et al. (2024).

3.3 Geographic Variation in Prevalence

Significant geographic heterogeneity exists in oral *Candida* colonization prevalence among ICU patients, reflecting differences in healthcare practices, antimicrobial stewardship, ICU infrastructure, and baseline population characteristics:

Table 1: Geographic variation in ICU patient oral Candida colonization prevalence

Geographic Region	Reported Prevalence	Study Design	Study Period	Reference
Portugal	27–53%	Prospective multicenter, n=675	2020–2022	Nascimento et al. (2024)
Belgium	54.8%	7-year surveillance, ICU subset	2017–2024	Belgian surveillance (2025)
India	72%	Regional cohort	2019–2020	Kaur et al. (2020)
Brazil	67%	Regional survey	2018–2019	Colombo et al. (2017)
United States	58%	Mixed ICU populations	2016–2020	Pfaller & Diekema (2019)
Italy	49%	European cohort study	2015–2018	Bassetti et al. (2019)

These variations in geography may be due to many reasons, including differences in antimicrobial prescribing practices and stewardship intervention intensity; variation in oral-care protocol use and fidelity of implementation; differences in ICU staffing ratios or resource availability; the availability and utilization of diagnostic resources, for example, those for bacteria identification or susceptibility testing; patterns of baseline oral health status among populations living in different locations where ICUs are located; prevalence of comorbidities such as diabetes mellitus (Nascimento et al., 2024) requiring chronic antibiotic prophylaxis or treatment by the hospital team (Pfaller et al., 2019). Social economic aspects and differences in healthcare infrastructure are also adding to the regional discrepancy. Crucially, restricted surveillance from low- and middle-income countries is likely to have provided underestimates of the actual worldwide burden of oral candidosis in critically ill patients.

Chapter 4: Candida Species Distribution and Epidemiological Shifts (2005–2025)

4.1 Historical Species Composition (2005–2015)

Previous surveillance studies performed from 2005 to 2015 continually suspected *Candida albicans* as the most prevalent species recovered from oral/respiratory samples in ICU population, with proportions ranging from 60 to 75% of strains among cohorts. During this early period, the distribution of non-albicans *Candida* (NAC) species did not significantly shift, with *C. glabrata, C. tropicalis* and *C. parapsilosis* predominating among NAC isolates.

4.2 Contemporary Species Distribution (2020–2025)

Recent surveillance information from 2020–2025 highlights significant changes in species epidemiology:

Candida albicans: Remained the most prevalent species at 52–62% of isolates

- Continued domination in mainland Europe and North America
- Predictive of negative outcomes in ICU (independent risk factor)
- Shows strong echinocandin susceptibility; azole susceptibility is mixed
- Nascimento et al. (2024) Portuguese cohort: 52.1% of isolates

***Candida parapsilosis* complex**: 12–31% of isolates

- Geographic variation: low in Europe (12%), high in Portugal (31.5%) and Latin America
- Critical findings: Progressive fluconazole resistance in Southern Europe outbreaks since 2018
- Arastehfar et al. (2023) in some clones to 66.6% but readily forms biofilms Good with central venous catheters
- Nascimento et al. (2024): 31.5% of Portuguese ICU isolates

***Candida glabrata* (*Nakaseomyces glabrata*):** 10–24% of isolates

- Increased risk in an ICU setting: 28% in ICU wards vs.<10%, other hospital wards (Belgian surveillance,2025)
- Intrinsic resistance to fluconazole; echinocandin susceptibility variable.
- Global fluconazole resistance rates 8–88%; ~10.1% thrown Northern Europe (Belgian surveillance, 2025)

- Emerging as an important ICU pathogen

Candida tropicalis: 4–17% of isolates

- Related to hematological disease and neutropenia.
- Resistant strains of fluconazole are increasing (10–17% worldwide)
- The Technology of Kiribati and Tuvalu (2025): 16.9% fluconazole resistant among hemato-oncology patients in Belgian surveillance

***Candida auris*, Emerging Multidrug-Resistant Pathogen**: *C. auris*, is a nosocomial pathogen discovered for the first time in 2009 (Satoh et al., 2009), and it has become a global threat of healthcare system with great impact in the ICU epidemiology. Regional emergence Outbreaks have now been associated with regions of the USA in late 2021, with current levels at 6.2% of yeast isolates amongst certain North American ICU populations (Nguyen & Ren, 2025). Characteristically, *C. auris* exhibits:

- **High fluconazole resistance**: 92% of isolates with MIC ≥32 μg/mL (Nguyen & Ren, 2025)
- **Amphotericin B resistance**: 32.2% of isolates with MIC ≥2 μg/mL (Nguyen & Ren, 2025)
- **Echinocandin resistance**: 4–5% of isolates exceed resistance breakpoints (Nguyen & Ren, 2025)
- **Environmental persistence** and high transmissibility in healthcare settings
- Needs molecular identification (MALDI-TOF or PCR); sometimes misidentified as *C. haemulonii* or *C. duobushaemulonii* on routine culture methods.
- Not yet detected in European ICU populations as of 2024–2025, though global surveillance remains essential given its pandemic potential.

4.3 Epidemiological Shifts and Clinical Implications

A significant epidemiological change in favour of NAC species has been reported in the last 20 years, with a roughly 12% increase per decade of non-albicans species worldwide (Pfaller et al., 2019; Sanguinetti et al., 2015). This change is medically important because :

1. **Intrinsic or acquired azole resistance**: several NAC species show either innate (*C. glabrata, C. krusei*) or acquired (*C. parapsilosis, C. tropicalis*) resistance to azoles
2. **Enhanced biofilm formation capacity**: NAC species often demonstrate superior biofilm-forming ability compared to *C. albicans*

3. **Reduced echinocandin susceptibility**: Although uncommon, echinocandin-resistant NAC strains are being documented with increasing frequency.

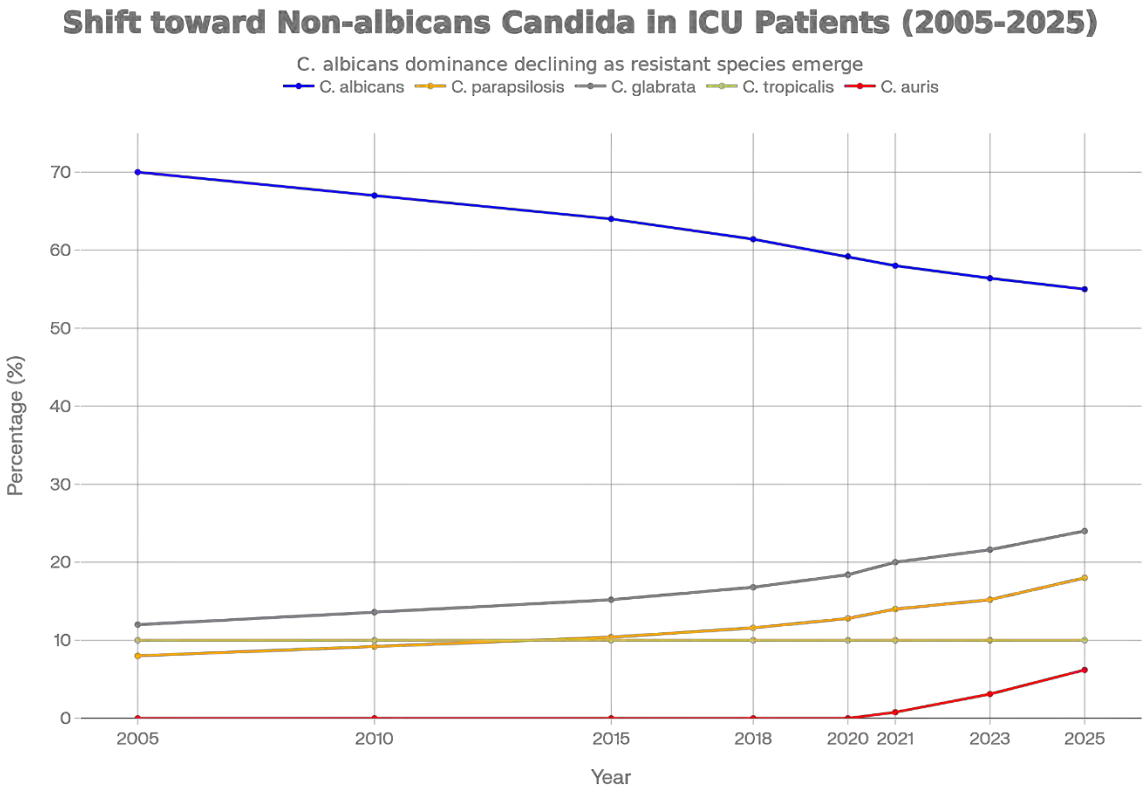

Figure 2. Evolution of *Candida* species distribution in ICU settings (2005–2025).

