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Readmissions for Recurrent Sepsis: New or Relapsed Infection?

Kimberley M. DeMerle, MD¹, Stephanie C. Royer, MD^{2,3}, Mark E Mikkelsen, MD, MS⁴, and Hallie C. Prescott, MD, MSc^{1,5}

¹Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

²Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

³Department of Internal Medicine, University of Cincinnati Medical Center, Cincinnati, OH, USA

⁴Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁵VA Center for Clinical Management Research, Ann Arbor, MI, USA

Abstract

Objective—Sepsis hospitalizations are frequently followed by hospital readmissions, often for recurrent sepsis. However, it is unclear how often sepsis readmissions are for relapsed/recrudescent versus new infections. The aim of this study was to assess the extent to which 90-day readmissions for recurrent sepsis are due to infection of the same site and same pathogen as the initial episode.

Design—Retrospective cohort study.

Setting—University of Michigan Health System.

Patients—All hospitalizations (May 15, 2013 to May 14, 2015) with a principal ICD-9-CM diagnosis of septicemia (038.x), severe sepsis (995.92) or septic shock (785.52), as well as all subsequent hospitalizations and sepsis readmissions within 90 days. We determined organism and site of sepsis through manual chart abstraction.

Interventions—None

Measurements and Main Results—We identified 472 readmissions within 90 days of sepsis, of which 137 (29.1%) were for sepsis. In sepsis readmissions, the site and organisms were most commonly urinary (29.2%), gastrointestinal (20.4%), gram negative (29.9%), gram positive (16.8%) and culture negative (30.7%). 94 (68.6%) readmissions were for infection at the same site as initial sepsis hospitalization. 19% of readmissions were confirmed to be same site and same organism. However, accounting for the uncertainty from culture-negative sepsis, as many as 53.2% of readmissions could plausibly be due to infections with both the same organism and same site.

Conclusions—Of the patients readmitted with sepsis within 90 days, two thirds had infection at the same site as their initial admission. Just 19% had infection confirmed to be from the same site

and organism as the initial sepsis hospitalization. Half of readmissions were definitively for new infections, while an additional 34% were unclear since cultures were negative in one of the hospitalizations.

Keywords

sepsis; hospital readmission; outcomes

Introduction

Sepsis is a common and costly reason for hospitalization that is associated with poor long-term outcomes(1,2). While patients increasingly survive initial hospitalization for sepsis, they go on to experience high rates of healthcare utilization and medical set-backs in the following year, especially in the first 90 days after discharge(3). Hospital readmission is particularly common, with rates of 90-day readmission ranging from 30% to >40%(4–6). High readmission rates after sepsis have been seen in a variety of settings, suggesting that the problem is not unique to any particular healthcare system(3,5,7)

Infection, particularly sepsis, is a leading cause of hospital readmission after sepsis (6–8). The high rate of subsequent infection may be due to variety of factors, including sepsis-induced immunosuppression(9), co-morbidities common in sepsis patients that predispose one to infection(10), genetic variations that pre-dispose patients to infections(11), or microbiome disruption during initial sepsis hospitalization (12). Indeed, recent studies indicate the gut microbiome may be severely deranged during critical illness, and at risk for transformation into infection in the event of physiologic stress(13).

Despite the importance of readmissions for recurrent sepsis, it remains unclear if these hospitalizations are predominantly due to relapse or recrudescence of the initial infection versus development of new infection. This distinction is important because it has fundamental implications for how we might address the problem. The primary aim of this study was to determine the extent to which 90-day readmissions for recurrent sepsis are due to infections with (1) the same versus a different site, and (2) the same versus a different primary organism.

Materials and Methods

We reviewed adult sepsis hospitalizations at the University of Michigan Health System (UMHS) from two calendar years (May 15, 2013 to May 14, 2015). UMHS is a tertiary referral academic center with 724 beds and approximately 47,000 inpatient hospitalizations yearly. This study was approved by the University of Michigan IRB (HUM00103891).

