Yield and clinical impact of blood cultures in patients admitted to an internal medicine ward

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SUMMARY

The purpose of this prospective observational study was to evaluate the yield and clinical impact of blood cultures in a 78-bed Internal Medicine ward of a medium-sized Italian acute care hospital. During a two-month study period, 154 (mean age: 75.2+12.2 years; 94 males) out of 620 (24.8%) hospitalized patients underwent 174 blood cultures and were enrolled in the study. The rate of true-positive cultures was 11.5% (20/174) and the rate of false-positive (contaminants) was 5.7% (10/174). A total of 23 microorganisms (5 multidrug resistant strains), most frequently *Escherichia coli* (n=10), *Klebsiella pneumoniae* (n=3) and *Staphylococcus aureus* (n=3), were isolated. The positivity rate was significantly higher in patients with urinary tract infection (31%) and abdomen infection (26.1%) than in patients with pneumonia (4.9%; p<0.01). Although the positivity rate in patients exposed to antibiotics was lower than in those not exposed, the difference was not statistically significant. Therapy changes due to blood culture positivity were observed in 7.1% of the patients overall. In-hospital death was observed in nine of the 136 patients with negative blood cultures (6.6%) and in none of the 18 patients with positive blood cultures. These results indicate that the yield and clinical impact of blood cultures is quite low in patients admitted to an Internal Medicine ward and suggest the need to improve the adequacy of the indications to perform the test.

Keywords: blood cultures; pneumonia; urinary tract infection; internal medicine; antibiotic de-escalation.

INTRODUCTION

Blood stream infection (BSI) is a serious medical condition associated with a high mortality rate, ranging from 14% to 37%, with the highest values registered in intensive care settings [1-6]. Diagnosis of BSI is established when the growth of one or more microorganism(s) is obtained in blood culture drawn from a patient with clinical signs of infection and the contamination has been ruled out. These infections are classified as primary, when no other site of infection is evident, or secondary, when associated with clinical or microbiological confirmation of infection at a defined body site [7].

The optimal management of patients with severe bacteremic infection largely depends on the possibility of identifying the causative microorganism. Despite some limitations, blood culture remains the gold standard test for the diagnosis of bacteremia, since it allows to isolate the etiological agent and to test its antibiotic drug susceptibility [8, 9]. Once the microorganism responsible for the infection and its suceptibilty to antibiotics are known, the clinician can tailor the empirical initial antibiotic therapy, selecting a more appropriate and effective pathogen-targeted therapy.

However, the clinical utility of blood cultures is limited by the low rate of positivity, which ranges from 3 to 10%, and by the high rate of contamination, which frequently exceeds 5% [10-15].

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Most of the studies that evaluated the efficacy of blood cultures in modifying therapeutic behavior were conducted in emergency departments or in intensive care units [16-18]. Conversely, there are still few studies on the utility of the test performed on patients admitted to Internal Medicine wards, despite being a widely used exam in this context [13, 19-21].
Based on these considerations, we conducted a prospective study to evaluate the yield of blood cultures and their impact on the management of antibiotic therapy in patients admitted to an Internal Medicine ward.

PATIENTS AND METHODS

Study design
We conducted a single-center prospective observational cohort study evaluating all patients consecutively admitted over a period of 62 days (from February 18 to April 20, 2019) in the Internal Medicine ward of the San Giovanni di Dio Hospital in Florence. The patients who underwent at least one blood culture test were enrolled in the study.
The main objectives of the study were the evaluation of:
- the rate of positive blood cultures;
- the rate of contaminated blood cultures;
- the clinical impact of blood cultures, defined as antibiotic therapy changes resulting from positive blood cultures.

Secondary objectives of the study were the evaluation of:
- the relationship between blood culture results and: site of infection, presence of risk factors for infection with multidrug resistant organisms (MDRO) and exposure to antibiotic treatment before blood culture collection;
- the clinical outcome (length of hospitalization and mortality).

It was decided to perform a prospective study to obtain better quality data, avoiding the lack of reliable data that frequently occurs with a retrospective design. This study was approved by the Department of Internal Medicine and by the Hospital Management.

