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Review Article



Evaluation of virulence factors in *Stenotrophomonas maltophilia*: a systematic review

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Abstract

Stenotrophomonas maltophilia is a common microorganism that is linked to opportunistic illnesses. Growing prevalence and severity of sickness were seen in immunocompromised hosts, especially opportunistic bloodstream infections and pneumonia syndromes. The present research involved studies published from PubMed and Google Scholar databases resulting in 100 open-access articles. A systematic review and meta-analysis were performed to study virulence factors of *S. maltophilia* as well as genes that play a role in bacteria's resistance to antibiotics that contribute to increased bacterial pathogenicity. The result showed virulence factors of *S. maltophilia* include (fimbrial operon, extracellular enzymes), biofilm production, antibiotic-resistant gene having the main roles in bacteria pathogenicity. In conclusion: *S. maltophilia* have a significant death rate, and the risk factors for mortality depend on the early diagnostic state and patient population. Additionally, to reduce bacteria's resistance to antibiotics, appropriate treatments must be used to treat and control infection.

Keywords: *Stenotrophomonas maltophilia*, Virulence factors, Antibiotic resistance gene

Introduction

Stenotrophomonas maltophilia is a Gram-negative, non-fermenting organism. It is a motile, obligate aerobe that has flagella (Brooke, 2012). A nosocomial infection with significant mortality rates, it was essentially an environmental bacterium which has attracted a lot of interest (Flores-Trevino et al., 2019).

The property of multi-drug resistance enhances the complexity of controlling *S. maltophilia* infection (Gajdacs and Urban, 2019). Some virulence factors have been characterized in *S. maltophilia* include Smf1-fimbrial operon, proteases, hemolysins, Exopolysaccharides (EPSs), siderophores, flagella, lipases, and lipopolysaccharides (LPSs). A pathogenicity island contains putative virulence genes that produce RTX (repeats-in-toxin) family proteins and parts of the transmembrane secretion system (Trifonova and Strateva, 2019).

S. maltophilia infections can result in a number of infectious complications, including bacteremia, endocarditis, respiratory tract infections, meningitis, urinary tract infections, skin and soft tissue infections, mastoiditis, bone and joint infections, peritonitis, typhilitis and biliary sepsis, wound infections, and infections related to central venous catheters (CVCs) (Looney et al., 2009). The capacity of *S. maltophilia* to create biofilms on a variety of abiotic surfaces and host tissues is another noteworthy characteristic. High resistance to various antimicrobial treatments and antiseptic solutions was provided by this ability, which also undermines the host immune system (De Oliveira-Garcia et al., 2003; Brooke, 2012). The structural extensions of *S. maltophilia* strains called flagella help explain why hospital outbreaks appear to be occurring (Oliveira-Garcia et al., 2002).

S. maltophilia adheres to many epithelial cells and colonizes or invades them, including those in the urinary and respiratory

systems, injured skin, and wounds. The capability to adhere to plastic venous catheters and endure in intravenous solutions may contribute to the emergence of bloodline-related diseases (DeOliveira-Garcia et al., 2003). In the pathogenesis of bacteria, swimming is a crucial part of virulence. Conjugation is a useful method for the horizontal spread of antibiotic resistance. A natural barrier to the admission of foreign chemicals may be provided by the double membranes of Gram-negative bacteria (Ferrand et al., 2020).

The purpose of this systematic review and meta-analysis: Evaluate the virulence factors of *S. maltophilia* and study the genes, which have relationship with *S. maltophilia* pathogenesis.

Methods

Literature review was conducted using two online databases: Google Scholar and PubMed. "*Stenotrophomonas*" in combination with "virulence factors" or "resistance gene" and in association with "virulence" or "infection" or "pathogen" or "disease" or "mortality" were used to look for abstracts and full texts. This search began on June 19th, 2022, and was repeated until September 1st, 2022, to include more recent publications. Furthermore, all shortlisted studies' reference lists were searched for respective publications.