Recurrent Sepsis Hospitalizations

We identified all sepsis hospitalizations at UMHS during the study period using an electronic query tool (DataDirect(14)). Specifically, we identified all medical and surgical inpatients 18 years with a principal International Classification of Diseases (ICD-9-CM) diagnosis of severe sepsis (995.92), septic shock (785.52), or septicemia (038.X). We used

this method for identifying sepsis hospitalizations because it is highly specific, and we sought to study patients with a high likelihood of having sepsis(15).

After identifying the cohort of sepsis hospitalizations, we identified all subsequent UMHS hospitalizations within 90 days of discharge. We selected 90-day readmissions because, while performance measures focus on 30-day readmissions, 90-day readmissions are clinically relevant because sepsis patients remain at heightened risk of readmission beyond 30 days(3). Moreover, we hypothesized that infections up to 90 days after sepsis may be causally associated with the initial sepsis hospitalization since microbiome disruption persists for up to several months following antibiotics(12,16,17). Furthermore, while not included in the most recent IDSA guidelines(18), pneumonia within 90 days of hospitalization was previously called health-care associated pneumonia(19) because of the higher rate of multi-drug resistant organisms seen within 90 days of hospitalization.

We classified each 90-day readmission as being due to sepsis versus other causes based on review of all ICD-9-CM codes and structured chart review. We reviewed all readmissions that could plausibly be for sepsis—those with any ICD-9-CM code for infection or infectious signs/symptoms (e-Figure 1). This ensured that we were able to capture readmissions for sepsis, even if sepsis was unrecognized or uncoded(15). This data was gathered prior to publication of the Sepsis-3 definition(20). Therefore, during chart review, sepsis was confirmed by the presence of infection in the setting of two or more Systemic Inflammatory Response Syndrome (SIRS) criteria with or without end organ damage(21,22).

The focus of our study was readmissions for sepsis within 90 days after index hospitalization for sepsis, and we refer to sepsis admission-readmission pairs as a “dyad” of sepsis hospitalizations. We abstracted cohort demographics, co-morbidities, and mortality for using DataDirect. We calculated a weighted Charlson co-morbidity index using the ICD-9-CM codes from the hospitalization claim(23,24). All hospital admission notes at UMHS include a co-morbidity screen to ensure that relevant co-morbidities get captured as billing diagnoses.

Characteristics of Infections during Sepsis Readmission and Initial Sepsis Hospitalization

Through structured chart review and chart abstraction, the etiology (organism and site) of sepsis was determined for both the readmission and initial hospitalization. (e-figure 1, e-table 1). We classified infectious organisms as gram positive, gram negative, *Clostridium difficile*, polymicrobial, viral, yeast or culture-negative. We defined same organism by the genus and species of bacteria identified on culture. During the study period, the following microbial studies were standard at UMHS: bacteria, fungal, and AFB cultures of blood, urine, and sputum; respiratory virus Polymerase Chain Reaction(PCR), *Legionella pneumophila* and *Streptococcus pneumoniae* urine antigen, *Clostridium difficile* ELISA with PCR confirmation. We classified infection site as respiratory, urinary, gastrointestinal, skin and soft tissue, central nervous system, multiple infection sites, neutropenic fever, central line, or not determined. For the main tables, we report infectious organisms and sites with fewer than 5 observations as “other”. We also abstracted the patient’s immune status(25). While all patients surviving sepsis hospitalization likely have some degree of immunosuppression(25), we classified patients as immune-compromised if they were

receiving immunosuppressive medications, chemotherapy, or had a bone marrow transplant within 2 years. We considered readmissions within 30 days of discharge to be early readmissions, and those in days 31–90 to be late readmissions (e-figure 2).

Statistical Analyses

We present patient and hospitalization characteristics as mean (SD), median (IQR), or number (%). We compared characteristics of infection during readmission versus index sepsis hospitalizations using McNemar's test for paired data(26).

We determined the proportion of sepsis dyads that were same site, same pathogen (same genus and species on culture), both same pathogen and same site, and at least one culture negative. We considered recurrent sepsis to be due to a new infection if site and/or pathogen was different versus relapse/recurrence of infection if both site and pathogen were the same. We chose to define infections secondary to the same site and same organisms as a relapse or recrudescence of the initial infection to recognize that this could occur due to complete resolution and relapse, or low-level persistence of infection and subsequent recrudescence of clinical symptoms.