Clinical setting
The study was conducted at the Internal Medicine ward of the San Giovanni di Dio Hospital, Florence, Italy, an acute care hospital of medium size (296 beds). The Internal Medicine ward consists of 78 beds and annually treats about 3,800 inpatients, most (92% in 2018) admitted from the general emergency department of the hospital. An antimicrobial stewardship program is active since april 2016 [22]. The ward is equipped with a full electronic clinical records system (ARGOS software, Dedalus, Italy).

Blood culture test
The criteria adopted for selection of patients undergoing blood culture were:
a) fever (≥38°C);
b) medical decision based on the clinical suspicion of a bacteraemic infection even in the absence of fever.

In the present study, a single blood culture test was defined as the collection of 2 or 3 blood samples at least 20 minutes apart from one another. Each sample consisted of about 20 mL of blood divided into two bottles, one for aerobes (BD BACTEC Plus Aerobic/F Culture Vials) and one for anaerobes (BD BACTEC Lytic/10 Anaerobic/F Culture Vials).
Blood cultures were collected by trained nurses; venipuncture was preceded by careful skin disinfection with chlorhexidine. After blood culture collection the bottles were temporarily stored at room temperature and transported to the microbiology laboratory. The samples were incubated until 6 days with an automated system (BD BACTEC-BD Diagnostics, Franklin Lakes, NJ, USA). Upon blood culture positivity, a gram staining was performed, and the results were promptly communicated to the medical staff. The microbe identification was obtained by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS).
A culture was defined as contaminated if one or more of the following skin-residing organisms was recovered from only one of paired blood culture sets: Coagulase-negative *Staphylococci*, *Propionibacterium sp., Micrococcus sp., Viridians group Streptococci, Corynebacterium sp., or Bacillus sp.* When one of these organisms was detected in more than one blood culture set, the test was considered to be true positive.

Data collection
Data were collected by two trained medical students, supervised by two expert physicians of

the Unit. For each enrolled patient, the following data were collected: age, gender, sites of infection, risk factors for infection with MDRO, the species of pathogen grown detected in blood culture and their supsceptibility to antibiotics, the classes of antibiotics used before and after the acquisition of blood culture results, the length of hospital stay and the in-hospital mortality.

Bacteria were considered MDR when resistant to 3 or more classes of antibiotics [23]. The following risk factors for MDR infection were considered: use of antibiotics and/or hospital stay ≥2 days in the 90 days prior to admission; solid tumor or haematological malignancies; chemo- or radio-therapy, immunosuppression, presence of indwelling medical devices [24].

Antibiotic management changes due to culture results were distinct into de-escalation and escalation. De-escalation was defined as the transition from a broad-spectrum empirical antibiotic therapy to a narrower spectrum targeted regimen; conversely, escalation was defined as the transition to a broader spectrum antibiotic therapy [25, 26]. Antibiotic treatment was classified as unchanged when the regimen was continued without adjustment or switched to a different route of administration without modifying the antibacterial spectrum.

Statistical analysis

Statistical analysis was performed using the Student's *t* test for continuous data and the Chi-square test or exact Fisher test for categorical data, as appropriate. The identification of predictors of blood cultures positivity was performed using a multivariate logistic regression analysis. Differences were considered significant for a value of $p<0.05$. The analyses were carried out using MedCalc® version 12.3.0 (MedCalc Software; Mariakerke, Belgium) and GNU PSPP Statistical Analysis Software PSPP program.

Compliance with ethical standards

Informed consent

Each patient was informed of the characteristics and purpose of the study and provided his written consent to participate. Data have been de-identified to preserve participant anonymity.

Conflict of interest

The authors declare that they have no conflicts of interest.

Statement of human and animal rights

The authors declare that all procedures performed in this study are in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

During the study period, 620 patients were admitted to the Internal Medicine ward. Among these, 154 subjects (24.8%) underwent at least one blood culture test and were enrolled in the study. They had a mean age of 75.2±12.2 years, with a male/female ratio of 1.56:1 (94 m and 60 f). A total of 174 blood cultures were collected, as 14 patients received more than one blood culture during their hospitalization. Thirty of 174 blood cultures were positive (17.2%), but 10 of these (5.7%) were false-positive, because the detected microorganisms were considered contaminants (Table 1). Overall, 20 out of 174 blood cultures (11.5%) yielded true positive result, and a total of 23 microorganisms were isolated, as three blood culture tests grew 2 different microorganisms each. A total of 18 patients out of 154 (11.7%) had at least one positive blood culture and one of them had 3 positive blood cultures for *Escherichia coli* at different times. Figure 1 shows a schematic summary of these results.

