ORIGINAL ARTICLE

Profiles of Deceased Patients with Coronavirus Disease 2019 (COVID-19) and Multidrug-Resistant Bacterial Coinfections at an Indonesian Tertiary Hospital

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ABSTRACT

Introduction: Antibiotic use in coronavirus disease 2019 (COVID-19) patients reached 70% during the pandemic, potentially inducing the invasion of multidrug-resistant organisms (MDROs). This study analyzed patients who died from COVID-19 with MDRO coinfections at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
Methods: We conducted a retrospective descriptive study of 120 deceased COVID-19 inpatients from January to December 2021. The inclusion criteria required: (1) positive MDRO cultures from ≥2 specimens, and (2) resistance to ≥1 agent across ≥3 antimicrobial categories. Patients with incomplete records or no antibiotic therapy were excluded. The data were presented using descriptive statistics to characterize patient demographics, microbiological profiles, and antimicrobial resistance patterns.
Results: The patients were predominantly male (60%), aged 41–80 years (78.33%), and hospitalized for 8–30 days (53.44%). The microbiological examinations revealed blood cultures as the main specimen source (43.10%), followed by sputum (27.59%), urine (19.40%), pus (7.33%), and cerebrospinal fluid (2.59%). The prevalent isolates varied by specimen type: coagulase-negative staphylococci (51%) in blood, *Pseudomonas* spp. in pus (17.65%), *Klebsiella* spp. in sputum (26.69%), and *Escherichia coli* in urine (37.78%). The cerebrospinal fluid cultures showed an equal distribution of Gram-negative bacilli, Gram-positive bacilli, and Gram-positive cocci (33.33% each).
Conclusion: This study characterizes the profiles of fatal COVID-19 cases with MDRO coinfections, demonstrating a predominance of older male patients with prolonged hospitalization. The identified resistance patterns and pathogen distribution, notably coagulase-negative staphylococci in blood, highlight the importance of improved infection surveillance and antibiotic stewardship to minimize the risk of coinfection in the future.

Keywords: Coronavirus disease 2019 (COVID-19); pneumonia; respiratory tract infection; multidrug-resistant organisms (MDROs); tropical disease

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Highlights:
1. While existing studies have examined multidrug-resistant organism (MDRO) coinfections in COVID-19 globally, this work offers a valuable standalone characterization of a high-risk subgroup in Indonesia, where resistance patterns arising from antimicrobial use during the pandemic created unique clinical challenges.
2. This study provides comprehensive data on the mortality of COVID-19 patients with MDRO coinfections at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, enhancing medical personnel's awareness of MDRO bacterial transmission and informing improvements in antibiotic stewardship programs within hospitals.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) initially emerged in Wuhan, China, in December 2019 (Zhou et al., 2020). Since then, COVID-19 spread globally, prompting the World Health Organization to declare a pandemic on March 11, 2020. COVID-19 results from infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), manifesting as pneumonia and acute respiratory distress syndrome in affected individuals (World Health Organization, 2022). Patients with COVID-19 are often given antibiotic therapy, which is not quite appropriate for their condition.

Previous research on COVID-19 patients showed that the prevalence of broad-spectrum antibiotic therapy, including fluoroquinolones and third-generation cephalosporins, reached 70% (Langford et al., 2020). This predominance possibly has triggered bacterial coinfections caused by multidrug-resistant organisms (MDROs). Coinfections in COVID-19 patients can complicate diagnoses, prolong treatments, increase costs, worsen prognoses, and elevate mortality risks (Chen et al., 2020). Furthermore, these coinfections adversely affect the patients' clinical condition, leading to complications such as impeded healing of post-surgical wounds, elevated morbidity and mortality rates, increased patient disability, and prolonged treatment durations, which consequently escalate treatment costs (Ministry of Health of the Republic of Indonesia, 2021).