For our primary analysis, we included all dyads and considered the readmission to be for relapse/recurrence of infection only if cultures confirmed the same organism during both hospitalizations. However, because cultures were negative in 45% of sepsis hospitalizations, we also performed two sensitivity analyses. First, we determined the proportion of recurrent sepsis hospitalizations that were for new infection if (a) culture negative dyads were considered new infection and (b) the culture negative dyads were considered relapsed/recurrent infection to see the plausible range of estimates. Second, we examined just the dyads with whose infectious organism was identified by culture during both hospitalizations. We conducted all analyses with Stata IC version 13 (StataCorp, College Station, TX). We used two-sided hypothesis testing and set significance at $p<0.05$.

Results

Characteristics of Patients with a 90-Day Readmission for Sepsis

We identified 472 readmissions within 90-days of 1850 index sepsis hospitalizations, for a 90-day readmission rate of 29.7% (Figure 1). Of these 90-day readmissions, 137 (29.1%) were for sepsis; 127 of these readmissions had a principal diagnostic code for sepsis, severe sepsis or septic shock, while an additional 12 sepsis readmissions were included based on chart review of all readmissions containing any diagnostic code for infection. 79 (57.7%) of readmissions were early, and 58 (42.3%) were late. The average patient with recurrent sepsis hospitalization was an older (mean 63 years), male (56.9%), with co-morbidities (median Charlson score 1). Approximately one in four patients were immune-compromised (Table 1).

Etiology of Recurrent Sepsis

The site of infection during sepsis readmission was commonly urinary ($n=40$, 29.2%), gastrointestinal ($n=28$, 20.4%), respiratory ($n=27$, 19.7%), or skin and soft tissue ($n=14$,

10.2%). 12 sepsis readmissions had infection at multiple sites, including urinary/gastrointestinal, urinary/respiratory, urinary/skin and soft tissue, and urinary/respiratory/gastrointestinal. The culprit organisms during sepsis readmission were commonly gram negative (n=41, 29.9%), gram positive (n=23, 16.8%) or *Clostridium difficile* (n=10, 7.3%) (Table 2). 42 readmissions were culture-negative. The most common sites of culture-negative sepsis were pneumonia (n=13, 30.9%), gastrointestinal (n=7, 16.7%) and urinary (n=6, 14.3%). There were no statistically significant differences in infectious etiology between early and later readmissions.

Site, Organism and Overall Concordance among Dyads

The site of sepsis was the same in 94 (68.6%) of the dyads (Table 3). Of these, 37 (39.7%) were urinary, 17 (18.0%) were gastrointestinal, 15 (15.9%) were respiratory, and 10 (10.6%) were skin and soft tissue. Of the 31 dyads with discordant sites, the most common sites of infection at readmission were gastrointestinal and respiratory (both n=9, 29.0%).

Gram positive infections were less common among readmissions ($p=0.03$). There was a numeric increase in culture-negative and *Clostridium difficile* sepsis in readmissions, neither of which met statistical significance ($p=0.47$ and $p=0.29$, respectively). The rate of gram negative and polymicrobial sepsis was similar between initial and recurrent sepsis hospitalizations (table 2).

The causative organism was different in 34.3% of the admission-readmission dyads (Table 3), while 45.9% of the dyads were culture negative for at least one hospitalization. Just 27 (19.7%) sepsis readmissions were definitively due to the same organism. Of the 27 readmissions for the same culprit organism, 12 (8.7%) were for gram negative infections and 8 (5.8%) were gram positive infections. (e-table 5). Of 74 dyads with positive cultures during both admissions, 47 (63.5%) were different organism and 27 (36.5%) were same organism (e-table 3).

There were 47 (34.3%) dyads that were same or unknown site; however, 38 (27.7%) had at least one culture negative admission (table 4). Therefore, we were unable to confirm new versus relapse/recrudescence of the original infection. Taking into account the uncertainty from the culture-negative dyads, 34–80% of the dyads had different organisms and 19–65% had the same organism. Only 26 (19%) of the admission-readmission dyads were definitively due to both the same site and same organism. But, given the uncertainty from the culture-negative dyads, as many as 53.2% of readmissions could have been for same site and same organism if all culture-negative readmissions were actually for the same organism (table 4).