The microorganisms responsible for bacteremia are shown in Table 2. *E. coli* was the most frequently isolated organism (n=10; 43.5%), followed by *Klebsiella pneumoniae* (n=3; 13%) and *Staphylococcus aureus* (n=3, 13%).

The analysis of antibiotic susceptibility revealed that 5 strains among the 23 isolates were MDRO (21.7%): 1 strain of Extended-Spectrum β-Lactamases (ESBL)-producing *E. coli*, 1 strain of carbapenem-resistant *K. pneumoniae*, 1 strain of methicillin-resistant *S. aureus* (MRSA), 1 strain of oxacillin-resistant *Staphylococcus epidermidis*, and 1 strain of AmpC beta-lactamase-producing *Citrobacter braakii.*

The percentages of positive blood cultures found in patients with urinary tract infection (31.0%) and abdominal infection (26.1%) were significantly higher than those obtained in patients with low respiratory tract infection (4.9%) (p value <0.01 for each comparison) (Table 3).

Table 1 - Microorganisms isolated in blood cultures.

Contaminating microorganism	*Number of false-positive blood culture isolates (10/174)*		
Staphylococcus epidermidis	5		
Staphylococcus hominis	2		
Staphylococcus haemolyticus	1		
Staphylococcus lugdunensis	1		
Staphylococcus pettenkoferi	1		
Microorganism	*Number of true-positive blood culture isolates (23/174)*	*MDRO (No/Yes)*	*Site of infection*
Escherichia coli	10	9/1	6 UT/2 Abdomen/2 Airways
Staphylococcus aureus	3	2/1	Abdomen/UT/UT
Klebsiella pneumoniae	3	1/2	UT/Airways/undetermined
Bacillus cereus	1	1/0	Abdomen
Enterococcus gallinarum	1	1/0	UT
Streptococcus pneumoniae	1	1/0	Airways
Staphylococcus epidermidis	1	0/1	Abdomen
Candidaa albicans	1	1/0	Abdomen
Citrobacter braakii	1	1/0	Abdomen
Streptococcus gordonii	1	1/0	Airways

UT=urinary tract

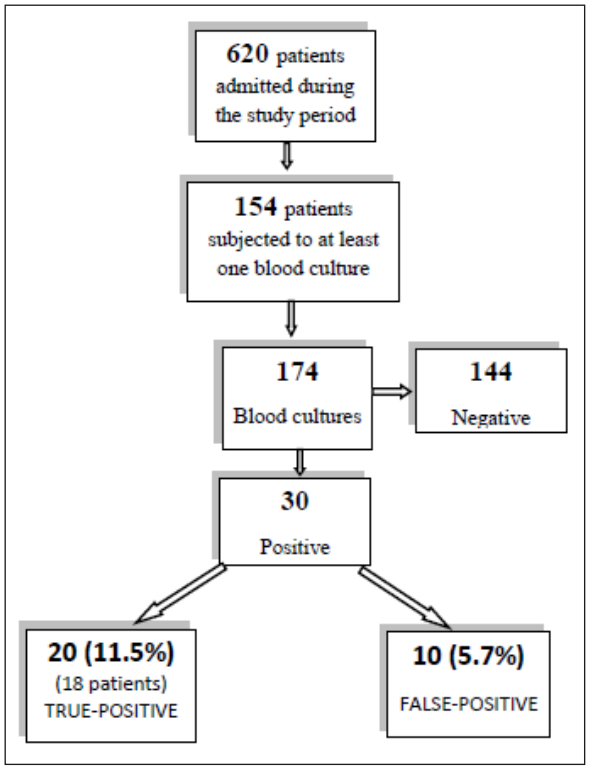

Figure 1 - Schematic summary of blood culture results.