Coinfections in COVID-19 patients can occur due to cellular and structural damage in the lungs, which compromises the immune system, facilitating bacterial invasion and attachment to the host's body (Hoque et al., 2021). Another factor contributing to coinfection in COVID-19 patients is the administration of antibiotic therapy, especially broad-spectrum antibiotics, during the pandemic, which may disrupt immune function and trigger inflammatory response (Hagan et al., 2019). The use of antibiotics in COVID-19 patients can induce the invasion of MDRO bacteria due to an imbalance in the human gastrointestinal microbiome (Kalluru et al., 2018).

Microorganisms categorized as MDROs, particularly bacteria, can develop resistance to one or more classes of antimicrobial agents (U.S. Centers for Disease Control and Prevention, 2024). Data from a teaching hospital in Terni, Italy, indicated that there was an increase in cases of carbapenem-resistant *Enterobacteriaceae* (CRE) from 6.7% in 2019 to 50% in March–April 2020 (Tiri et al., 2020). Another study conducted in Italy also revealed a heightened incidence of MDRO bacterial coinfections during the pandemic, rising from 4.5 cases to 30 cases per 1,000 patients compared to the pre-pandemic era (Mangioni et al., 2023). In Indonesia, notably in Surabaya, there is limited research on COVID-19 patients with MDRO bacterial coinfections, resulting in a lack of data on pathogen distribution and resistance patterns within the population.

This study aimed to characterize the clinical and microbiological profiles of deceased COVID-19 patients with MDRO bacterial coinfections at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2021. This study is anticipated to offer comprehensive data on the mortality of COVID-19 patients with MDRO bacterial coinfections, hence increasing healthcare professionals' awareness regarding MDRO bacterial transmission in hospitals. The findings of this study are expected to enhance antibiotic stewardship programs concerning COVID-19, specifically at Dr. Soetomo General Academic Hospital.

METHODS

This study used a descriptive research design with a retrospective approach, utilizing secondary data derived from the medical records of deceased inpatients with COVID-19 and MDRO bacterial coinfections at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January to December 2021. To ensure robust identification of MDRO bacterial coinfections, we applied stringent criteria adapted from Michels et al. (2021), requiring: (1) positive cultures from two or more distinct specimens, and (2) demonstration of resistance to at least one agent across a minimum of three antimicrobial categories. The exclusion criteria in the study were patients with incomplete data from medical records or no antibiotic therapy. The total sampling technique was employed to acquire patients who met the inclusion and exclusion criteria.

Our analysis included 120 patient medical records, providing a comprehensive overview of demographic characteristics (age and sex), clinical course (treatment duration), and microbiological findings (specimen types, bacterial identification, and antibiotic resistance patterns). All included cases had a confirmed COVID-19 diagnosis through reverse transcription polymerase chain reaction (RT-PCR) testing. The microbiological analysis involved bacterial cultures from multiple specimen types, including blood, cerebrospinal fluid (liquor cerebrospinalis), pus, sputum, and urine (Ankurita, 2023). MDRO coinfections were confirmed by a positive MDRO bacterial culture through repeated isolation and collection of bacterial species.

All data collected in this study were statistically analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA, 2017). The data were presented using descriptive statistics (frequency distributions) to characterize patient demographics, microbiological profiles, and antimicrobial resistance patterns (Zhang et al., 2021). The ethical approval for this study was issued by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with registration number 1446/LOE/301.4.2/IX/2023, dated 12/09/2023.

RESULTS

Table 1 shows that 1,658 COVID-19 fatalities were documented in patient medical records at Dr. Soetomo General Academic Hospital Surabaya, Indonesia, from January to December 2021. We obtained 120 medical records that met the inclusion criteria and were eligible as research samples. According to the available medical records, 232 specimens were collected, consisting of blood, sputum, urine, pus, and cerebrospinal fluid in frequencies of 100, 64, 45, 17, and 6, respectively. The data revealed that the majority of the patients were male, comprising 72 individuals or 60% of the samples. The predominant age range was 41–60 years at 45% and 60–80 years at 33.33%. The majority of the deceased COVID-19 patients with MDRO bacterial coinfections at the hospital, comprising 53.44% of the samples, experienced a prolonged hospitalization, ranging from 8 to 30 days.