The database search yielded a total of 100 studies, which were then examined for respective content using the inclusion criteria listed below. Researches with original research and written in English were contemplated as potentially eligible for inclusion. When infected with bacteria, we described virulence as a decrease in host fitness, as measured by an increase in fatality or tissue impairment. We used a second collection of rules to screen on the experimental studies experiments to determine those that contained comparable quantitative data, which is required for a meta-analysis. Inclusion criteria were as follows: (i) virulence was evaluated directly and indirectly through genetic analysis; (ii) virulence was measured in vivo; (iii) virulence was quantified through the production of intracellular or extracellular enzymes; and (iv) virulence was measured according to the site of infection.

Inclusion Criteria

Antibacterial/antimicrobial research, virulence factors, biofilm formation, and genes involved in virulence factors

Exclusion Criteria

Literature reviews, systematic reviews, case studies, and editorials are all excluded. Nonclinical sources of bacteria were used in the studies.

Search strategy

The following search phrases were used to conduct an all-field search of the electronic bibliographic databases ScienceDirect

and PubMed/MEDLINE: Factors involved in virulence OR virulence AND factors OR virulence AND genes OR anti-infectives OR anti-infectives OR antimicrobial AND resistance OR resistance gene).

The search was conducted over 20 years, from 2002 to 2022. This time limit was set in response to potential changes in *S. maltophilia* virulence, microbiology, epidemiology, and antimicrobial susceptibility patterns. For each database searched, the number of records retrieved was recorded. To supplement the electronic search, reference lists from identified studies were manually checked.

Data Extraction

The following variables were recorded in each article reviewed: author, publication year, study groups, sample size, screening for virulence factors, genes involved in antibiotic resistance and virulence factors, conclusions, and study quality.

Results

There is growing concern about emerging *S. maltophilia* as opportunistic pathogens and their virulence factors with extended spectrum antibiotic resistance, so it is being extensively studied. The flow chart below shows how the studies are classified. The majority of the studies found that *S. maltophilia* infected the respiratory system which causes pneumonia, cystic fibrosis and other disease associated to respiratory system. Also, all most bacterial isolates, which discussed in this research have resistant to antibiotics because they contain several genes that responsible for resistant, like *Sul 2* gene. The percentage of this gene found in two studies was 50.9%, 100% respectively. While other studies focused on distinct phenomena in this bacterium, such as quorum sensing, biofilm production, swimming and twitching that have a role in pathogenicity. Some studies found the ability of bacteria for production extracellular enzymes such as protease, lipase, and lecithinase. This enzyme may have role as virulence factor in the infected host.

According to previous studies *S. maltophilia's* pathogenesis mechanisms are still being discovered and researched. Examples of *S. maltophilia* virulence factors include motility, biofilm formation, iron acquisition processes, outer membrane components, protein secretion systems, extracellular enzymes, and antimicrobial resistance mechanisms. *S. maltophilia* uses a wide variety of antimicrobial defenses and is innately resistant to a wide range of antibiotics. Surveillance studies have revealed an increase in drug resistance for *S. maltophilia*, necessitating the development of new anti-opportunist strategies. This environmental bacterium's interactions with other microorganisms are being investigated. *S. maltophilia* and its products are used in biotechnology for a variety of purposes, involving agriculture, biocontrol, and bioremediation.