Temporal shift in distribution of Candida species in oral and respiratory specimens in intensive care unit patients over a 20-year period. *C. albicans* (blue line) is still the most frequent species, however its frequency has been decreasing over time with 70% of isolates in 2005 and 55% in 2025 which corresponds to a decrease of 12% per decade. Non-albicans *Candida* (NAC)-species have a percent increase parallel to this: *C.parapsilosis* complex (orange line) from 8% to 18%; *C. glabrata* (gray line) from 12% to 24%, and similarly, *C. tropicalis* (yellow line) steady at ~10%; the long-predicted nightmare species, *C. auris* (red line), emerged in 2021 to reach a prevalence of 6.2% in North American ICUs by year-end=2025. The data were collected from multicenter surveillance studies (Pfaller & Diekema 2007, 2019; Arastehfar et al. (2023), and Nguyen & Ren (2025). Each data point is the pooled prevalence of published surveillance studies for that year.

C. albicans persisted as the main yeast in 70% (2005) to 55% (2025), decreasing by evolving into a rate of 12 % decline per decade, while NACs are now responsible for >45% isolates (Arastehfar et al., 2023).

Species distribution (2005-2025)- C. albicans (hardly supported) as a dominant species decreased; NAC, in particular *C. parapsilosis* and *C. glabrata*, increased; emergence of *C. auris* since 2021 might be assumed.

The epidemiological transition is due to selective pressure from:

- Extended use of antifungal prophylaxis in ICUs.
- Frequent or prolonged exposure to antibiotics changing the flora of the mouth.
- Greater use of invasive biofilm niche-creating procedures.
- Cross-border movements and healthcare infected by resistant clones

In view of this, accurate species identification by culture combined with MALDI-TOF or molecular methods has been indispensable to optimize therapy and avoid invasive disease.

Chapter 5: Pathogenesis: Mechanisms Underlying Oral Candidosis in ICU Patients

Candidosis of the mouth in critically ill patients is a combined effect of three main pathogenetic factors; (1) severe impairment of immunity typical for critical illness, (2) transient suppression of protective oral microbiota, and (3) ICU-related factors that favour fungal colonization and maintenance.

5.1 Immune Dysregulation in Critical Illness

Profound changes in innate and adaptive immune responses are seen during critical illness as follows (Hotchkiss et al., 2013):

- **Neutrophil dysfunction:** Diminished chemotaxis, phagocytosis and NET (neutrophil extracellular trap) formation.
- **Disordered cytokine signal cascades**: Early hyperinflammatory phase and late immunosuppression state, T helper cell ratio disturbance and T lymphocyte exhaustion.
- **Complement cascade defects**: Decreased opsonization and complement bacteriolysis.
- **Impairment of mucosal immunity**: Diminished production of antimicrobial peptides (lactoferrin, lysozyme), low salivary immunoglobulin A, and impaired mucosal barrier (Fidel et. al., 2011)

These immune alterations impair active antifungal mechanisms in the oral cavity, allowing exaggerated Candida overgrowth despite ongoing systemic anti-infection threshold markers.

5.2 Disruption of Oral Microbiota and Loss of Colonization Resistance

Almost all ICU patients receive broad-spectrum antibiotics, which leads to a drastic shift in the oral bacterial microbiota by killing commensals that normally suppress fungal expansion through niche competition and metabolite production (Pappas et al., 2016; Sanguinetti et al., 2015). This effect is proportional to the duration and spectrum of antibiotics. Bergmans et al. (2001) showed in their prospective study that more than one cohort showed a direct dose–response relationship between cumulative antibiotic exposure and increased oral Candida burden in mechanically ventilated patients (León et al., 2009; Blot et al., 2020).

Colonization resistance is particularly lost with:

- β-lactam type antibiotics (anaerobic, enterococcus)
- Fluoroquinolones (wide gram-negative activity + anaerobic)
- Combination therapy (synergistic perturbation of microbiota)

5.3 Diminished Flow of Saliva and Compromised Mechanical Clearance

The reduced salivation seen in mechanically ventilated patients is due to:

- Sedation-induced xerostomia
- Dehydration and fluid restriction
- Trauma to mucosa from endotracheal tubes

This reduced salivary flow compromises:

- **Mechanical clearance**: Decreased ability to clean itself with saliva.
- **Antimicrobial peptide function:** Reduced dilution and localization of lactoferrin, lysozyme, and histatins on oral surfaces
- **Buffer system of pH:** It is typically a reduction in the NC (neutralizable component) that makes the salivary buffer systems less effective, allowing for acidification and progression to fungal growth.
- **Diet:** Low glucose, and other nutrients in saliva decreases bacterial load, allowing fungi to take over.

5.4 Mucosal Barrier Injury and Biofilm Formation

Insertion of the endotracheal tube directly traumatizes oral and oropharyngeal mucosa, resulting:

- Epithelial integrity and barrier function disruption
- Microulcerations enhancing fungal adhesion.
- Inflammatory infiltration facilitated fungal invasion.
- Overexpression of Candida adhesin receptors on injured epithelium to Top

Biofilm formation is a critical pathogenic mode. *Candida* species colonize and produce surface-associated biofilms on oral mucosa, dentures, and endotracheal tubes from 24 to 48 h after initial colonization. These biofilms manifest as (Ramage et al., 2012; Mukherjee et al., 2003):

- **Phenotypic resistance**: A 1000-fold increase in anti-fungal agent tolerance relative to planktonic cells.

- **Hypoxic core development:** Focal areas of anerobic metabolism with impaired drug delivery
- **Exo-polymers matrix**: Consisted of polysaccharides and proteins which covered the fungal cells and protected them from immune-mediators and antimicrobials.
- **Concomitant gene expression**: Changes in VF (virulence factor) expression and enhancement of DEP (drug efflux pump) expression.
- **Polymicrobial interactions**: Mixed Candida–bacterial infection causes more severe disease resulting from the bacteria-upregulated expression of the fungal virulence factor candidalysin (Rodrigues et al., 2017)

Chapter 6: Risk Factors for Oral Candidosis in ICU Patients

6.1 ICU-Related and Procedure-Specific Risk Factors

Mechanical ventilation and intubation: This represents one of the most powerful and constant independent risk factors for oral *Candida* colonization/infection in ICU, since patients who required mechanical ventilation have around 2.8 times more likely to be colonized with oral *Candida* than non-ventilated ICUs (León et al., 2009; Blot et al., 2020). Mechanistic factors include:

- Endotracheal tubes causing mucosal damage by pressure effects
- Exposure-related impaired salivary clearance of the tube
- Biofilm formation on tube surfaces
- Aspiration of infected oropharyngeal secretions into lower respiratory tract
- Time of mechanical ventilation associated with colonization load

Exposure to broad-spectrum antibiotics: Exposure to systemic antibiotic treatment for long periods or at high doses raises the risk of oral candidosis by about 2.3-fold (Blot et al., 2020; Sobel, 2007). Risk increases with:

- Length of treatment (risk increases greatly if >7 days)
- Breadth of spectrum (combination therapy >monotherapy)
- Agents with strong anaerobic coverage
- Time of occurrence in the ICU course (cumulative dysbiosis)

Prolonged ICU stay: A prolonged ICU length of stay is a cumulative risk factor as there is ongoing exposure to invasive procedures, antimicrobials and environmental pathogens. Nascimento et al. (2024) found the prevalence of colonization increased from 27.3% at admission to 52.7% on day 8 after admittance in ICU, showing that this risk factor is time dependent.

Enteral and parenteral nutrition: Enteral nutrition modifies oral pH and availability of nutrients, which lead to micro-environments that promote *Candida* overgrowth. Furthermore, total parenteral nutrition also predisposes patients to candidosis effecting immune response and mucosal barrier (Bergmans et al., 2001).

Inadequate or inconsistent oral hygiene protocols: Lowered status of the oral cavity among mechanically ventilated, sedated and critically ill patients is common in ICUs where dental or mouth

hygiene facilities are lacking. Irrational oral hygiene practice has been reported to lead to more frequent oral candidosis, as well as higher incidence of VAP (Scannapieco et al., 2003).

