

Influenza A Outbreak in an Ambulatory Stem Cell Transplant Center

Senu Apewokin,¹ Keyur Vyas,² Laura K. Lester,^{6,7} Monica Grazzuiti,¹ Dirk T. Haselow,⁷ Frankie Wolfe,³ Michelle Roberts,³ William Bellamy,⁴ Naveen Sanath Kumar,¹ Dolris Hunter,¹ Jeannette Lee,⁵ Jennifer Laudadio,⁴ J. Gary Wheeler,⁷ and Robert Bradsher²

¹Myeloma Institute for Research and Therapy, ²Division of Infectious Diseases, ³Infection Control, Department of Nursing, and Departments of ⁴Pathology and ⁵Biostatistics, University of Arkansas for Medical Sciences, Little Rock; ⁶Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; and ⁷Arkansas Department of Health, Little Rock

Background. In the era of cost-consciousness regarding healthcare, provision of medical services in an outpatient setting has become increasingly attractive. We report an influenza outbreak in an ambulatory stem cell transplant center in 2013 that highlights unique identification and infection control challenges in this setting.

Methods. Nasopharyngeal swabs were performed on patients with suspected influenza-like illnesses (ILI), defined by subjective fever or measured temperature of $\geq 37.7^{\circ}\text{C}$ ($\geq 100^{\circ}\text{F}$) with cough or sore throat during July 25, 2013 through August 7, 2013. In addition, testing was triggered by an elevated C-reactive protein (CRP). Specimens were analyzed by using eSensor Respiratory Viral Panel. Clinical and epidemiologic information was collected in real time, and frequencies were calculated on demographics, baseline clinical parameters, treatment methods, comorbidities, and symptoms of affected persons.

Results. Thirty-one patients had influenza A (H3N2) infection during July 25, 2013 through August 7, 2013. Only 7 patients (23%) met the Centers for Disease Control and Prevention and Council of State and Territorial Epidemiologists ILI case definition. Twenty-five patients (81%) had received ≥ 1 transplant, with 13 (42%) having occurred within 1 year before the outbreak. Twenty-five patients (81%) had received B-cell active chemotherapy <60 days before influenza diagnosis, 6 (19%) were neutropenic, and 25 (81%) lymphopenic. Among clinical and laboratory markers analyzed, abnormal CRP was the most sensitive screening tool for influenza. Twelve (39%) patients were hospitalized (median stay, 10 days; range, 2–20). No deaths occurred.

Conclusions. Immunocompromised hosts with influenza have atypical presentations. Existing surveillance case definitions might be insufficient to reliably identify influenza outbreaks in such patients.

Keywords. ambulatory; C-reactive protein; hematopoietic stem cell transplantation; influenza A; vaccination.

BACKGROUND

Medical advances and the need for cost-saving initiatives have increased the appeal of outpatient procedures, including stem cell transplantation. Consequently, the

scope of services provided by ambulatory centers is rapidly expanding to include services that were previously provided only in an inpatient setting. Stem cell transplantation, which has largely replaced bone marrow transplantation as the primary modality for treating certain hematologic malignancies, is now performed at ambulatory chemotherapy infusion centers. Unfortunately, infection control guidelines specific to ambulatory transplant centers do not exist; therefore, measures designed for inpatient transplant units are frequently adopted but often impractical to implement. Existing infection control measures might meet the majority of traditional cancer chemotherapy infusion centers' needs, but whether these measures are equally effective in centers that perform ambulatory stem cell transplantation is unclear.

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Correspondence: Senu Apewokin, MD, Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, 4301 W. Markham Rd., Ste #816, Little Rock, AR 72205 (skapewokin@uams.edu).

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Influenza outbreaks in the healthcare setting are not uncommon [1], but outbreaks in outpatient centers pose unique challenges for infection control personnel, especially when they involve immunocompromised patients. We report an off-season influenza outbreak in an ambulatory stem cell transplant center, highlight unique challenges posed by such patient populations for influenza prevention, and outline measures undertaken to control the outbreak.