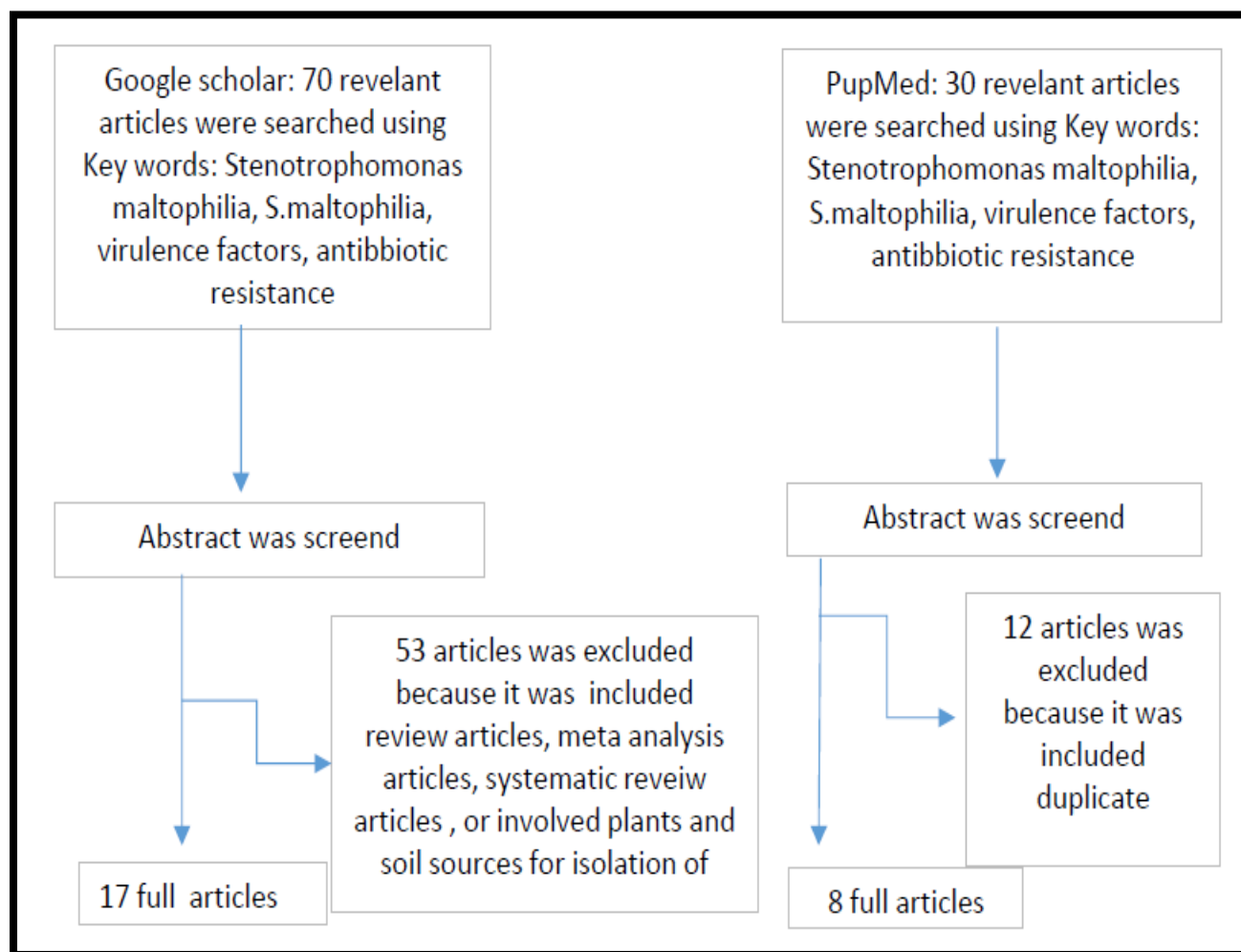


Fig. 1 Flow chart of searching and bias of previous studies

Table 1. Previous studies are included in the current systematic review

Study	Purpose of study	No. of sample	Finding
Hanes et al., 2002 Turkey	evaluated comparative risk variables between those for the emergence of late-onset <i>S. maltophilia</i> VAP and those for late-onset VAP caused by other gram-negative bacteria (SM-VAP)	513 patient	<i>Stenotrophomonas pneumonia</i> was linked to higher morbidity but not mortality, whereas insufficient empiric antibiotic therapy was linked to higher mortality but no change in morbidity.
Di Bonaventura et al., 2007 Italy	Examine the virulence characteristics of two non-respiratory reference strains of <i>S. maltophilia</i> and 11 clinical isolates of <i>S. maltophilia</i> from CF patients.	13 isolates	<i>S. maltophilia's</i> pathogenicity is a complicated, multifaceted process that is still far from fully understood. It will be vital in this situation to thoroughly understand the cellular and <i>S. maltophilia</i> uses molecular processes to invade the lung. can cause persistent airway inflammations
Chhibber et al., 2008	This study sought to determine whether isolates of <i>S. maltophilia</i> included any potential virulence factors.	five septicemic clinical isolates	Identify a variety of virulence traits that might be enhancing <i>S. maltophilia's</i> pathogenicity. Future research should make an effort to pinpoint the precise function of these virulence traits in vivo by using either genetically engineered strains or purified versions of this organism.