6.2 Host-Related Risk Factors

Old age: Independent effect of old age includes increased susceptibility, mediated by immunosenescence with reduced T cell function and impaired T cell response (alleles), decreased neutrophil response, decreased salivary production (age-related xerostomia), high comorbidity burden and high baseline colonization rates from sustained dysbiosis (Sobel, 2007; Fidel et al., 2011).

Diabetes mellitus: This represents a well-established and biologically plausible risk factor (approximately 2.6-fold increased risk), mediated by (Achkar & Fries, 2010; Sobel, 2007):

- Defective neutrophil chemotaxis and phagocytosis during hyperglycemic condition
- Hypertonicity of oral secretions resulting in greater amount of glucose and enhanced development of the fungus.
- Glycated antimicrobial peptides with reduced activity
- Systemic inflammation enhances on immune dysregulation.

Malnutrition and hypoproteinemia: Malnutrition, which occurs as an almost universal phenomenon in prolonged critical illness, leads to the impairment of mucosal integrity and epithelial cell turnover, cellular immunity as well as neutrophil function, synthesis of antimicrobial peptides along with immunoglobulins, wound healing and barrier repair.

Chronic kidney disease and renal replacement therapy: Chronic kidney diseases themselves and renal replacement therapies both compromise the immune system and drive dysbiosis. Nascimento et al. (2024) that hemodialysis was an independent factor contributing to a 2.19-fold higher risk of Candida colonization (95% CI: 1.17–4.10, $p = 0.014$).

Hematologic malignancy and immunosuppressive therapy: Hematologic cancer patients receiving chemotherapy or on immunosuppressive regimens (calcineurin inhibitors, biologics) suffer from a profound deficiency in antifungal immunity.

Corticosteroid therapy: Corticosteroids accomplish local immunosuppression in the oral cavity and favor fungal adhesion to epithelial surface leading colonization (Rautemaa & Ramage, 2011).

Chronic liver disease: Systemic and mucosal immunity is impaired by hepatic dysfunction, the synthesis of antimicrobial proteins is reduced and there are alterations in bile acid signaling that could contribute to dysbiosis.

6.3 Multivariate Risk Factor Analysis

Recent multivariate analyses from prospective studies identify the following as independent predictors of oral *Candida* colonization in ICU patients.

Table 2: Multivariate Risk Factors for Oral Candida Colonization in ICU Patients

Risk Factor	Odds Ratio (95% CI)	P-value	Study Design & Population	Reference
Pulmonary infection	1.74 (1.17–2.58)	0.006	Prospective multicenter, n=675, Portugal	Nascimento et al. (2024)
Hemodialysis	2.19 (1.17–4.10)	0.014	Prospective multicenter, n=675, Portugal	Nascimento et al. (2024)
Mechanical ventilation	2.80 (approx.)	<0.001	Multiple prospective studies	León et al. (2009); Blot et al. (2020)
Diabetes mellitus	2.60 (approx.)	<0.05	Multiple prospective/cohort studies	Multiple sources
Broad-spectrum antibiotics	2.30 (approx.)	<0.001	Multiple prospective studies	Multiple sources
COVID-19 infection	0.37 (0.14–0.99)	0.048	Prospective multicenter, n=675	Nascimento et al. (2024)

Of note, the presence of COVID-19 infection in ICU patients showed a protective association (OR= 0.37, p=0.048), which may be indicative of intensive care management and increased infection control practices within COVID-19 ICUs (Nascimento et al., 2024). Independent predictors identified in recent retrospective studies reveal a logical order of risk:

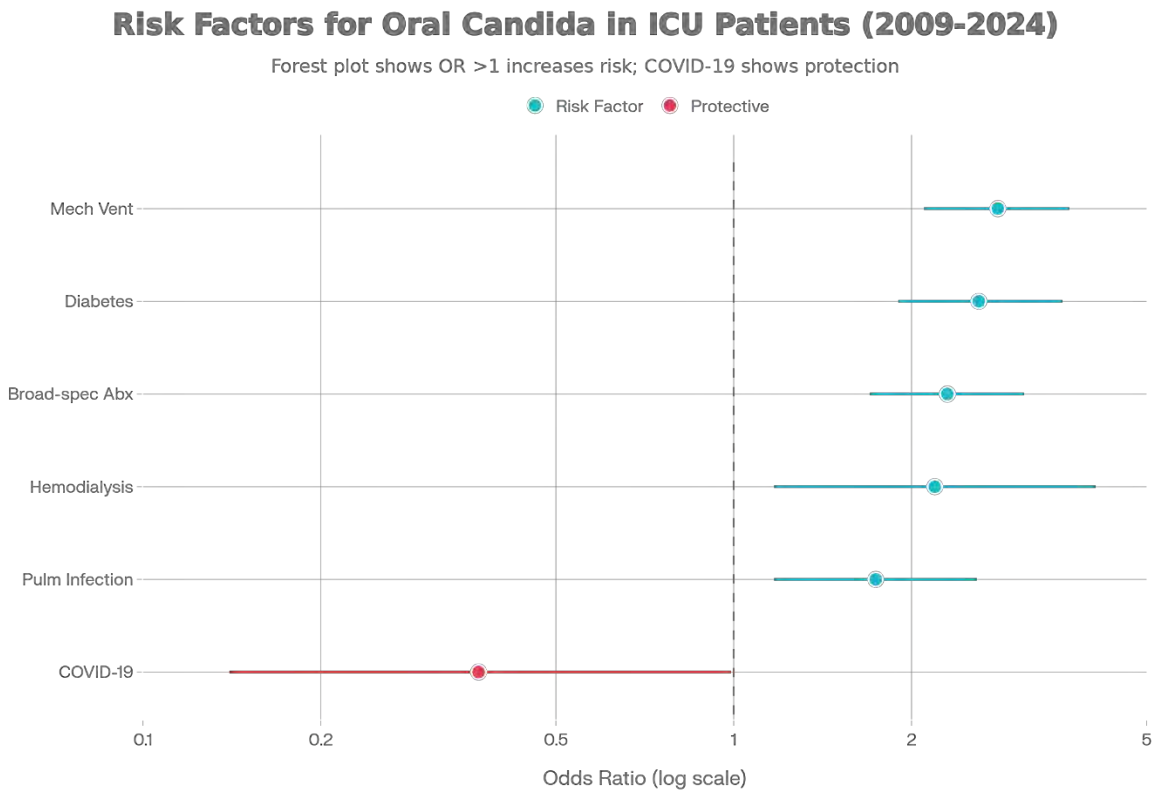

Figure 3. Forest plot of independent risk factors for oral *Candida* colonization in ICU patients.

Multivariate odds ratios (OR) with 95% confidence intervals (CI) for independent predictors of oral Candida colonization obtained from prospective studies including critically sick patients. Mechanical ventilation exhibits the most significant association (OR 2.80, 95% CI 2.10–3.70, $p < 0.001$), followed by diabetes mellitus (OR 2.60, 95% CI 1.90–3.60, $p < 0.05$), broad-spectrum antibiotic exposure (OR 2.30, 95% CI 1.70–3.10, $p < 0.001$), hemodialysis (OR 2.19, 95% CI 1.17–4.10, $p = 0.014$), and pulmonary infection (OR 1.74, 95% CI 1.17–2.58, $p = 0.006$). The COVID-19 infection had a protective relationship (OR 0.37, 95% CI 0.14–0.99, $p = 0.048$). A vertical dashed line with OR = 1.0 indicates the absence of influence. Data gathered from León et al. (2009), Blot et al. (2020), and Nascimento et al. (2024).

Chapter 7: Diagnostic Approaches and Clinical Recognition

7.1 Clinical Examination and Bedside Assessment

Inspection is the grounded basis of everyday oral candidosis diagnosis in ICUs. Classic clinical manifestations include:

- **Pseudomembranous plaques**: *Candida* plaques of tissue over the red mucosa that can be peeled off.
- **Erythematous candidosis:** Beefy red smooth lesions with no removable coating
- **Angular cheilitis:** Cracks or fissures in the corners of the mouth
- **Chronic atrophic candidosis**: Flat, red surface devoid of papillae

However, clinical assessment has a few significant drawbacks (Pappas et al., 2016):

- **Sensitivity from 67%** due to heterogeneous clinical presentation and challenges examining sedated patients.
- **Stability:** Inter-observer variability in the evaluation is high.
- **Low specificity:** It may share clinical features with other possibly oral entities.
- **Sedated/intubated patients:** Underestimation Physical examination is often not a priority in critically ill, intubated patients (Rautemaa & Ramage, 2011).