Outcomes by Readmission Status

Of 1588 patients discharged alive from sepsis hospitalization during the two-year study period, 12.1% died within the next 90 days. Patients with a 90-day readmission had 13.6% 90-day mortality, versus 11.5% 90-day mortality in patients without a readmission, $p=0.24$. 90-day readmissions for sepsis, however, were associated with 21.2% mortality, compared 10.5% 90-day mortality in patients readmitted for non-sepsis diagnoses, $p=0.002$.

Discussion

In this study, we found that approximately two thirds of recurrent sepsis hospitalizations were due to infection at the same site as the initial sepsis hospitalization. One in five were confirmed by positive culture data to be due to infections from both the same site and same organism as the initial infection. Overall, our findings expand our understanding of sepsis readmissions by demonstrating that the majority (ranging from approximately 50–80%) of recurrent sepsis admissions were not for recrudescence or relapse of the patient's initial infection, but rather a new infection.

Our study re-confirms that both infection and sepsis are important causes of hospital readmission(3,5,7). Although several studies have evaluated readmission after sepsis hospitalizations, few studies have specifically examined the cause of infection in recurrent sepsis hospitalizations. Ortego *et al.* found that about half of 30-day readmissions following sepsis were secondary to infection, most commonly skin/soft tissue and respiratory(27). In Prescott *et al.*, 6.4% of sepsis survivors had a 90-day readmission for sepsis(6). However, neither Ortego *et al.* nor Prescott *et al.* characterized whether readmissions were secondary to new infection versus persistence of the initial infection.

We hypothesize that the high proportion of sepsis readmissions due to new infection (new site and/or new organism) in our study reflects an impaired host response, both after sepsis and from impairment of the gut microbiome after antibiotics. Clinical and animal models have demonstrated suppression of both the innate and adaptive immunity after sepsis(9,25). Furthermore, longer duration of antibiotics may increase risk for infection-related readmission(7), by altering the microbiome and thereby impairing host defense. However, up to one half of readmissions in both our study and in Sun et al. were due to the same infection as the initial hospitalization. This suggests that shortening antibiotic duration for all patients is not a tenable solution either. Rather, future work must examine how to tailor antibiotic treatment duration to specific patients and specific infections, such that the infection is effectively treated with the least disruption to the microbiome.

Even though a large proportion of recurrent sepsis infections are not simply a relapse of the same infection, the index infection may still be directly predisposing the patient to subsequent infection in the same site. In our study, two thirds of recurrent sepsis hospitalization were due to infection at the same site and, among the 47 dyads that were confirmed discordant organisms, 65% were secondary to the same site as the initial sepsis hospitalization. Future work should be done to identify risk factors for infection-related readmissions after sepsis. The local effects of sepsis, including both microbiome and anatomic disruption, may be contributing factors to recurrent infection at the same site. For example, in critical illness, hypoperfusion and subsequent reperfusion of the intestinal mucosal frequently causes bacterial translocation, and thus a risk factor for recurrent infection(28). Another potential risk factor that should be further investigated is the presence of underlying disease that may predispose patients to developing infection at the same site such as persistent nidus of infection, barrier to infection clearance, or prior indwelling catheters, intravenous lines or invasive procedures. Additionally, variations in a patient's DNA may create a phenotype that predisposes patients to sepsis(11).

One prior study by Sun *et al.* found that half of infection-related readmissions after sepsis were due to a new infection, while half were due to the same infection(7). While our study demonstrated only about one fifth of readmissions were confirmed to be secondary to persistence/recrudescence of the original infection, there was uncertainty in culture negative admissions. It is possible that as many as half of sepsis readmissions could be same site and same organism, if culture-negative dyads were indeed the same organisms. Similar to our study and prior studies(29–32), Sun *et al.* found 37.2% of index sepsis admissions were culture negative. However, in Sun *et al.* the categorization of new versus recurrent infection was handled differently. The cases of culture negative index admissions and culture positive infection readmissions were classified as new infections, whereas we considered these uncertain. Like our study, Phua *et al.* demonstrated that a common cause of culture-negative sepsis is pneumonia(29). With the growing use of culture-independent techniques, it may be possible to uncover the etiology of culture-negative sepsis to provide further insight on management, especially use and length of broad-spectrum antibiotics. An alternative explanation, which requires dedicated study, is whether readmission after sepsis leads clinicians to more commonly anchor on infection as the cause of re-hospitalization, manifesting as culture-negative sepsis. If found to be partially correct, many sepsis survivors may be exposed unnecessarily to subsequent antibiotics.