The outbreak was first recognized by infection control personnel when a cluster of positive influenza A polymerase chain reactions (PCR) were reported in patients receiving care at the Myeloma Institute of Research and Therapy (MIRT) at the University of Arkansas for Medical Sciences (UAMS) by the molecular laboratory starting on July 25, 2013. Because this was uncharacteristic for that time of the year and no influenza activity had been reported by the Centers for Disease Control and Prevention (CDC) (FluView, available at <http://www.cdc.gov/flu/weekly/>), case identification and tracking were initiated by an investigation team comprising infectious disease (ID) physicians and infection control personnel.

MATERIALS AND METHODS

The MIRT at the UAMS is a referral center where patients with hematologic malignancies, particularly B cell-related malignancies, are treated. The majority (>90%) of the institute's 300–500 stem cell transplants performed annually are for an underlying diagnosis of multiple myeloma (MM). Patients typically are treated according to total therapy protocols with induction, conditioning for stem cell transplant recipients, consolidation, and maintenance performed, as previously described [2–4]. Patients come from Arkansas as well as other states and nations. The majority of the stem cell transplantations performed are autologous and occur in an outpatient setting that has the capacity to accommodate 180 visits daily. Transplant-ineligible patients also receive their care at this center. The center has 14 private rooms, 10 infusion pods that accommodate 4 seated patients each, and 1 pod that accommodates 6 patients (ie, total of 42 chairs and 14 beds). The waiting area seats 89 patients in a 2347-square-foot space. A refreshment stand and 8 computers are provided for patient use while awaiting care. High-efficiency particulate absorption (HEPA) air filtration is not provided in any of the waiting or patient care areas. Patients who experience complications during their treatment course in the ambulatory setting are admitted for continued care in the inpatient setting.

Case Definition and Laboratory Testing

Testing for influenza was not only symptom-driven but was also triggered by elevated C-reactive protein (CRP), which is assessed daily as part of routine care for all patients treated at MIRT. A nasopharyngeal swab was performed on all patients suspected of having influenza-like illness (ILI) or an elevated

CRP (>10 mg/L) on or after July 25, 2013. Influenza-like illness was defined as subjective fever or measured temperature of $\geq 37.7^{\circ}\text{C}$ ($\geq 100^{\circ}\text{F}$) with cough or sore throat, consistent with CDC and the Council of State and Territorial Epidemiologists (CSTE) surveillance definition for ILI. Testing was subsequently expanded to include employees and family members with ILI. Any patients in other areas of the hospital who had ILI were also subject to testing. All specimens were analyzed by the UAMS Department of Pathology's molecular diagnostics laboratory by using the eSensor Respiratory Viral Panel (RVP) (GenMark Dx, Carlsbad, CA). This assay is a qualitative nucleic acid multiplex diagnostic test that provides for the simultaneous identification of multiple respiratory viral pathogens, including the following: influenza A virus, influenza A virus (H1) seasonal subtype, influenza A virus (H3) seasonal subtype, influenza A virus 2009 pandemic (H1N1) subtype, influenza B virus, respiratory syncytial virus subtype A or subtype B, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, human metapneumovirus, human rhinovirus, adenovirus species B/E, and adenovirus species C. Because of the unusual timing of influenza, samples were repeated to confirm positivity by PCR both at UAMS and the Arkansas Department of Health (ADH). Information regarding demographics, baseline clinical parameters, treatment modalities, comorbidities, and symptoms were collected by using a standardized interview form and clinical chart abstraction. This investigation was reviewed by CDC for human subjects protection and deemed to be public health practice.

Statistical Analysis

Frequencies of the collected data were calculated, and graphic representations demonstrating the outbreak were created by using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) and Epi Info 7 (CDC, Atlanta, GA).