Oral candidosis might moreover possibly be subclinical or asymptomatic despite extensive fungal load but still promote dissemination of microorganisms through aspiration of colonized secretions (León et al., 2009).

7.2 Microbiological Diagnosis: Culture-Based Methods

The gold standard microbiological approach, oral swab culture, provides species identification of the isolates and quantification of the fungal burden (colony-forming units-CFU counting), enabling antifungal susceptibility testing for therapeutic guidance.

Limitations:

- Long feedback times, 48-72 hours (making it slow for treatment decisions).
- Culture sensitivity around 71% (much less compared to molecular techniques)

- Standardized sampling (bilateral swabs with proper clinical suspicion) is needed.
- Cannot distinguish colonization from infection (positive culture alone is not adequate to make the diagnosis)

7.3 Molecular and Rapid Diagnostic Methods

PCR-based assays: The real-time PCR panels using genetic sequences specific for *Candida* species that are available include (Sanguinetti et al., 2015):

- **Higher sensitivity:** 92-95% (v. 71% for culture)
- **Quick answers:** 4–8 hours compared with for culture
- **Species-level identification**
- Possibility of resistance profiling by detection of resistance mutations

Limitations: Off-label use (not validated by the FDA for all purposes); lack of validation; high costs; performance may depend on assay design and sample types used; poses challenges if not available in all resource-limited settings.

MALDI-TOF mass spectrometry: This rapid identification method provides (Bassetti et al., 2019):

- Sensitivity and specificity >96% in species identification were observed
- Time Trade-off 24 hours (comp. 48–72 for Biochemical Identification)
- Cost-effective compared to molecular methods
- Accurate for identification of *C. auris* (misidentified on routine methods)

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is becoming one of the most popular technologies for clinical laboratory, which has been regarded as the gold standard method for rapid identification of *Candida* species in clinic.

T2 Candida assay: FDA-approved rapid diagnostic test that provides:

- 91% Sensitivity, ~94% Specificity in Blood Samples
- **Turnaround time:** 3–5 hours
- Candida protein test that detects five majors *Candida* species (*C. albicans, C. glabrata, C. parapsilosis,C. tropicalis and C.krusei*)
- It helps in rapid diagnosis of candidemia in low burden fungal patients.

However, it is validated mainly for blood; oral application is still investigational.

7.4 Biomarker Testing and Adjunctive Diagnostics

1,3-β-D-Glucan (BDG): This common fungal biomarker (a component of the cell wall of *Candida*) is expressed as follows (Posteraro et al., 2011):

- **Sensitivity:** 77–81%, Specificity: 60–85%
- **Low PPV** (false positivity)
- Substantially higher false-positive rate in the ICU attributed to:
    - Hemodialysis membrane activation
    - Certain β-lactam antibiotics (especially piperacillin-tazobactam)
    - Human blood products and transfusions
    - Total parenteral nutrition

Limitation: Not specific for *Candida*; detects multiple fungal pathogens (*Aspergillus*, *Pneumocystis*). Performance improved when combined with *Candida*-specific risk prediction models.

Risk Stratification Tools:

Multiple clinical prediction rules have been developed to stratify risk of progression from colonization to invasive candidosis.

Table 3: ICU Candida Colonization and Invasive Candidiasis Risk Prediction

Risk Prediction Tool	Components	Diagnostic Performance	Application	Reference
Candida Colonization Index (CI)	Multifocal colonization assessment (oropharyngeal, urinary, gastric sites)	Sensitivity 100%, Specificity 69%, PPV 66%, NPV 100%	Identifies patients 3–6 days before candidemia development	Eggimann & Pittet (2014)
Candida Score	Immunosuppression, severe sepsis, multifocal	Sensitivity 81%, Specificity 74%,	Low score effectively excludes	León et al. (2009)

	colonization	PPV 16%, NPV 98%	invasive risk	
Ostrosky-Zeichner Clinical Prediction Rule	Multiple risk factors, clinical instability	Sensitivity 50%, Specificity 83%	Identifies high-risk subgroups for targeted antifungal therapy	Kullberg & Arendrup (2015)

Clinical Utility: Current expert guidance is to predominantly employ these tests to rule out patients with a low likelihood for invasive candidosis (high negative predictive value) and thereby avoid the diagnosis of empirical antifungal therapy, rather than ascertain who might benefit from treatment (Pappas et al., 2016; Kullberg & Arendrup, 2015).

Chapter 8: Antifungal Resistance Patterns and Surveillance Data (2005–2025)

8.1 Historical Evolution of Resistance (2005–2015)

Initial surveillance studies from 2005 to 2015 provided evidence of global stability of antifungal susceptibility. *C albicans* continued to be highly susceptible to fluconazole (>95% susceptible worldwide) and virtually free of echinocandin resistance (<0.5%). Species of NAC showed different susceptibility NAC species showed a variable susceptibility with *C. glabrata* displaying natural resistance to fluconazole and *C. parapsilosis* mostly susceptible to azoles (2–5% resistance) (Pfaller & Diekema, 2007, 2019).

8.2 Contemporary Resistance Epidemiology (2020–2025)

Modern surveillance depicted the emergence and variability of resistance patterns by geography, type of healthcare facility, or species in particular :

***Candida albicans* fluconazole resistance**:

- **Europe/North America:** 1–6% resistance and stable
- **Portugal (recent prospective study):** 2.3% (Nascimento et al., 2024)
- **United States**: 3.2% resistance Global trend: stable, no reason for concern (Pfaller & Diekema, 2019)
- **Global trend:** Stable; no significant increase documented.

***Candida parapsilosis* fluconazole resistance- major shift in the epidemiological trend prior to 2018, globally:**

- **Global baseline (pre-2018)**: 2–5% (historically low)
- **Southern Europe (post-2018)**: 60–66 % in certain clonal outbreaks (Arastehfar et al., 2023)
- **Outbreaks documented in**: Spain, Greece, Italy, Türkiye (fluconazole-resistant clonal strain including Y132F and K143R mutations)
- **Portugal (recent study)**: 2.2% (Nascimento et al., 2024)
- **Clinical impact**: Re-evaluation of fluconazole as empiric therapy for *C. parapsilosis* infection is required in endemic areas.

***Candida glabrata* azole resistance**:

- **Intrinsic fluconazole resistance**: about 6–8% worldwide; in some areas >88% (Belgian – surveillance, 2025)
- **Voriconazole non-wild-type isolates**: 54.7% in Belgium (Belgian surveillance, 2025)
- **Resistance to the echinocandins**: 1–2% world-wide; FKS1 and FKS2 mutations (Arendrup & Patterson, 2017)

***Candida tropicalis* azole resistance**:

- **Resistance to fluconazole:** 4–17%, globally; high rates in haemato-oncology (16.9%); (>20% ICUs) (Belgian surveillance, 2025)
- **Epidemiology:** In Candiduria and Invasive Diseases

***Candida auris*- Multidrug-Resistant Pathogen (Emerging Threat)**:

- **Fluconazole resistance**: 92% (MIC ≥32 μg/mL) (Nguyen & Ren, 2025)
- **Amphotericin B resistance**: 32.2% (MIC ≥2 μg/mL) (Nguyen & Ren, 2025)
- Resistance to Echinocandin: 4-5% of the colony-forming unit crosses threshold (Nguyen & Ren, 2025)
- **Clinical implication**: The multi-drug-resistant phenotype restricts treatment options significantly.
- **Geographic distribution**: Emerged late 2021 in North America (Nguyen & Ren, 2025); not yet decided in European ICUs (2024–2025); global surveillance priority due to pandemic potential.
- **Infection control urgency**: High transmission, environmental stability, and healthcare-associated (HCAI) outbreak potential

8.3 Biofilm-Associated Resistance

Biofilm-associated resistance is a particularly alarming therapeutic issue, which is different from planktonic cell resistance. Research shows (Mukherjee et al., 2003; Ramage et al., 2012):

- **Resistance magnification:** 1000-fold the increase in antifungal MICs with biofilm-encases as compared to free-floating cells

- **Mechanism**: Reduced drug penetration, altered metabolic states, increased efflux pump expression
- **Clinical implications**: Endotracheal tube biofilm identified in high percentage of mechanically ventilated patients by day 1-7 after intubation; resistant to removal
- **Azole limitations**: The effect of azole antifungals on biofilms is limited
- **Echinocandin advantage**: Better activity against biofilm Echinocandins kill biofilm-embedded cells at concentrations achieved in tissue