Table 4 shows some characteristics of patients with positive and negative blood cultures. Age was similar, while patients with positive blood cultures were more frequently male. The presence of one or more risk factors for MDRO infection was observed in almost all patients with positive blood cultures (17/18), while it was significantly less frequent in patients with negative blood cultures ($p<0.01$). Seventy-six of the 174 blood cultures (43.4%) were collected after the beginning of empiric antibiotic therapy (in most cases administered at home or in the Emergency Room). The rate of exposure to antibiotic treatment was lower in patients with positive blood cultures (5/18 =27%) than in patients with negative blood cultures (57/79 =72%) (Table 4), but the difference was not statistically significant. On multivariate analysis, only the presence of one or more risk factors for MDRO infection resulted as a predictor of positive blood cultures (Table 5).

The empiric initial antimicrobial therapy was modified in 61.1% of patients with positive blood culture and in 19.9% of patients with negative blood culture ($p<0.001$). Overall, a change in antibiotic therapy due to a positive blood culture was recorded in 11 of the 154 patients (7.1%).

Table 2 - Patients with positive blood cultures.

Gender	*Age*	*Site of infection*	*Microorganism*	*Empiric ABT*	*Therapy change**	*Targeted ABT*
M	81	abdomen	*Citrobacter braakii*	Pip/tazo	N	–
M	79	airways	*S. gordonii*	CFTX, Macrolide	D	glycopeptide
F	79	abdomen	*E. coli*	Amoxi/clav	N	–
M	91	urinary tract	*MSSA*	Pip/tazo	N	–
M	71	urinary tract	*MRSA*	Pip/tazo	D	glycopeptide
F	74	urinary tract	*E.coli*	Pip/tazo	D	Amoxi/clav
M	56	undetermined	*K. pneumoniae*	Pip/tazo	D	CFTX
M	78	urinary tract	*E.coli, E.coli, E.coli*	Pip/tazo	E	Pip/tazo, aminoglycoside
M	45	abdomen	*MSSA, B. cereus*	Amoxi/clav	E	Amoxi/clav, Clindamicin
M	70	airways	*E.coli*	Pip/tazo	N	Pip/tazo
F	75	urinary tract	*E.coli*	Carbapenem	D	CFTX
M	65	urinary tract	*E.coli ESBL+*	Pip/tazo	N	–
M	79	urinary tract	*E. gallinarum, K. pneumoniae*	Pip/tazo	N	–
M	85	urinary tract	*E.coli*	Pip/tazo, aminoglycoside	D	Pip/tazo
M	83	airways	*K. pneumoniae*	Pip/tazo	D	CFTX
M	83	urinary tract	*E.coli*	Carbapenem	D	Aminoglycoside
M	83	abdomen	*Candida albicans*	Pip/tazo	E	Pip/tazo, fluconazole
M	74	airways	*S. pneumoniae, S. epidermidis*	Pip/taz, Linezolid	N	–

M=male, F=female. Pip/tazo=piperacillin/tazobactam; Amoxi/clav=amoxicillin/clavulanate; CFTX= ceftriaxone. N=non-change; D=de-escalation; E=escalation. *Therapy change after blood culture positivity.

The changes mainly consisted in antibiotic de-escalation (Table 4). Empirical therapy was appropriate in 15 of 18 patients (83.3%) with positive blood cultures.

The length of hospital stay was not significantly different in patients with positive blood cultures and in patients with negative blood cultures (Table 4).

No in-hospital deaths were recorded in patients with positive blood cultures, while patients with negative blood cultures had an in-hospital mortality rate of 6.6% (Table 4).

Table 3 - Number and percentage of blood cultures divided by infection site.

Site of infection	*Number (%) of blood cultures*	*Number (%) of positive blood cultures*
Urinary tract	29 (16.7)	9/29 (31.0)
Low respiratory tract	81 (46.6)	4/81 (4.9)
Abdomen	23 (13.2)	6/23 (26.1)
Skin and soft tissue	9 (5.2)	0/9 (0)
Undetermined	32 (18.3)	1/32 (3.2)

DISCUSSION

The main objectives of this prospective observational study were to evaluate the yield and the clinical impact of blood cultures in an Internal Medicine ward. During the 2-month study period 174 blood cultures were collected in 154 patients with a positivity rate of 11.5%. These results indicate that the yield of blood cultures in an Internal Medicine ward is rather low. Similar results have been obtained in other clinical settings, like the Intensive Care Unit and the Emergency Depart-

Table 4 - Characteristics of patients with positive and negative blood cultures.