Table 1. General characteristics of the COVID-19 patients

Characteristics	n (%)
Deceased patients	
With MDROs	120 (7.23%)
Without MDROs	1538 (92.77%)
Sex	
Male	72 (60%)
Female	48 (40%)
Age (years)	
<20	2 (1.67%)
21–40	23 (19.17%)
41–60	54 (45%)
61–80	40 (33.33%)
>80	1 (0.83%)
Treatment duration (days)	
1–7	55 (45.83%)
8–30	64 (53.33%)
>30	1 (0.83%)

Note: MDROs=multidrug-resistant organisms.

In this study, we conducted a microbiological examination on COVID-19 patients to identify the bacterial species infecting them. The most common specimen examined was blood, with a total of 43% of all specimens (Figure 1). Other specimens used for the microbiological examination, including sputum, urine, pus, and cerebrospinal fluid, were not more prevalent compared to blood specimens.

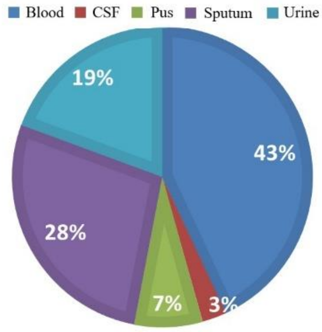

Figure 1. Distribution of examined specimens for the microbiology cultures

Figure 2 illustrates the distribution of bacterial classifications for each specimen type, whereas Table 2 delineates the distribution of bacterial isolates corresponding to specimen types and bacterial groups. The most prevalent type of bacteria identified across all samples was Gram-negative bacilli, accounting for 54.74% of the cases. The bacterial species with the highest prevalence was coagulase-negative staphylococcus, comprising 22.84% of all samples. However, each specimen contained different types of bacteria.

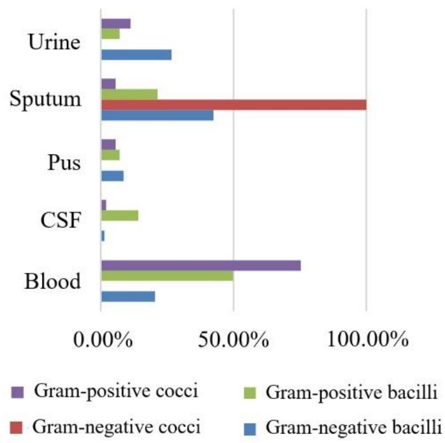

Figure 2. Distribution of bacterial groups across all examined specimens

The data indicated that the most prevalent bacteria in the blood specimens were Gram-positive cocci, specifically coagulase-negative staphylococci, reaching 67% of the total samples. The distribution of bacteria in the cerebrospinal fluid specimens was equal at 33.33% for each bacterial group identified. The predominant Gram-negative bacilli in the pus, sputum, and urine specimens were *Pseudomonas* spp. at 17.65%, *Klebsiella* spp. at 29.69%, and *Escherichia* coli at 37.78%, respectively. Moreover,