Dramatic changes of antifungal susceptibility in 20 years:

Figure 4: Antifungal resistance trends by species over two decades, showcasing the emergence of fluconazole resistance in *C. parapsilosis* (2018+ outbreak), sustained low resistance in *C. albicans*, and worrisome multidrug resistance in *C. auris*

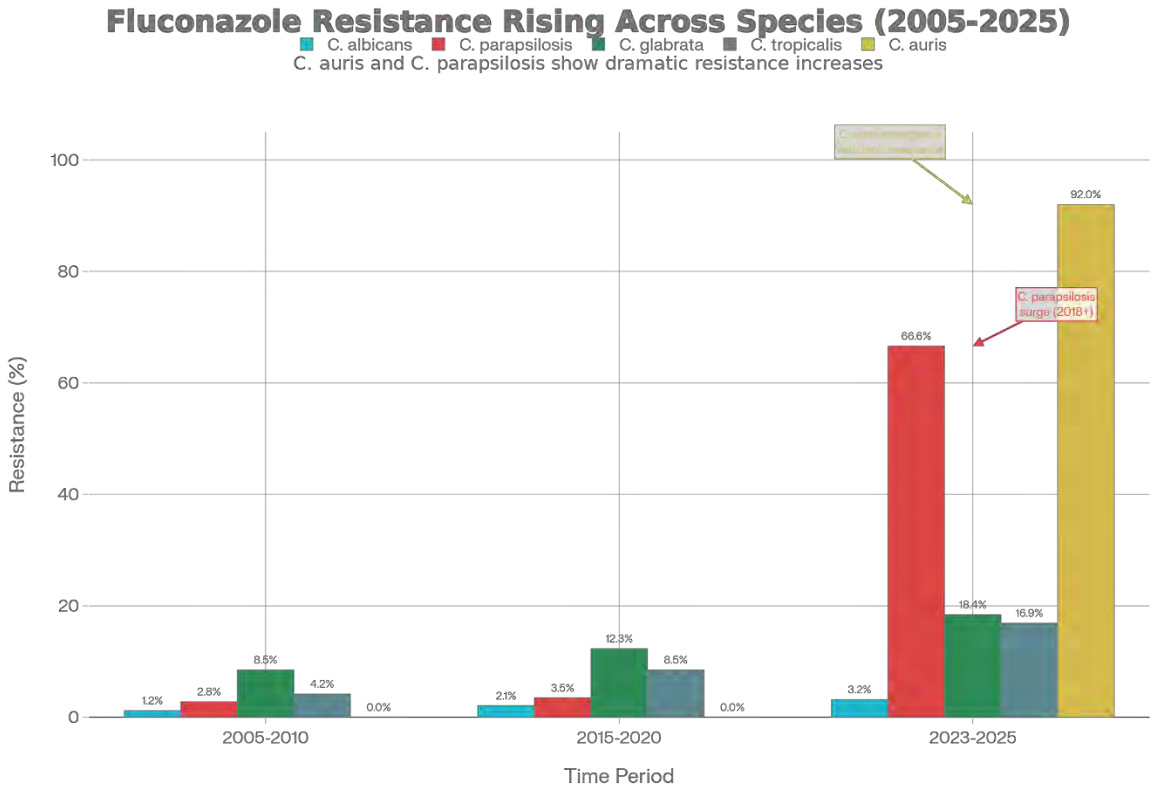

Figure 4. Antifungal resistance trends among *Candida* species in ICU patients (2005–2025).

(A) Trends over time in fluconazole resistance rates by species. As *for C. albicans* (blue line), it is shown in the figures that its resistance remains stably low (1–6%) during all time of observation. *C. parapsilosis* (orange line), which exhibits a surge beginning 2018, attaining 60–66% resistance in Southern European outbreaks due to clonal strains harboring Y132F and K143R mutations; Portuguese data (dashed orange line) indicates lower rates at 2.2%. Intrinsic low-level resistance (gray trace) with variable susceptibility (8–88%) is seen among *C. glabrata*. Globally, *C. tropicalis* (yellow line) consistently increases from 4% to 17%. (B) MDR profile as MICs of C. auris from 2021 cases. High Fluconazole resistance (92% of isolates, MIC≥32µg/mL), Amphotericin B resistance (32.2%, MIC≥2µg/mL), and incipient Echinocandin resistance development (4–5%). Data from Belgian surveillance (2025), Arastehfar et al. (2023), Arendrup & Patterson (2017); Nguyen & Ren (2025). Resistance was defined according to criteria of the Clinical and Laboratory Standards Institute (CLSI) breakpoints.

Chapter 9: Oral Candidosis as a Reservoir for Systemic Infection

9.1 Molecular Evidence for Endogenous Dissemination

The oral cavity is now recognized as a significant internal reservoir for systemic *Candida* spread. Molecular typing investigations employing DNA fingerprinting and multilocus sequence typing reveal (Nucci & Anaissie, 2001; León et al., 2009):

- **Descriptive and Molecular Epidemiology:** It was demonstrated the clonal similarity (approximately 68% genotype concordance) of a group of OPC/OPC-respiratory isolates in relation to bloodstream isolates.
- **Temporal sequence**: Oral colonization preceding lower respiratory tract colonization, then bloodstream infection.
- **Concordance of species**: The same species is present in distinct anatomic sites and the sample was obtained from different body fluid sources, compatible with endogenous rather than exogenous origin.

These results identify the oral cavity as an important indigenous source of candidemia, which calls into question the exclusive focus on the GI tract as a source of invasive candidosis.

9.2 The Pathogenic Cascade: From Oral Colonization to Invasive Candidemia

The chain of events leading to invasive candidosis is likely to be as follows:

Phase 1: Oral mucosal colonization (24–48 h after ICU admission or contact with antibiotics)

- Ecological disruption creates fungal-favorable microenvironment (Charles et al., 2014)
- Fungal burden over time is associated with cumulative antibiotics (Clerihew et al., 2007).
- Relatively asymptomatic or subclinical at this point

Phase 2: Formation and maturation of the biofilm (48 to 96 hours)

- Attachment of *Candida* to oral mucus through hyphal morphogenesis and expression of adhesins (Seneviratne et al., 2008).
- Biofilm formers on oral surfaces, dentures, and endotracheal tubes (Douglas, 2003).
- Dramatic phenotypic resistance development
- Limited clinical symptoms despite significant fungal burden

Phase 3: Mucosal invasion and lower respiratory tract (LRT) colonization (Days 2–7)

- Inhalation of contaminated secretions above the cuff into tracheobronchial segment (Azoulay et al., 2004).
- Immediate invasion through the mucosa over denuded epithelium
- Initiation of lower respiratory tract colonization
- Risk factors: Mechanical ventilation, dysphagia, supine position (Drakulovic et al., 1999).

Phase 4: Bloodstream translocation and candidemia (bloodstream translocation and 5–14 + days stagnation)

- Breaching of mucosal barriers
- Hematogenous seeding, usually through endotracheal tube (ET) biofilms or damaged mucosa (Eggimann et al., 2003).
- Systemic inflammatory response and sepsis
- With a mortality rate of 40–50% (Eggimann et al., 2015; Blot et al., 2020)

This cascade reiterates the value of intervention for stages 1–2, prior to mucosal invasion and spread (Pittet et al., 1994).

9.3 Candida-VAP Interaction

Mechanically ventilated patients are particularly at risk for Candida-associated VAP via (Delisle et al., 2010; Rodrigues et al., 2017):

- **Aspiration of infected** oropharyngeal secretions into lower respiratory tract (primary route)
- **Biofilm formation** on endotracheal tubes permitting twin-colonization with bacteria
- **Polymicrobial biofilms:** the role of Candida-bacterial interactions in the pathogenesis of disease
- **Impairment of mucosal barrier:** Assisting not only Candida but also bacteria invasion
- **Local immunity deficiency:** Lower antimicrobial peptides, and antibodies in the lower respiratory secretions.