In this study, age, major co-morbidities, use of intensive care unit, and use of mechanical ventilation were similar between patients with no readmission, sepsis readmission, and non-sepsis readmission. However, mortality was significantly higher in patients readmitted for sepsis compared to both patients with no readmission and patients readmitted for a non-sepsis diagnosis. This finding supports the hypothesis that recurrent infection may be an important (and potentially modifiable) mediator of the excess late mortality experienced by sepsis patients(33).

Our study has several limitations. First, the study population is drawn from a single center, so may not generalize to all patients with recurrent sepsis hospitalizations. Secondly, we relied on explicit ICD-9-CM claims and Sepsis-2 definitions to identify initial sepsis hospitalizations. We confirmed each case by chart review, so are highly confident that our cases were indeed sepsis. It is possible that we may have missed some index sepsis hospitalizations for which sepsis was not coded. However, we suspect the number of missed index sepsis hospitalizations is small as our review of all readmissions with any infection code yielded just 12 additional sepsis readmissions for our study sample. Furthermore, given the data was gathered prior to publication of the Sepsis-3 definition, there may have been differences in the patients that were captured. However, in a different study of a similar cohort of patients that were discharged from UMHS with the same principal diagnoses, we found that greater than 85% of these patients met criteria for sepsis-3 on admission. Third, we focused our study on causes of infection for readmissions within 90 days and a recent study demonstrates the risk for recurrent sepsis extends beyond 90 days from hospital discharge(34). We did not examine readmissions beyond 90-days and could not examine all risk factors for recurrent sepsis, such as antibiotic exposure during the index hospitalization(35). Fourth, we assessed the primary cause of infection during index and recurrent hospitalization, but did not evaluate recurrent sepsis within the same hospitalization. However, our finding that most recurrent sepsis hospitalizations are for new

infection is consistent a prior study showing that most episodes of recurrent sepsis within the same hospitalization are also due to a new infection(36). Lastly, because we did not have access to patients' records outside UMHS, recurrent sepsis hospitalizations at other institutions were missed.

Conclusions

Recurrent sepsis is a common cause of hospital readmission after sepsis. Our study demonstrates that, while two-thirds of recurrent sepsis hospitalizations had the same site of infection, just one fifth were confirmed to be the same site and same organism as the initial sepsis hospitalization. Half of all readmissions were definitively new infections (new site and/or new organism), while another third were unclassifiable due to culture negativity during one or both hospitalizations. Overall, after taking into account the uncertainty of culture negative sepsis hospitalizations, one half to four fifths of recurrent sepsis hospitalizations were for new infections (new site and/or new organism), while one fifth to one half were recrudescence/relapse of the same infection at the same site.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KMD and HCP acquired the data, designed the study, analyzed the data, interpreted the data, and drafted the manuscript. SCR and MEK interpreted the data and revised the manuscript critically for intellectual content. KMD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations

ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
SD	Standard deviation
SIRS	Systemic Inflammatory Response Syndrome
UMHS	University of Michigan Health System

PCR Polymerase Chain Reaction

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Figure 1. Identification of Study Cohort

*The specific focus within this study cohort is the 137 dyads of index admissions and 90-day readmissions for sepsis