Table 2. Total bacterial isolates identified from the microbiology cultures

Bacterial isolates	Specimen types					Subtotal (%)
	Blood (%)	CSF (%)	Pus (%)	Sputum (%)	Urine (%)	
Gram-negative bacilli	11.21%	0.86%	4.74%	23.28%	14.66%	54.74%
Acinetobacter baumannii	6.47%	0%	0.86%	4.74%	1.29%	13.36%
Aeromonas hydrophila	0%	0%	0.43%	0%	0.43%	0.86%
Cedecea lapagei	0%	0%	0%	0%	0.86%	0.86%
Enterobacter cloacae	0%	0%	0.43%	0.86%	0.43%	1.72%
Escherichia coli	1.72%	0%	0.86%	3.02%	7.33%	12.93%
Klebsiella spp.	0.86%	0.43%	0.43%	8.19%	3.88%	13.79%
Kluyvera ascorbata	0%	0%	0%	0.43%	0%	0.43%
Morganella morganii	0%	0%	0%	0.43%	0%	0.43%
Proteus mirabilis	0%	0%	0%	0.43%	0%	0.43%
Providencia alcalifaciens	0.43%	0%	0%	0%	0%	0.43%
Pseudomonas spp.	1.72%	0%	1.29%	4.31%	0.43%	7.76%
Stenotrophomonas maltophilia	0%	0.43%	0.43%	0.86%	0%	1.72%
Gram-positive bacilli	3.02%	0.86%	0.43%	1.29%	0.43%	6.03%
Bacillus cereus	0%	0%	0.43%	0%	0%	0.43%
Brevibacillus brevis	0%	0%	0%	0.43%	0%	0.43%
Corynebacterium spp.	2.59%	0.86%	0%	0.43%	0.43%	4.31%
Gemella haemolysans	0%	0%	0%	0.43%	0%	0.43%
Leuconostoc citreum	0.43%	0%	0%	0%	0%	0.43%
Gram-negative cocci	0%	0%	0%	0.86%	0%	0.86%
Moraxella (Branhamella) catarrhalis	0%	0%	0%	0.43%	0%	0.43%
Neisseria animaloris	0%	0%	0%	0.43%	0%	0.43%
Gram-positive cocci	28.88%	0.86%	2.16%	2.16%	4.31%	38.36%
Aerococcus viridans	0.43%	0%	0%	0%	0%	0.43%
Alloiococcus otitidis	0%	0%	0%	0%	0.43%	0.43%
Enterococcus spp.	3.02%	0%	0%	0%	3.45%	6.47%
Staphylococcus aureus	3.02%	0.43%	0.86%	2.16%	0%	6.47%
Coagulase-negative staphylococci	21.98%	0.43%	0%	0%	0.43%	22.84%
Grand total	43.10%	2.59%	7.33%	27.59%	19.40%	100%

Note: CSF=cerebrospinal fluid (liquor cerebrospinalis).

there was an interesting note that Gram-positive cocci bacteria, such as *Moraxella (Branhamella) catarrhalis* and *Neisseria animaloris*, were only found in the pus specimens, each constituting 0.43%.

According to data shown in Table 3, the most common antibiotic group that all bacterial types exhibited resistance to was the beta-lactam penicillin group, accounting for 17.09% of all samples. However, each bacterial group demonstrated different patterns of antibiotic resistance. For example, Gram-negative bacilli and Gram-positive cocci exhibited increased resistance to specific antibiotic groups. Gram-negative bacilli indicated a resistance rate of 13.33% to third-generation cephalosporins, while Gram-negative cocci showed a higher resistance rate of 21.05% to the same antibiotic group. Among Gram-positive bacilli, the highest resistance observed was 23.30% against fluoroquinolones. On the other hand, Gram-positive cocci developed the highest resistance, reaching 25.16%, to beta-lactam penicillin antibiotics. Additionally, certain bacterial groups exhibited resistance against specific antibiotic groups, such as Gram-negative bacilli that developed resistance to lipopeptides, whereas Gram-positive cocci specifically demonstrated resistance to fusidic acid.

DISCUSSION

This study, conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, revealed that 120 out of 1,658 deceased COVID-19 patients had MDRO bacterial coinfections. A total of 1,538 datasets were excluded due to incomplete medical records or no history of antibiotic administration. Nevertheless, the prevalence of MDRO bacterial coinfection among deceased COVID-19 patients warrants analysis, as it reached 7.23%. The data