RESULTS

Thirty-one patients, 1 employee, and 4 family members tested positive for influenza A (H3N2) by the RVP among 124 persons tested during July 25, 2013 through August 7, 2013. Of the persons tested, 98 (79%) had received care in the outpatient transplant center, and positive results were only found among these. The characteristics of the 31 patients who tested positive are displayed in Table 1 and associated comorbidities in Table 2. The majority of these patients were male (22; 71%) and aged >60 years (21; 68%), typical of the demographics of the center's myeloma patient populations. The primary underlying cancer was MM in 26 (84%) of these patients, whereas lymphoma was present in 3 (10%) and acute myelogenous leukemia in 1 patient (3%). Fourteen (45%) patients had received influenza vaccination during the prior year. Twenty-five patients (81%) also had received at least 1 transplant, and 13 (42%) of these had been transplanted <1 year before the outbreak. Twenty-five patients

Table 1. Demographics and Baseline Characteristics of Influenza Patients (n = 31)

Characteristics	No. (%) ^a
Sex	
Female	9 (29.0)
Male	22 (71.0)
Age (yrs)	
<50	2 (6.5)
50–59	8 (25.8)
60–69	12 (38.7)
≥70	9 (29.0)
Race	
Black	9 (29.0)
White	22 (71.0)
Primary diagnosis	
AML/GVHD	1 (3.2)
Lymphoma	2 (6.5)
MALT lymphoma	1 (3.2)
MM	26 (83.9)
Unknown	1 (3.2)
CRP	
<10	9 (29.0)
10–49	11 (35.5)
50–99	6 (19.4)
≥100	4 (12.9)
Unknown	1 (3.2)
ALC	
<500	25 (80.6)
500–999	5 (16.1)
1000–1499	1 (3.2)
ANC	
<500	6 (19.4)
500–999	7 (22.6)
1000–1499	3 (9.7)
≥1500	15 (48.4)
Number of transplants before influenza diagnosis	
1	17 (54.8)
2	6 (19.4)
≥3	2 (6.5)
None	6 (19.4)
Number of days from prior chemo cycle to influenza diagnosis	
0	3 (9.7)
1–6	5 (16.1)
7–13	8 (25.8)
14–20	4 (12.9)
21–29	3 (9.7)
30–59	5 (16.1)
60–89	1 (3.2)
≥90	2 (6.5)
Chronic steroid treatment ^b	18 (58.0)
Vaccinated during 2012–2013 influenza season	14 (45.2)

Table 1 continued.

Characteristics	No. (%) ^a
Smoker	7 (22.6)
Lower respiratory tract infection ^c	9 (37.5)

Abbreviations: ALC, absolute lymphocyte count; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; CRP, C-reactive protein; GVHD, graft-versus-host disease; MALT, mucosa-associated lymphoid tissue; MM, multiple myeloma.

^a Data are presented as no. (%) unless otherwise indicated.

^b Mean minutes dose of 0.3 mg/kg per day of prednisone equivalent for >3 weeks.

^c Only 24 patients had complete information.

(81%) had received B-cell active chemotherapy <60 days before their influenza diagnosis, and 6 (19%) were neutropenic. Four of 6 nontransplant patients identified had other underlying immunosuppressive states (eg, hepatitis C with no cirrhosis, human immunodeficiency virus infection, chronic renal failure, or diabetes). The symptom distribution reported by the influenza-positive patients is illustrated in Figure 1. The most common symptom at the time of presentation was cough (17; 55%), followed by sinus congestion (13; 42%). Fever was uncommon and was documented in only 8 (26%) patients and subjectively reported in 6 (19%) patients. Shortness of breath was present in 6 (19%) patients. A majority (21; 68%) of these patients also had elevated CRP values, in spite of ongoing corticosteroid therapy, which triggered testing for infectious agents, including community respiratory viruses. Only 7 (23%) patients met the CDC-CSTE definition for ILI. Of those patients with complete evaluations that included radiologic studies, 9 of 24 (37.5%) developed lower respiratory tract disease defined by the presence of new radiological abnormalities and/or oxygen saturation of 92% or less. Twelve (39%) patients were hospitalized in relation to their ILI symptoms for a median of 10 days (range, 2–20). Three patients required an intensive care unit stay, and although 1 of these patients required ventilatory support, that patient ultimately made a full recovery and was discharged. The timeline of the outbreak is displayed in Figure 2. All patients identified

Table 2. Comorbidities of Influenza Patients (n = 31)

Comorbidity	No. (%)
Renal insufficiency	8 (25.8)
Dialysis	3 (9.7)
Diabetes mellitus	2 (6.5)
Chronic obstructive pulmonary disease	2 (6.5)
Asthma	2 (6.5)
Human immunodeficiency virus	2 (6.5)
Hepatitis B	1 (3.2)