Table 1

Characteristics of Patients with Recurrent Sepsis Hospitalization

Characteristics	Sepsis Readmissions N=137	No Readmission N=1116	Non-Sepsis Readmissions N=335
Age, median (IQR)	63 (52–71)	61 (47–72)	61 (50–70)
Race, N (%)			
<i>African American</i>	17 (12.6%)	134 (12.0%)	39 (11.6%)
<i>Caucasian</i>	118 (86.1%)	879 (78.8%)	267 (79.8%)
<i>Other</i>	2 (1.5%)	103 (9.2%)	29 (8.6%)
Male, N (%)	78 (56.9%)	613 (54.9%)	170 (50.8%)
Married, N (%)	72 (52.5%)	533 (49.6%)	172 (52.5%)
Charlson Index, Median (IQR)	1 (0–3)	1 (0–2)	0 (1–3)
<i>Congestive Heart Failure, N (%)</i>	30 (21.9%)	171 (15.3%)	57 (17.0%)
<i>Diabetes, N(%)</i>	29 (21.7%)	236 (21.1%)	81 (24.2%)
<i>Chronic Pulmonary Disease, N (%)</i>	29 (21.7%)	238 (21.3%)	83 (24.8%)
<i>Metastatic Solid Malignancy, N (%)</i>	19 (13.9%)	105 (9.4%)	27 (8.6%)
<i>Rheumatologic Disorder, N(%)</i>	11 (8.0%)	60 (5.4%)	18 (4.2%)
<i>Liver Disease, N(%)</i>	8 (5.8%)	75 (6.7%)	28 (8.4%)
90-Day Mortality, N (%)	29 (21.2%)	128 (11.5%)	35 (10.5%)
Intensive Care Unit, N (%)	49 (35.8%)	413 (37.0%)	130 (38.8%)
Mechanical Ventilation, N (%)	25 (18.3%)	206 (18.5%)	67 (20.0%)

Table 2

Characteristics of Infection in 137 Sepsis Admission-Readmissions Dyads

Characteristics	Index Hospitalization (n=137)	Readmission (n=137)	p-value
Organism, N (%)			
Gram Negative	40 (29.2%)	41 (29.9%)	0.99
Gram Positive	37 (27.0%)	23 (16.8%)	0.03*
Culture Negative	36 (26.3%)	42 (30.7%)	0.47
Polymicrobial	17 (12.4%)	14 (10.1%)	0.61
<i>Clostridium difficile</i>	5 (3.6%)	10 (7.3%)	0.29
Viral	2 (1.5%)	7 (5.1%)	0.18
Site, N (%)			
Urinary	50 (36.5%)	40 (29.2%)	0.03*
Gastrointestinal	26 (18.9%)	28 (20.4%)	0.79
Respiratory	21 (15.3%)	27 (19.7%)	0.21
Skin and Soft Tissue	14 (10.2%)	14 (10.2%)	0.99
Multiple Sites	12 (8.8%)	12 (8.8%)	0.99
Other	7 (5.1%)	9 (6.6%)	0.63
Not Determined	7 (5.1%)	7 (5.1%)	0.99

Table 3

Concordance of Infection Characteristics in Initial versus Recurrent Sepsis Admission

Concordance of Infection Characteristics	Dyads n=137
Organism Concordance, N (%)	
Different Organism	47 (34.3%)
Same Organism	27 (19.7%)
At least one culture negative	63 (45.9%)
Both culture negative	15 (10.9%)
Culture Negative/Organism Present	21 (15.3%)
Organism Present/Culture Negative	27 (19.7%)
Site Concordance, N (%)	
Same Site	94 (68.6%)
Different Site	31 (22.6%)
Unknown Site	12 (8.7%)

Table 4

Index Admission-Readmission Dyads for Organism and Site causing Sepsis

Organism Causing Sepsis (n=137)	Site of Sepsis (n=137)		
	Different Site N=31	Same Site N=94	Unknown N=12
Different Organism, N(%)	14 (10.2%)	30 (21.9%)	3 (2.2%)
Same Organism, N(%)	0 (0%)	26 (19.0%)	1 (0.7%)
Both Culture Negative, N(%)	1 (0.7%)	11 (8.1%)	3 (2.2%)
Culture Negative /Organism Present	10 (7.3%)	10 (7.3%)	1 (0.7%)
Organism Present /Culture Negative	6 (4.4%)	17 (12.4%)	4 (2.9%)

Dark grey cells represent dyads with new infection (N=64, 46.7%); light grey cells represent dyads for whom infection may have been new or may have been a relapse/recrudescence (N=47, 34.3%); the white cell represents dyads with relapsed/recurrent infection (N=26, 19.0%).