Table 3. Antibiotic resistance patterns across the identified bacterial groups

Antibiotics	Gram-negative bacilli	Gram-positive bacilli	Gram-negative cocci	Gram-positive cocci	Subtotal
Beta-lactam combination agents	12.95%	2.91%	26.32%	6.61%	10.63%
Beta-lactam penicillins	13.01%	21.36%	0%	25.16%	17.09%
Monobactams	4.74%	0%	10.53%	0%	3.09%
First-generation beta-lactam cephalosporins	5.69%	0%	0%	0.13%	3.65%
Second-generation beta-lactam cephalosporins	1.14%	3.88%	0%	6.99%	3.09%
Third-generation beta-lactam cephalosporins	13.33%	2.91%	21.05%	0%	8.75%
Fourth-generation beta-lactam cephalosporins	3.98%	0%	5.26%	0%	2.57%
Phenicols	5.05%	0.97%	0%	5.08%	4.86%
Lipopeptides	0.13%	0%	0%	0%	0.08%
Lincosamides	0.19%	12.62%	0%	7.37%	2.97%
Macrolides	0.06%	5.83%	0%	6.73%	2.41%
Fusidic acid	0%	0%	0%	1.02%	0.32%
Aminoglycosides	6.19%	11.65%	5.26%	10.80%	7.87%
Oxazolidinones	0%	0%	0%	0.76%	0.24%
Carbapenem	4.30%	0%	0%	0%	2.73%
Fluoroquinolones	11.88%	23.30%	5.26%	7.50%	10.91%
Nitrofurans	0.88%	0%	0%	0.13%	0.60%
Streptogramins	0.06%	0%	0%	1.91%	0.64%
Rifamycins	0%	0%	0%	0.25%	0.08%
Tetracyclines	7.64%	5.83%	10.53%	6.10%	7.10%
Folate antagonists	5.81%	5.83%	5.26%	8.89%	6.78%
Other cell wall or membrane-active agents	2.91%	2.91%	10.53%	2.16%	2.73%
Glycopeptides	0.06%	0%	0%	2.41%	0.80%
Total	100%	100%	100%	100%	100%

indicated that most of the patients analyzed were male, accounting for 60% of the total samples.

Bacteria categorized as MDROs are microorganisms that can exhibit resistance to one or more classes of antimicrobial agents (U.S. Centers for Disease Control and Prevention, 2025). Antimicrobial resistance has been generally considered a major public health problem because it can cause adverse effects, such as prolonged hospitalization, increased treatment costs, additional morbidity, and heightened mortality rates (Sy et al., 2022). Risk factors for infection include MDRO prevalence, extended hospitalization or intensive care unit (ICU) stays, antibiotic therapy within the past three months or longer, the use of catheters or other medical devices, immune deficiency, malnutrition, dialysis treatment, and the presence of diabetes or other comorbidities (Pletz et al., 2015).

Some bacteria can develop resistance to antibiotics, which can make infections more difficult to treat and increase the risk of transmitting dangerous and deadly infectious diseases (Mancuso et al., 2021). The ability of bacteria to develop resistance may arise from the presence of the R plasmid, which contains numerous resistance genes. Bacteria can acquire resistance genes from antibiotic-producing organisms, such as *Streptomyces* and other organisms that are distributed in the soil. *Streptomyces* produce antibiotics to fight other microorganisms, thereby developing resistance genes to protect themselves. These resistance genes can be transferred to bacteria, increasing their likelihood of antibiotic resistance development (Larsson & Flach, 2022).

The bacteria that develop into MDROs are usually referred to as the "ESKAPE" pathogen. This collection of bacteria, encompassing both Gram-positive and Gram-negative strains, comprises *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. The results of this study indicated that ESKAPE bacteria were found in 49.57% of the specimens, with the distribution as follows: *Klebsiella pneumoniae* (13.79%), *Acinetobacter baumannii* (13.36%), *Pseudomonas aeruginosa* (7.76%), *Enterococcus* sp. (6.47%), *Staphylococcus aureus* (6.47%), and *Enterobacter cloacae* (1.72%). These bacteria cause nosocomial infections in hospitals, which threaten critical or immunocompromised patients and can result in unfavorable outcomes such as elevated mortality rates, morbidity, increased costs for treatment, and challenging diagnostic determinations (Santajit & Indrawattana, 2016). In addition, ESKAPE bacteria were more frequently found in COVID-19 patients with severe symptoms compared to those with mild symptoms only (Catalano et al., 2023).