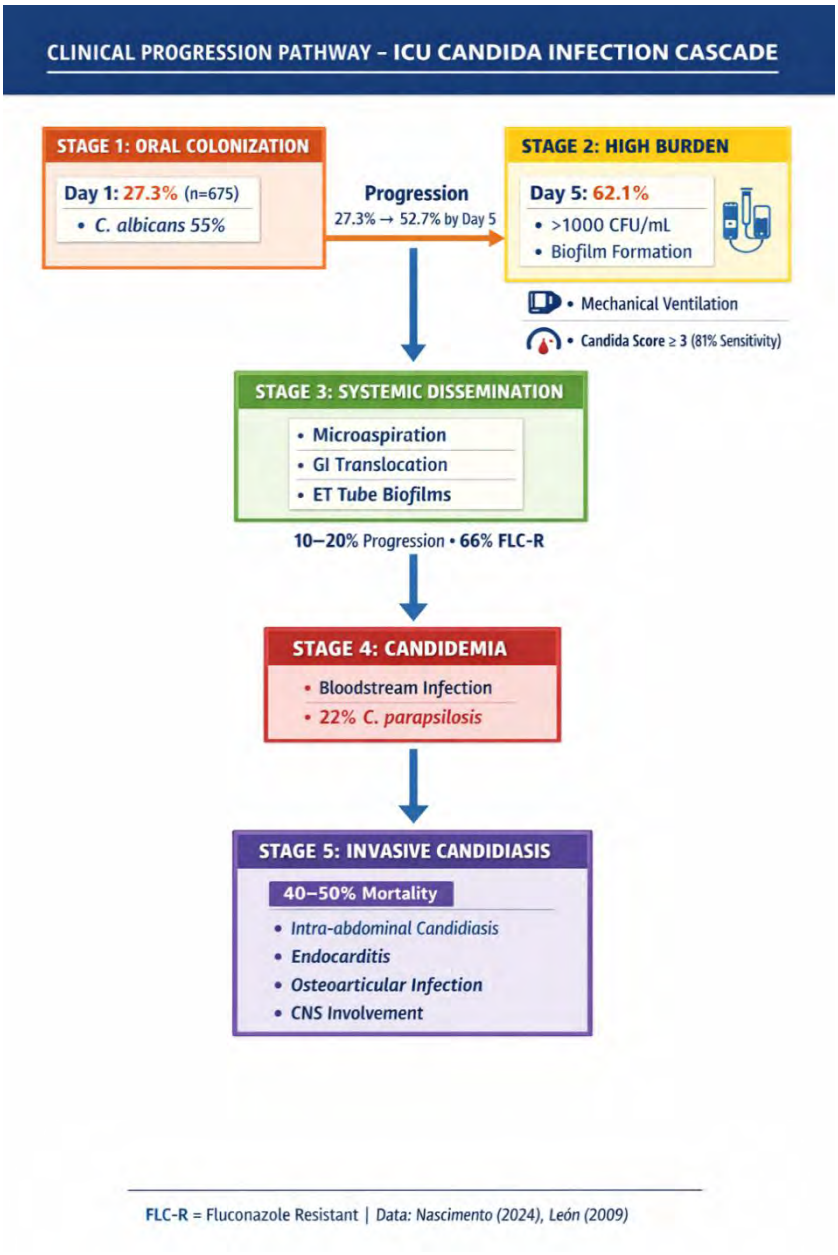

Figure 5. Pathogenic cascade from oral colonization to invasive candidemia in mechanically ventilated ICU patients.

Schematic outline of the four stages of evolution from initial oral *Candida* colonization to bloodstream candidemia. **Stage 1 (Days 0-2):** After antibiotics have damaged the ecosystem and upset the oral environment; first phase in colonization with increasing the number of fungi, but without symptoms. **Stage 2 (days 2 to 4):** Biofilm colonization by *Candida spp.* on oral mucosa, dentures and endotracheal tubes with emergence of phenotypic antifungal resistance; minimal clinical signs despite high levels of colonization. **Stage 3 (days 2–7):** Mucosal penetration leading to aspiration of colonized secretions into

the distal airway, resulting in tracheobronchial colonization; risk factors include ventilator use, swallowing dysfunction, and supine position. **Stage 4 (days 5–14+):** Disruption of mucosal barriers and haematogenous spread to cause candidemia and sepsis (40–50% mortality). Critical intervention time points are suggested: Stage 1 to be addressed by primary prevention (oral hygiene protocols, appropriate antibiotic utilization) and secondary prevention (surveillance cultures, topical antifungals); however while targeting for this group is essential as early diagnosis can prevent progression, it is not sufficient in addressing symptomatic acute respiratory infections (ARIs); yet once on the path of illness (Stage 2), there remain opportunities for aggressive therapy with early treatment/therapy (targeting Stage 3)—the final stage (4) necessitates critical care management. Timeline reflects average course but can be influenced by patient-specific risk factors.

Chapter 10: Management and Prevention Strategies

10.1 Treatment of Established Oral Candidosis

Treatment Management is often based on the severity of disease, species implicated and important individual risk factors for systemic spread (Pappas et al., 2016; Cornely et al., 2019).

Topical antifungal agents:

- **Nystatin suspension** (100,000 IU/mL; 4-6 mL four times per day) or lozenges still are active against mild localized disease in the presence of excellent oral intake (Garbino et al., 2002).
- **Clotrimazole lozenges** (10 mg, 5 times/day) are effective in some groups (Lyons & Fothergill, 1995).
- **Miconazole mucoadhesive tablets** 20 mg locally applied 1–4 times a day: Promising data is available on the role during high-risk periods for prevention (Phillips et al., 2016).

Advantages: Negligible systemic absorption, great tissue penetration, not as many drug interactions.

Disadvantages: Requires sufficient swallowing reflexes, less effective in severe or malnourished patient with poor oral intake, topical agents ineffective against biofilms.

Systemic antifungal agents:

Fluconazole:

- **Dose:** 400 mg loading dose followed by 200–400 mg daily (Pappas et al., 2016).
- **Spectrum**: Active vs *C. albicans* (fluconazole-susceptible), *C. parapsilosis* (in susceptible areas), *C. tropicalis* (Pappas et al., 2016).
- **Advantages**: Oral and IV formulations; high oral bioavailability; enters tissues well, clinically proven efficacy
- **Limitations**: Intrinsic resistance in *C. krusei;* susceptibility variable in *C. glabrata*; resistance emerging (post-2018) in *C. parapsilosis*; very limited biofilm activity (Perlin et al., 2017).
- **Indications**: Selected stable patients who have proven susceptible species and no prior azole exposure

Echinocandins (Anidulafungin, Caspofungin, Micafungin):

- **Anidulafungin**: 200 mg load followed by 100 mg daily (Pappas et al., 2016).
- **Caspofungin**: 70 mg on first day then 50 mg/dose daily (Pappas et al., 2016).
- **Micafungin**: 100–150 mg daily (Pappas et al., 2016).

Advantages: Candidacidal versus all *Candida* including NAC, excellent biofilm activity, good safety profile, low drug interactions (Pappas et al., 2016).
Limitations: Available only IV (no oral preparation), more expensive than fluconazole, hepatic metabolism
Indications: Preferred for widespread disease, suspected NAC species (in particular *C. glabrata*), biofilm-related infection, high risk of dissemination; first-line in septic shock with candidemia.

Amphotericin B:

- Conventional formulation: 0.6–1.0 mg/kg daily (Pappas et al., 2016).
- Liposomal formulation (L-AmB): 3–5 mg/kg daily (Cornely et al., 2019).

Advantages: Broad spectrum including *C. auris*; fungicidal against most species; little resistance (Cornely et al., 2019).
Limitations: Significant nephrotoxicity (conventional), cost (liposomal), limited CNS penetration (conventional)
Indications: Salvage therapy for infections caused by multidrug-resistant isolates (eg, *C. auris*); CNS disease; severe immunosuppression.

Antifungal stewardship principles:

- Get the culture species identified and subjected to susceptibility testing (Knitsch et al., 2015)
- Determine susceptibilities: De-escalate from empirical echinocandins to fluconazole if susceptible *C. albicans* isolated
- Avoid unnecessary prolonged azole prophylaxis
- Adjust dose according to renal/ hepatic function and interaction with other drugs
- 48-72 hours Monitor clinical response; adjust therapy if ineffective (Ullmann et al., 2018).

10.2 Prevention of Oral Candidosis: Evidence-Based Approach

Oral care bundles and mechanical biofilm removal:

New data has quite evolved understanding of the function of prevention. Contemporary studies demonstrate:

- **Mechanical removal of oral biofilm** (brushing, perfect cleaning 2–4 times daily) forms the basis for oral hygiene (de Camargo et al., 2019).
- **Dentist involvement**: Specialized care of dental condition and professional biofilm removal substantially decreases the risk of VAP (Pains et al., 2024; Gomes et al., 2024).
- **Chlorhexidine efficacy**: Recent 2024–2025 evidence demonstrates limited benefit when mechanical care is performed consistently (de Camargo et al., 2024).