India			
Nicoletti et al., 2011 Italy	Furthermore, virulence-associated genes for the StmPr1 and StmPr2 proteases and esterase were tested for their existence and expression, and their contribution to virulence was investigated. These profiles were created using data from PFGE (pulsed-field gel electrophoresis), RFLP (restriction fragment length polymorphism) of the gyrB gene, and 16S rRNA gene sequencing.	52 strains	All <i>S. Maltophilia</i> strains displayed a huge variety of none displayed swarming motion; only swimming and twitching. Smf-1 gene was fully sequenced. PCR-amplified solely from <i>S maltophilia</i> strains that were clinically generated. Finally, by infecting larvae of the wax moth Galleria mellonella, representative <i>S maltophilia</i> strains deficient in the production of proteases and esterase activity were tested for pathogenicity.
Xu et al., 2011 China	investigate the risk factors for lower respiratory tract infections caused by <i>Stenotrophomonas maltophilia</i> in the medical intensive care unit (MICU) at Fujian Provincial Hospital.	35 patients	The presence of severe illnesses, tracheotomies, mechanical ventilation, and the use of broad-spectrum antibiotics are significant risk factors for <i>S. maltophilia</i> lower respiratory tract infection in MICU.
Thomas et al., 2014 Malaysia	<i>S. maltophilia</i> extracellular enzymes were analyzed and compared in both invasive and non-invasive clinical specimens using substrate plate assays.	108 clinical isolates	Regardless of where they came from, all clinical isolates produced measurable levels of the enzymes, produced melanin, and exhibited a swimming and swarming motility pattern. These finding suggest that clinical isolates of <i>S. maltophilia</i> constitute a source of pathogenic potential.
Zhuo et al., 2014 China	identify any noteworthy changes among a group of 24 clinical isolates of <i>S maltophilia</i> , biofilm formation attributes were studied. Additionally, the association between biofilm development and the detection of the rmlA, spgM, and rpfF genes was assessed.	37 <i>S. maltophilia</i> isolates	Clinical strains of <i>S. maltophilia</i> greatly differ in some aspects of genotype and phenotype when it comes to the formation of biofilms. They have also added new knowledge and expanded existing understanding of the relevant genes.
García et al., 2015 Argentina	determine how iron affected <i>S. maltophilia</i> pathogenicity, quorum sensing (QS), EPS generation, oxidative stress response, and OMP regulation.	strain <i>S. maltophilia</i> K279a	<i>S. maltophilia's</i> response to oxidative stress was caused by MnSOD. The virulence of the strains employed in this paper could be evaluated using the <i>G mellonella</i> infection model. According to the description of the role played by iron in the regulation of possible virulence/survival factors, F60 was more virulent than K279a in the killing assay.
Hu et al., 2016 A China	Identify the genetic processes behind resistance to trimethoprim/sulfamethoxazole (SXT).	300 isolates	Clinical <i>S. maltophilia</i> isolates from China with SXT resistance have increased prevalences of sul, dfrA, int1 and resistance gene cassettes in class 1 integron. The presence of the dfrA and sul1 genes in integrons as well as the transposase-linked sul2 gene may indicate widespread and quick diffusion of resistance genes in bacteria.
Hu et al., 2016 B China	Research the factors underlying SXT resistance to stop it from spreading.	41 <i>S. maltophilia</i> samples with sul2 positivity	In <i>S. maltophilia</i> isolates, transposase and the SXT resistance gene sul2 were tightly correlated. These findings imply that acquired resistance, which may be boosted by mobile components, plays a significant part in <i>S maltophilia's</i> resistance to SXT.
Amoli et al., 2016 Iran	Look at the extracellular enzymes, biofilm-forming capacity, and rpfF gene related in quorum sensing that these bacteria possess.	777 blood samples, 100 sputum samples, and 2947 urine samples	The study showed that bacteria isolates were extremely capable of creating extracellular enzymes and biofilm formation, as well as possessing a variety of virulence factors, including the rpfF gene that produces diffusion signal factor, which is necessary for quorum sensing.