Based on the timing of its detection, coinfection can be divided into two types: early and late. Early coinfection can be interpreted as a coinfection detected within 48 hours of hospital admission. In comparison, late coinfection is defined as a coinfection detected 48 hours or more after the admission of a patient to the hospital (Cheng et al., 2020). Antibiotics must be closely monitored because the higher the dose of antibiotics given, the higher the possibility of coinfection with resistant bacteria (Mirzaei et al., 2020).

Research conducted by Son et al. (2021) revealed that male patients, around 55% of the total cases, had a higher incidence of coinfection compared to females. Similar findings were observed by Wong et al. (2023) in Hong Kong: a higher proportion of male patients, specifically 65.4% of the total samples, were more likely to experience COVID-19 with MDRO bacterial coinfections.

The majority of deceased COVID-19 patients with bacterial MDRO coinfections in this study were in the age range of 41–60 years, comprising 78.33% of the total samples. These findings quite align with those of Son et al. (2021) and Wong et al. (2023), suggesting that COVID-19 patients with bacterial MDRO coinfections had a median age of 68–77 years.

In this study, most patients required long-term care before passing away, with around 53.44% hospitalized for 8–30 days. This is consistent with findings from studies conducted by Cohen et al. (2021) and Greco et al. (2022), as they noted a relatively long duration of hospitalization for COVID-19 patients with bacterial coinfections.

In the microbiological examinations, Gram-negative bacilli were identified most frequently, with a prevalence of 54.74%. Similar findings were also recorded in other studies, including Słabisz et al. (2023), who found that the prevalence of coagulase-negative staphylococcus was greater during the COVID-19 pandemic, namely 17% versus 11% prior to the pandemic. In another study conducted by Asmarawati et al. (2021) at Universitas Airlangga Hospital, Surabaya, Indonesia, it was revealed that Acinetobacter baumannii was a prevalent pathogen for coinfections. The bacteria were most commonly found in sputum, as many as 15.7% of the total specimens. Meanwhile, prior research conducted by Indrasari et al. (2022) at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, showed that the most commonly found MDROs were extended-spectrum beta-lactamase (ESBL)-producing bacteria, accounting for 48.82% of all isolates. The identified bacterial isolates included *Klebsiella pneumoniae* (17%), *Escherichia coli* (26.54%), *Enterobacter aerogenes* (0.27%), *Enterobacter cloacae* (3.72%), and other *Enterobacteriaceae* (1.54%).

The highest resistance to antibiotics varied among different bacterial groups. Gram-negative bacteria exhibited the highest resistance to beta-lactam cephalosporins, while Gram-positive bacteria showed the greatest resistance to beta-lactam penicillins. These findings indicate a serious threat of antibiotic resistance, supported by a study in Terni, Italy, which noted an increased prevalence of carbapenem-resistant Enterobacteriaceae during the COVID-19 pandemic (Tiri et al., 2020).

This study has several limitations, including the possibility of nosocomial infections to affect the results of antimicrobial susceptibility testing in COVID-19 patients, which could lead to misinterpretation of multidrug resistance. Another limitation of this study is the lack of data on the combination of antibiotic resistance, due to limited space and time for research. Further research with more robust analysis is necessary to gain a more comprehensive understanding of the topic. Nevertheless, this study provides an overview of bacterial resistance in COVID-19 patients who died in 2021.

CONCLUSION

This study indicates that MDRO bacteria primarily infect older male COVID-19 patients with prolonged hospital stays. Consequently, several aspects can be periodically addressed to enhance antibiotic stewardship programs, ensuring that the incidence of bacterial resistance against antibiotics remains consistently low throughout time.

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CONFLICT OF INTEREST

There are no potential conflicts of interest.

ETHICS CONSIDERATION

This research has obtained approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with reference number 1446/LOE/301.4.2/IX/2023, dated 12/09/2023.

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AUTHOR CONTRIBUTION

JBF contributed to the conceptualization and

design, collection, analysis, and interpretation of the data, drafting of the article, and provision of administrative support. MR and J contributed to the critical revision of the article for important intellectual content and final approval of the article. RS participated in the critical revision of the article for important intellectual content and provided statistical expertise.

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