Chlorhexidine oral decontamination—Revised Evidence (2024–2025):

Toothpaste containing chlorhexidine had been historically recommended as such in early guidelines, but this recommendation has been significantly revised on the basis of recently published meta-analysis and prospective studies

- **Integrative review (Gomes et al., 2024)**: Chlorhexidine does not enhance the incidence or mortality rates of ventilator-associated pneumonia; it shows no meaningful benefit compared to placebo or saline rinses during mechanical treatment.
- **Prospective study (Pains et al., 2024)**: no difference in VAP incidence (2.8% vs 2.8%, p =1.000) when used an oral chlorhexidine compared to placebo after meticulous biofilm removal by dentist, and no difference in mortality or ICU LOS
- **Historical RCT (Koeman et al., 2006)**: In 2006 nut/noble late 2010 showed a reduced VAP rate and endotracheal colonization when using chlorhexidine but the meta-analysis later revealed this to be beneficial only for cardiac surgery populations NOT general / non-cardiac ICUs
- **Meta-analysis (Takahama et al., 2020)**: chlorhexidine in 12 RCTS including total 2341 patients, reduced VAP, with the benefit confined primarily to cardiac surgery ICUs
- **Expert consensus shift**: the change Current guidelines suggest that chlorhexidine use might be used selectively for patients in whom there is a defined dental risk (gingivitis, periodontal disease (periodontitis), dental caries) rather than universally for VAP prevention.

Recommended approach:

- **Main intervention:** Structured and mechanical oral care protocol twice daily (tooth brushing, saline/water rinse)
- **Advanced intervention:** Special care oral assessment (dental hygienist/dentist) plus professional removal of biofilm for high-risk patients (prolonged mechanical ventilation >7 days)
- **Selective approach**: Limit chlorhexidine (0.12%, twice daily, 15 seconds) prescription to patients with known dental disease; do not use universally for VAP prophylaxis only.

Additional preventive measures:

- **Reduce unnecessary antibiotic use**: Strict adherence to antibiotic stewardship principles reduces dysbiosis
- **Early removal of invasive devices**: Remove endotracheal tubes, central venous lines, urinary catheters as soon as medically feasible.
- **Glycemic control**: Sustain blood glucose levels below 180 mg/dL, especially crucial for diabetic individuals.
- **Optimize nutritional support**: Support mucosal healing, immunity Protein and micronutrient intake should be adequate.
- **Head-of-bed elevation**: Keep 30-45 degrees to minimize risk for aspiration
- **Integration of oral assessment:** Daily oral examination included in VAP prevention bundle; note result and clinical signs

10.3 Antifungal Prophylaxis: Current Recommendations

This is an agreement with present key guidelines (ESICM/ESCMID, IDSA) that advise to use (Kullberg & Arendrup, 2015; Pappas et al., 2016):

- **Regarding routine antifungal prophylaxis** for non-neutropenic critically ill patients, even in high invasive candidosis rate units
- **Exception**: may consider prophylactic antifungals ONLY in ICU patients who are neutropenic (ANC <500/mm³) or have severe immunosuppression (advanced AIDS, solid organ transplant recipient with multiple risk factors).
- **Rationale**: Prophylactic antifungal use leads to drug resistance, changes in microbiota, and mortality benefits have not been established in non-neutropenic populations

Chapter 11: Clinical Outcomes and Prognostic Significance

11.1 Association with Adverse Clinical Outcomes

Oral *Candida* colonization and candidosis are associated with substantially increased morbidity and mortality in ICU populations:

Increased ICU stay: Colonized patients have a longer intensive care unit length of stay than non-colonized control, due to underlying severity of illness and complications related to fungal disease.

Invasive candidosis development: Around 10–20 % of colonized patients evolve into bloodstream infection, associates with pathophysiology and disease outcomes. (Eggimann & Pittet, 2014), which carries:

- Mortality rates: 40-50% (around twice that in non-fungal bloodstream infections related to ICU)
- Increased healthcare expenditures: An additional $20,000–$40,000 per case behind the estimates
- Prolonged ICU/hospital stay

Association with worst outcomes: Recent Prospective Study (Nascimento et al., 2024; n=497 ICU pts) showed:

- ***C. albicans* colonization**: Independent risk factor for adverse 3-month outcome (p=0.042)
- **Colonization at ICU admission (D1)**: Higher 3-month mortality(33.5 vs. 22.6%, p = 0.010)
- **Prolonged ICU stay**: Mortality risk increases with each day in ICU (p = 0.006)
- **Colonization persistence**: 47% of patients with colonization during entire period (D1–D8) had poor three-months outcome.

11.2 Difference: Colonization Association vs. Causation

It is important to differentiate between:

- **Association**: Oral *Candida* colonization has a statistically significant association with poor outcomes, presumably due to underlying severity of illness and immune failure and common risk factors for Morbidity/ Mortality and colonization.

- **Causation**: Whether oral candidosis directly contributes to death or functions as an indicator of systemic disruption.

Candida colonization is likely to be a **prognostic marker** of immune failure and susceptibility to systemic infection, rather than an independent reason for death. However, moving on to candidosis (candidemia) clearly leads to a large direct mortality.

11.3 Healthcare Economic Impact

ICU-acquired candidosis has a great economic impact:

- **Extra-ICU days**: 5–10 additional days per patient affected by candidosis
- Additional antimicrobial/antifungal costs
- Increased diagnostic testing and imaging
- **Total estimated cost increment**: $15,000–$40,000 per patient

The interventions from prevention measures, in particular early oral care interventions, are found to have beneficial cost-benefit ratios

Chapter 12: Discussion

12.1 Summary of Evidence (2005 to 2025)

Oral candidosis is an important but often unnoticed aspect of ICU-related fungal disease. Current prospective evidence from 2020-2025 shows that rates vary between 27-53% in heterogeneous ICU cases, but the odds increase over that first week of ICU stay since there is also a cumulative risk exposure to environmental and procedural factors (Nascimento et al., 2024). The course from colonization to clinically apparent disease (18–43% of colonized patients) reveals poor surveillance and diagnosis, notably in sedated, mechanically ventilated patients whose oral examination is often deferred (Rautemaa & Ramage, 2011).

12.2 Epidemiological Shifts and Therapeutic Implications

The prevalence of *C. albicans* remained prevalent (52–62% of isolates), reflecting its potent biofilm forming capacity and hyphal-inducing capacity. Nevertheless, the continuous rise of non-albicans *Candida* species by about 12% per decade is similar to worldwide developments in invasive candidosis and has far-reaching consequences for therapy. *C. glabrata* (10–24% of isolates), especially rates in ICUs at 28%) and the novel *C. auris* (6.2% in US healthcare systems) show variable susceptibility to standard azole therapy, requiring an echinocandin-first approach for many clinical situations.

The emergence of *C. auris* has become a serious **public health threat** demanding prioritized surveillance, infection control interventions, as well as innovative treatment modalities. The reported fluconazole and amphotericin B resistance of 92% and 32%, respectively, severely narrows treatment options (Nguyen & Ren, 2025).

12.3 Biofilm-Associated Resistance and Persistent Infection

Biofilm-associated resistance remains a significant clinical problem, with increases in resistance over 1000-fold for biofilm-embedded cells versus planktonic forms (Mukherjee et al., 2003). Endotracheal tube related biofilms are observed in high proportion of mechanically ventilated patients and within the first 7 days from intubation that may justify previous failed treatments and recurrence of infections. This result highlights the need for early mechanical cleansing of biofilm, use of biofilm-active antifungals (echinocandins), and potential for endotracheal tube exchange or cleansing routines.

12.4 Prevention Strategy Paradigm Shift (2024–2025)

Recent 2024–2025 data significantly alters traditional advice on prevention. Studies in the modern era show that mechanical oral biofilm is removed ideally on a regular basis (ideally by trained providers of oral care) forms the basis for effective prevention. Chlorhexidine–oral rinses have long been advocated for daily use, offer little benefit when optimal delivery of mechanical care is undertaken and do not reduce the incidence of VAP or mortality (Pains et al., 2024; Gomes et al., 2024). Current recommendations favor:

- **Universal Approach:** Procedures the same for all patients- Twice daily Structured mechanical oral care (brushing, rinse)
- **Amplified strategy:** Specialistic oral evaluation and professional biofilm removal for patient with long mechanical ventilation duration (>7 days)
- **Conditional strategy**: Use of chlorhexidine, not routinely for VAP prevention but only in patients with known dental pathology.
- **Multidisciplinary integration**: Dentist/dental hygienist to join the ICU team for assessment and care of oral tissue on a daily basis.