Jeon et al., 2016 Korea	Examined the causes of death among patients with <i>S maltophilia</i> bacteremia.	142 bacteremia patients	In order to decrease mortality in patients with <i>S maltophilia</i> bacteremia, removal of central venous catheter CVC should be taken into consideration.
Chen et al., 2017 China	Identify the independent risk factors connected to attributable mortality and investigate appropriate therapeutic options for <i>Stenotrophomonas maltophilia</i> bacteremia, researchers examined the demographics, clinical characteristics, risk factors, drug resistance, and treatment choice of <i>Stenotrophomonas maltophilia</i> bacteremia.	95 patients	For individuals with a high attributable mortality rate, bacteremia caused by <i>Stenotrophomonas maltophilia</i> is a serious condition. According to in vitro susceptibility data, TMP/SMZ is the agent that is most susceptible. Consider levofloxacin and tigecycline to be two further hopeful alternatives.
Alcaraz et al., 2018 Argentina	Examine the clonal relationships, susceptibility, and presence of specific putative virulence factors in the isolates of <i>Stenotrophomonas maltophilia</i> .	63 isolates	There were only two small clusters of linked <i>S. maltophilia</i> types, despite the high genetic diversity that was seen. The most effective medications were trimethoprim-sulfamethoxazole and minocycline. The pathogenesis of <i>S. maltophilia</i> in the <i>G. mellonella</i> model is multifactorial, and additional research is required to clarify the function of each possible virulence component.
Saied et al., 2019 France	Determine the factors that increase the incidence of <i>Stenotrophomonas maltophilia</i> ventilator-associated pneumonia (VAP) and whether this condition has an impact on ICU mortality.	102 patients	The week prior to the SM-VAP, exposure to ureido/carboxypenicillin or carbapenem, as well as the respiratory and coagulation components of the SOFA score > 2, were independent risk factors for the SM-VAP. Age and chronic heart failure were SM-VAP mortality risk factors.
Saraie et al., 2019 Iran	Examine whether clinical isolates of <i>S. maltophilia</i> from Iranian patients exhibit any instances of antibiotic resistance and the mechanisms behind that resistance.	44 <i>S. maltophilia</i> isolates	There is a substantial probability of sulfonamide and fluoroquinolone resistance in clinical strains of <i>S. maltophilia</i> due to the existence of the sul and Smqnr genes in isolates with integrons.
Cruz-Córdova et al., 2020 Mexico	The objective of this research was to describe the molecular epidemiology of <i>S. maltophilia</i> forms linked to an outbreak in the Federico Gómez Children's Hospital of Mexico (HIMFG).	21 clinical strains & Nine environmental strains	The molecular epidemiology, along with some of the traits associated with colonization patterns, including virulence genes and resistance, are pathogenic characteristics that can encourage The spread, persistence, and HIMFG outbreak were made possible by <i>S maltophilia</i> .
Yero et al., 2020 Spain	This study reveals a link between the DSF-based QS system and the virulence and resistance traits in <i>S. maltophilia</i> species as well as probable high-risk clones circulating in European hospitals.	78 geographically and genetically diverse clinical strains	According to this study, the QS system is essential in <i>S maltophilia's</i> pathogenicity and persistence. Additionally, because the rpf variant and the isolates' phylogenetic groups, as determined by their MLST profiles, are significantly correlated.
Duan et al., 2020 China	To investigate the molecular epidemiological traits of <i>S maltophilia</i> , which was isolated from patients at a Shanghai pediatric teaching hospital	104 strains	The majority of infected individuals had previously used antibiotics, had underlying illnesses, and had a high virulence gene positivity rate. The tensions could be defeated by three antibiotics and were capable to forming biofilms effectively.
Saleh et al., 2021 Iraq	Phylogenetic analysis of <i>S maltophilia</i> isolates is required. <i>S maltophilia</i> in Iraq: type, pathogenicity, and multidrug resistance variables.	3569 samples	Identified <i>S. maltophilia</i> in Iraq with high levels of antibiotic resistance and pathogenicity. The elimination of <i>S maltophilia</i> is crucial because there is a risk that resistance genes will spread to other nosocomial infections.