	Patients with positive blood cultures (n=18)	*Patients with negative blood cultures (n=136)*	*p value*
Age (years) + SD	75.1+11.0	75.2+12.4	0.9
Males	15/18 (83.3 %)	79/136 (58.1%)	<0.05
Patients with >1 risk factors for MDRO infection	17/18 (94.4%)	49/136 (36.0%)	<0.01
Previous antibiotic exposure	5/18 (27.8%)	57/136 (41.9%)	0.44
Patients with antibiotic therapy change De-escalation Escalation	11/18 (61.1%) 8 3	27/136 (19.9%) 24 3	<0.001 0.14 0.36
Lenght of hospital stay (days)	15.1+8.5	12.3+9.1	0.21
Number of in-hospital deaths	0/18 (0%)	9/136 (6.6%)	0.60

Risk factors for MDRO infection: use of antibiotics and/or hospital stay ≥2 days in the 90 days prior to admission; solid tumor or haematological malignacies; chemo or radiotherapy, immunosuppression; presence of medical devices.

Table 5 - Independent predictors of postive blood cultures evaluated by multivariable logistic regression analysis.

Predictors	*OR*	*95% confidence interval*	*P value*
1 or more risk factors for MDRO infection	4.62	1.60-13.54	.005
Male gender	3.45	0.92-12.86	.065
Antibiotics at time of cultures	0.45	0.14-1.41	.169

ment, where the positivity rate ranges from 3.6 to 13% [10-12, 27]. A recent retrospective observational study conducted at a Dutch university hospital indicated an overall positivity rate of 7% and in a large prospective cohort study performed at a single medical Center the true-positive rate was only 3.6% [13, 21]. In assessing the extent of the clinical impact, it is necessary to consider 2 groups of patients: the entire population of patients undergoing blood culture and the patients with positive blood cultures. Considering the first group, the overall clinical impact was relatively low, as in only 7.1% of patients a change in antibiotic treatment, due to positive blood culture, was observed. On the other hand, in the relatively few patients with positive blood cultures (11.7%), the results induced a change in antibiotic therapy in over 60% of cases. In most patients the antibiotic changes consisted in a narrowing of the spectrum, the so-called de-escalation, which determines advantages both for patient and the environment, reducing the impact on antibiotic resistance. De-escalation was performed, albeit to a smaller extent (19.9%), also in patients with negative blood cultures, as a consequence of results from other body sites cultures and of clinical picture evolution. It should be noted that the clinical benefit of de-escalation is particularly important in Italy, which is one of the European countries with the highest level of antibiotic resistance [22]. In other studies, positive blood cultures were able to modify the management of the patient with infection up to 90% of the cases [9, 17].

These results, in our opinion, should stimulate the identification of validated clinical criteria to select patients with high or at least moderate pre-test probability of having positive blood cultures. In fact, performing a blood culture when the chances of bacteremia are very low will hardly produce a positive result. Available guidelines do not provide uniform and comprehensive indications and blood cultures are usually collected in patients with fever and/or leukocytosis, but none of them, alone or in combination, has been shown highly predictive of positive result [21, 28, 29]. The analysis of numerous studies allowed to stratify the probability of bacteremia into 3 ranges: low probability (<14%) in ambulatory outpatients, patients with cellulitis and patients with community-acquired pneumonia or community-acquired fever, intermediate probability (19%-25%) in those with pyelonephritis and high probability (38%-69%) in

patients with severe sepsis, septic shock, or acute bacterial meningitis [30].

Several studies have evaluated the value of multivariable scores for prediction of bloodstream infections. High values of sensitivity and negative predictive power were obtained using the so-called "Shapiro decision rule", which suggests obtaining a blood culture in the presence of 1 major (suspected endocarditis or temperature >39.5°C) or 2 minor criteria [16]. When no major and fewer than 2 minor criteria are present, the risk of bacteremia was very low (0.9% in the validation cohort).