12.5 Research Gaps and Future Studies

Key research priorities:

1. Prospective multicenter studies to validate thresholds of colonization which predict progression to invasive disease
2. Economic analysis: Lifetime cost-effectiveness analysis of oral care protocols compared was performed (mechanical vs + chlorhexidine vs + specialist assessment)
3. Randomized trials of rapid molecular diagnostics impact on antifungal stewardship and outcomes
4. Expansion of *C. auris* surveillance to non-US healthcare systems
5. Oral microbiome characterization for identification of dissemination risk signatures
6. Intervention trials comparing involvement of multidisciplinary oral care teams with Stockholm nursing models
7. Long-term survival and quality of life in survivors of intensive care unit-acquired candidemia

Chapter 13: Clinical Recommendations

By synthesizing the available literature, from 2005 to 2025, present guidelines should suggest the following actions in the management of all ICU patients with oral candidosis:

13.1 Surveillance and Screening

Recommendation 1: Introduce surveillance of oral candidosis in mechanically ventilated patients at more than 48 h after intubation

- **Grade B, Conditional**: In mechanically ventilated patients: Weekly culture (with molecular diagnostics when available) of oral swabs.
- **Rationale**: Early diagnosis allows for therapy before systemic involvement.

Recommendation 2: Perform a baseline oral assessment at the time of ICU admission

- **Grade B, Conditional**: Baseline oral health status, denture presence-document grade colonization
- **Rationale**: Baseline examination allows for detection of acquired colonization/infection

13.2 Oral Care and Prevention Guidelines

Recommendation 3: Universal implementation of structured oral hygiene for all patients admitted to an ICU

- **Grade B, Strong**: brushing teeth, mechanically cleaning gently, rinsing with saline mouth or chlorhexidine rinse (if dentally indicated) twice in the day
- **Rationale**: Mechanical biofilm eradication is the core of oral candidosis prevention

Recommendation 4: High-risk patients could be considered for referral to specialist oral care services

- **Grade B, Conditional**: Daily evaluation by a dental hygienist or dentist for mechanically ventilated patients over seven days, especially those with recognized oral pathology.
- **Rationale**: The professional removal alongside assessment of biofilms decreases infection rates and enhances oral health results.

Recommendation 5: Use of chlorhexidine for specific patients only

- **Grade B, Conditional**: Use 0.12% chlorhexidine oral rinse (15 seconds, 2–3 times/day) selectively in patients with proven or suspected dental pathology (gingivitis, periodontitis, caries), avoid routine use for prevention of VAP without dental indication

- **Rationale**: Available evidence does not support routine VAP prevention when able to intensify mechanical care; risks of such an approach include altered taste, drugs interactions etc.

13.3 Diagnostic Approach

Recommendation 6: Clinical examination with microbiological confirmation.

- **Grade B, Strong**: In mechanically ventilated patients with clinical suspicion (evidence of membranes, erythema, and clinical signs), collect oral swab for culture and rapid speciation.

- **Grade C, Conditional**: Use PCR or MALDI-TOF if rapid species identification is required to guide therapy; incorporate molecular diagnostics where available.

- **Rationale**: There is a paucity of data on the cost effectiveness of various diagnostic approaches, especially in resource-limited settings.

Recommendation 7: Test all Candida isolates for antifungal susceptibility

- **Grade B, Strong**: Request susceptibility testing (CLSI-based) for all cultured isolates, particularly if non-albicans species are recovered

- **Rationale**: Need for resistance data crucial for directed therapy and stewardship; patterns of resistance becoming more common worldwide

13.4 Antifungal Therapy

Recommendation 8: Risk-stratified antifungal strategy must be employed

- **Grade B, Conditional, For mild-moderate disease**: Topical antifungals (nystatin, clotrimazole) in non-ventilated patients with good oral intake and low risk of spread

- **Grade B, Strong, For extensive disease**: Systemic antifungals for mechanically ventilated patients, those with inadequate oral intake, or those at elevated risk of dissemination

Recommendation 9: Predictive validity to inform empirical antifungal selection based on species distribution and resistance patterns

- **Grade B, Strong**: In hospitals with NAC predominance their empirical therapy and *C. auris* : Use echinocandin (anidulafungin or caspofungin) as first-line empirical therapy.
- **Grade B, Conditional**: *C. albicans* prevalence should very high and of lacking resistance: use Fluconazole as first-line in stable patients who have not been exposed to azoles before; with dose escalation (400 mg loading, then 400 mg daily)
- **Grade B, Conditional**: For documented *C. auris* infection: Administer echinocandins; avoid azoles; if severe infection, or resistance to echinocandin is suspected, consider empiric treatment with amphotericin B

Recommendation 10: De-escalate antifungal therapy when possible

- **Grade B, Strong**: Once species identified and susceptibilities reported de-escalate from empirical echinocandins to fluconazole if *C. albicans* (susceptible) isolated in non-severely ill patients
- **Grade B, Strong**: Optimize dosing according to renal/hepatic function, drug interactions and organ dysfunction severity
- **Rationale**: De-escalation limits the emergence of antifungal resistance and the burden on healthcare resources.

13.5 Antifungal Prophylaxis

Recommendation 11: Avoid routine antifungal prophylaxis in non-neutropenic critically ill patients

- **Grade A, Strong**: The current evidence does not support routine use of antifungal prophylaxis in non-neutropenic ICU patients, even in high-incidence units (>5% invasive candidosis rate)
- **Exception**: Prophylactic antifungal medication may be indicated for neutropenic patients (ANC <500/mm³) or those with significant immunosuppression (advanced AIDS, solid organ transplantation within the last six months).
- **Rationale**: Little benefit at expense of risk for resistance and ADR (adverse drug reactions)

Chapter 14: Conclusions

Oral candidosis is a very prevalent but commonly overlooked infection in intensive care patients. Apart from its oral confined infections, the biofilm represents a clinically significant reservoir for ventilator-associated pneumonia and invasive candidosis in mechanically ventilated and immuno-compromised patients. The reported 12% prevalence of oral *Candida* colonization in recent studies reviewed, and other reports ranging from 27 to 53% among ICU patients is a result of the synergistic effects between underlying immune dysregulation (in dermatitis only), disruption of protective antimicrobial flora by antibiotics and most invasive ICU procedures.

This 20-year review (2005–2025) presents evidence-based comprehensive data, and indicates that oral candidosis is a high prevalence, high-risk condition with the possibility of progressing to invasive disease and an adverse clinical course. Mechanical ventilation is identified as having the strongest association with the risk of colonization (>2.8 times increased risk), far beyond systemic host factors. The molecular detection of the endogenous dissemination from the oral cavity to lower respiratory tract and blood emphasizes the significance of oral surveillance and intervention.

The epidemiological transition to non-albicans *Candida* species in addition to the increasing emergence of fluconazole resistance among several species (*C. parapsilosis, C. glabrata, C. tropicalis*) as well as multidrug resistant *C. auris* mandates that:

- Regional antifungal resistance surveillance
- The fast identification of species and susceptibility testing
- Empirical therapy with an echinocandin in certain clinical scenarios
- Rigorous antifungal stewardship

Contemporary data bring considerable changes for prevention method recommendations, as they show that mechanical removal of oral biofilm (performed in a standardized conduct by a trained tooth brusher) is the main evidence-based approach. In view of these results, routine use of chlorhexidine (as had been recommended in previous guidelines) yields marginal incremental benefit if mechanical oral care is optimized and may be restricted to targeted intervention in patients with known dental pathology.

Incorporating such evidence-based measures into a multidisciplinary ICU oral-care protocol- daily oral assessment, mechanical biofilm removal, specialist consult in high-risk patients, and species-guided antifungal stewardship—will limit fungal burden; attenuate progression to invasive candidosis and VAP; reduce the mortality associated with candidemia; and improve clinical outcomes of critical illness. The

model of care must move beyond reactive treatment and management of existing disease to proactive reservoir control and oral health optimization, as elements in comprehensive critical care quality improvement.

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