Bostanghadiri et al., 2021 Iran	Examine the <i>S. maltophilia</i> clinical isolates' antimicrobial susceptibility pattern, biofilm production, and biofilm gene existence.	85 clinical isolates	Despite the relatively low occurrence of multiple antibiotic resistance among <i>S. maltophilia</i> isolates, careful antimicrobial use and rigorous infection prevention and control, guidelines are required to stop the spread of resistant isolates.
Govende et al., 2021 South Africa	Focused on identifying the virulence signatures, efflux pumps, antibiotic resistance genes, and patterns of antibiotic resistance in <i>Acinetobacter</i> spp. and <i>S. maltophilia</i> found in samples of river sediment, plant rhizosphere, and river water	Environmental isolates	<i>S. maltophilia</i> exhibited multidrug resistance against the typical antibiotics used to treat them. The existence of antibiotic resistance genes in the strains, the efflux pumps, that have been documented to confer antibiotic resistance or other factors, may have contributed to the resistance.
Abbas and Dhahi, 2022 Iraq	Patients with TCC-bladder cancer or those who had a negative cystoscope can be used to isolate and identify bacteria, as well as to determine patterns of antibiotic sensitivity and assess some virulence characteristics.	6 patients	All isolates were resistant to antibiotics because they contain genes that make them resistant isolates as well as biofilm production, virulence factors that contributes to bacterial pathogenesis.
ElBaradei and Yakout, 2022 Egypt	Investigating the impact of ascorbic acid on the development of <i>S. maltophilia</i> biofilms and genotypic characterisation of the many genes linked with virulence.	20 <i>S. maltophilia</i> isolates	A therapeutic and a clinical problem in <i>S. maltophilia</i> is biofilm formation. A viable answer to this problem is still biofilm inhibition. Additionally, in <i>S. maltophilia</i> , vitamin C can prevent biofilm production in a concentration-dependent way.
Wang et al., 2022 China	In order to improve clinical care, risk variables for <i>S. maltophilia</i> pneumonia in ICU patients were studied.	Eight studies with a 2,320 case sample size	<i>S. maltophilia</i> pneumonia is linked to a number of risk factors in ICU patients. In order to lower the likelihood of <i>S. maltophilia</i> infection, clinical staff members should focus more on assessing the risk of infection in ICU patients and improving the prevention and management of high-risk groups.

Discussion

S. maltophilia is found in a variety of natural environments, involving water, soil, and hospitals, and it can parasitize the human skin, respiratory, and digestive tracts. It is a very commonplace pathogenic agent (Wang et al, 2022).

A meta-analysis in this study was done to identify risk factors for *S. maltophilia* pneumonia in the ICU based on general situation, co-morbid underlying diseases, invasive procedures, and antibiotic use. Previous research has shown that *S. maltophilia* produces an extensive assortment of virulence factors and has a high percentage of antibiotic resistance; however, depending on the clinical source, isolates from the respiratory tract are more virulent than the others.

S. maltophilia genetic heterogeneity studies have determined numerous new genogroups and suggested that this pathogen has adapted to its environments. *S. maltophilia's* pathogenesis mechanisms are still being discovered and researched. Examples of *S. maltophilia* virulence factors include motility, biofilm formation, iron acquisition processes, outer

membrane components, protein secretion systems, extracellular enzymes, and antimicrobial resistance mechanisms. *S. maltophilia* uses a wide variety of antimicrobial defenses and is innately resistant to a wide range of antibiotics. Drug resistance for *S. maltophilia* has increased, as shown by surveillance investigations, necessitating the development of new anti-opportunist strategies(Thomas et al, 2014 ; Brooke , 2021).

Conclusion

The emergence of *S. maltophilia* as an opportunistic pathogen has more recently augmented because this organism's capability to adapt in harsh environments; therefore, it is critical to change antimicrobial strategies to keep up with *S. maltophilia's* progression, as well as to monitor drug resistance status and determine genetic transfers that are happening between different bacterial species. Previous research has identified new molecular and cellular targets that, when disrupted, lead to decreased collaboration among different species. The monitoring of aqueous-associated environments, as well as regular cleaning and disinfection regimens for surfaces of medical equipment that come into direct or indirect connection with patients, are required for the prevention of biofilm formation and the lowering of infection risk in the medical setting.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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