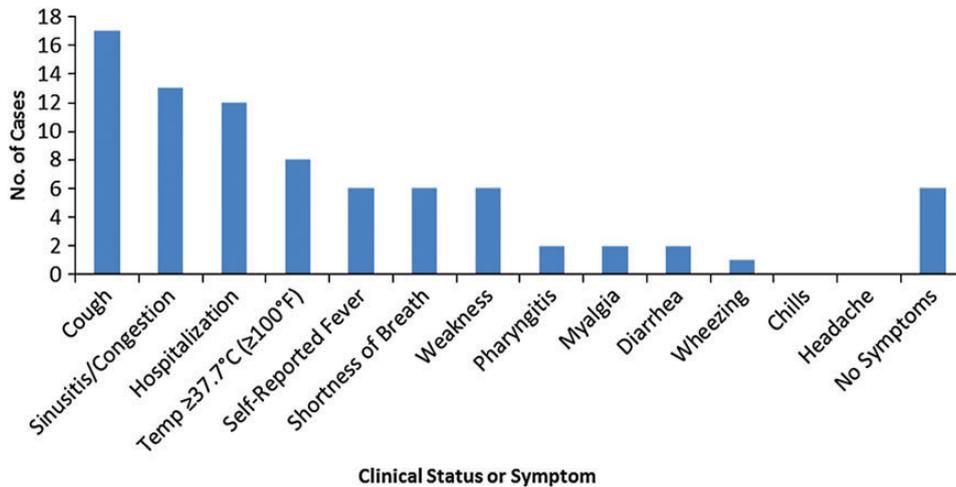


Fig. 1. Symptom distribution and clinical status for influenza A (H3N2) cases in cancer treatment center, July 25–August 7, 2013.

during the outbreak made a full recovery from the influenza infection and were in their usual state of health up to 5 months later. The involved employees and family members were asked to follow up with their primary physicians.

Outbreak Response

With the nonseasonal identification of influenza aiding early recognition of the outbreak, interventions were implemented to identify infected patients and limit spread to others. These interventions led to control of the outbreak within 14 days after identification of the first patient, with no spread to patients or staff in other clinics or areas of the hospital. No outbreak-attributable deaths occurred.

Institutional and local resources were enlisted early on, and such measures as patient cohorting, enhanced cleaning of waiting areas and transport shuttles, provision of personal protective equipment, and increased signage and supplies to encourage hand hygiene were instituted by the infection control team on the day the outbreak was discovered. Surgical masks were provided to all patients entering the center for the duration of the

outbreak. After identification of the outbreak, all physicians on the medical campus were alerted to remain vigilant for ILI and consider testing for respiratory viruses. Social distancing was facilitated by rescheduling all nonemergency transplantations and chemotherapy. Furthermore, satellite clinics were established for patients receiving maintenance therapy beginning on the day of the outbreak, continuing until no new cases had been reported for 1 month and existing cases had 2 documented negative RVPs ≥ 1 week apart. Patients who tested positive were treated with oseltamivir, whereas RVP PCR testing was done weekly until test negative. Given that this outbreak occurred midsummer, influenza vaccine and institutional oseltamivir stocks were limited; therefore, ADH provided oseltamivir from the state stockpile for all exposed family and staff. The center's molecular laboratory increased the number of RVP PCR runs from once daily to twice daily, including weekends, to enable rapid identification of cases. Arkansas Department of Health provided viral subtyping, and CDC assessed for antiviral resistance as well as susceptibility to the existing and forthcoming vaccine. The CDC also facilitated a partial distribution of the 2013–2014 influenza vaccines order to UAMS ahead of schedule by the manufacturer. Given the limited supply of vaccine available, personnel at high risk were identified, and vaccine was rapidly provided on location to all staff with close contact to MIRT patients on the bone marrow transplant unit, the outpatient transplant center, and other ancillary departments (eg, apheresis laboratories). Vaccination was encouraged and also made available for free by ADH for family members and caregivers of MIRT patients.

DISCUSSION

This report describes the rapid identification, investigation, and control of a nonseasonal outbreak of influenza A in an outpatient hematopoietic stem cell transplant (HSCT) population.