Skin contaminants in blood culture bottles are common and constitute as many as half of the positive cultures. False-positive cultures can lead to unnecessary investigations and treatments and to increase hospital stay and costs [14]. In this study, the contamination was observed in 10 of the 174 samples, equal to 5.7%, a value higher than the threshold value of 3%, identified by the guidelines as an indicator of correct sampling [29]. To minimize the risk of contamination, meticulous care should be taken in skin preparation prior to venipuncture [29]. Another important aspect is the close collaboration with microbiologists, who must promptly notify the isolation of contaminants.

In this study, the positivity rate of blood cultures in patients with pneumonia was very low (4/81; 4.9%), confirming the data reported in the literature; furthermore, an MDRO was isolated in none of the 4 positive patients [30-32]. These results can be explained by the low propensity of pneumonia to give bacteremia, and by the fact that the microorganisms normally involved in pneumonia, especially community-acquired, are in most cases sensitive to the common antibiotics used in empirical therapy. A recent study showed that in 456 patients hospitalized for pneumonia, blood culture positivity was 6.6%, only half of which was actually attributable to lung infection, and in just 2 cases (0.4%) the isolated bacterium was MDRO [33]. Furthermore, an adequate therapeutic change following the result of blood cultures was observed only in about 2% of cases. The authors conclude that the collection of blood cultures should not be routinely recommended even in the case of severe community and hospital-acquired pneumonia. The current IDSA/ATS guidelines recommend performing blood cultures only in patients hospitalized with severe CAP or who are at risk of MRSA or *Pseudomonas aeruginosa* infections [34]. Similar considerations can be made for patients with cellulitis, which only rarely yield positive blood cultures, as confirmed by our results [35, 36].

Conversely, a significantly higher positivity rate was observed when blood cultures were performed in patients with urinary (31%) and abdominal (26.1%) infections. In these patients, 5 MDRO were isolated, allowing doctors to provide targeted antibiotic treatment. These results are in agreement with the literature reports [30, 37].

A suggestion provided by the data of the present study is to consider the presence of one or more risk factors for MDRO infection as a predictor of blood culture positivity. This result can be explained by the more frequent occurrence of bacteremia in immunosuppressed or device-carrying patients [38]. However, targeted studies with a higher number of patients are needed to verify these data.

Another factor that negatively influences the yield of blood cultures is the beginning of antibiotic therapy before blood sampling [29]. In the present study over 40% of blood cultures were collected in patients already on antibiotic therapy. The antibiotic exposure was associated with lower blood culture positivity rate, but the difference was not statistically significant probably due to the relatively low number of cases. In a recent study, analyzing 576 blood cultures from 363 patients hospitalized in a medical area, the absence of a recent antibiotic therapy is resulted to be the most highly predictive clinical feature of blood culture positivity (7.2% vs 1.4%) [21]. It is not easy to increase the percentage of blood cultures collected in the absence of antibiotic exposure, because most patients start antibiotics before entering the hospital. However, some improvements can be achieved by adopting strict blood culture collection procedures prior to the administration of antibiotics in emergency and internal medicine departments.

In this study, the positivity of blood cultures was not associated with a significant increase of length of hospital stay. In-hospital mortality was surprisingly lower in patients with positive blood cultures (0 deaths in 18 patients) than in those with negative cultures (9 deaths in 136 patients), but the study was not designed for this purpose and

it is not appropriate to draw reliable conclusions. However, we can hypothesize that the availability of an antibiogram allow to establish an effective targeted therapy that could determine positive effects on mortality rate, as recorded in a recent study [39].

The prospective design of the study made it possible to produce reliable results on an important clinical topic such as the yield of blood cultures in patients admitted to Internal Medicine. These data highlight the current low clinical yield of blood cultures and strongly suggest the need for studies aimed at identifying predictive factors of positivity. A limitation of this study is that it has been conducted in a single center with a relatively small number of patients. The data obtained are in any case in agreement with those obtained in other studies and we believe that they can be generalized with good approximation to other departments of Internal Medicine (10-13, 20, 27).

CONCLUSIONS

The results of this study indicate that blood cultures are ordered in a high percentage (about 25%) of patients admitted to an internal medicine department but that their clinical impact is quite low. To increase their yield and clinical impact, blood cultures should not be ordered in patients with very low pre-test probabilities. To this end, it will be necessary to accurately identify reliable predictive factors of positivity through *ad hoc* studies.

Conflicts of interest: none

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