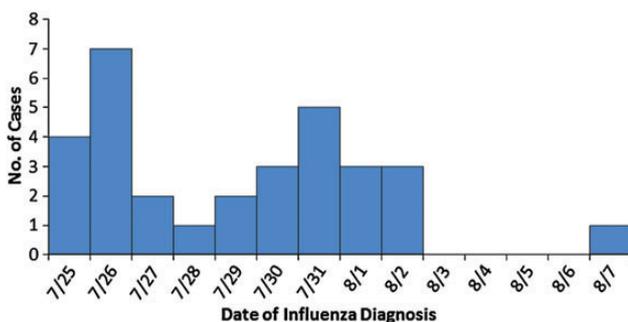


Fig. 2. Epidemiologic curve for influenza A (H3N2) cases in cancer treatment center, July 25–August 7, 2013.

After the outbreak was recognized, a task force comprising ID physicians, infection control practitioners, and clinical managers was formed, and vital interventions were instituted within hours. Advanced preparation of patient-specific protocols for such occurrences, as well as institutional experience during the 2009 influenza A pandemic, contributed to rapid outbreak control.

In addition, certain preexisting infrastructural components also enhanced the response. For example, clinical operations at MIRT were fully electronic and heavily dependent on mass communication through Listserv. All clinicians and key nursing staff were provided with smartphones on their day of hire. The availability of such communication tools permitted rapid implementation of directives as well as quick dissemination of information. These resources also permitted standardized collection of clinical and epidemiologic information in real time as the outbreak evolved. The team was therefore able to identify patterns quickly and allocate resources appropriately.

Only 1 employee contracted influenza as a result of this outbreak. This employee was placed on nonpunitive sick leave to reduce risk of transmission. The low attack rate observed among employees may be attributable to high vaccination coverage among employees during the prior year. For 2 consecutive years, the center instituted a mandatory influenza vaccination policy for all employees. Consequently, the institution's influenza vaccine coverage was 95.6% among 12 390 employees for the 2012–2013 influenza season. The only employee who contracted influenza during the outbreak had a medical exemption from influenza vaccination during the 2012–2013 season. This employee had a severe egg allergy and received vaccine when the hypoallergenic vaccine was unavailable at our institution. Selected control measures used to control the outbreak are outlined in Table 3.

Unique Challenges Facing Ambulatory Stem Cell Transplant Centers

Multiple factors likely facilitated the rapid containment and favorable outcomes observed. Early recognition of the outbreak was possible because of vigilance and surveillance provided by the infection control team. Respiratory viral illnesses are not uncommon among the center's patient population; however, the typical viruses identified during the summer months are parainfluenza, respiratory syncytial virus, and metapneumovirus. Influenza prevention measures among the general population might not be applicable to such populations as cancer patients, and our report highlights some of the elements clinicians need to take into account when developing protocols for prevention among such patients. Cancer patients are encouraged to get influenza vaccinations yearly, and vaccination has been demonstrated to provide adequate protection even for patients undergoing conventional cancer chemotherapy [5,6]. However, investigators have reported reduced vaccine efficacy among

Table 3. Factors Facilitating Rapid Containment of Influenza A (H3N2) Outbreak

<ul style="list-style-type: none"> • Existent mandatory influenza vaccination policy for all employees • Early recognition of outbreak by existent surveillance mechanisms • Ready availability of infectious disease/infection control expertise to direct response and existence of patient-specific protocols • Rapid communication and collection of clinical epidemiologic information in real time • Rapid institution of infection control measures (eg, enhanced cleaning and provision of personal protection equipment) • Increased social distancing by rescheduling of nonemergent chemotherapy and transplantation • Rapid initiation of oseltamivir prophylaxis • Enlisting of regional and national resources early in outbreak to characterize strain (eg, strain, subtype, susceptibility to antivirals, susceptibility existing and forthcoming vaccine) • Increasing inventory of oseltamivir and flu vaccine • Increasing laboratory resources to accommodate increased testing • Early provision of vaccines to high-priority staff and family members • Non-punitive sick leave for employees with influenza-like illness

specific cancer patient populations, particularly patients receiving rituximab (an anti-CD20 antibody) [7]. This drug targets B cells [8], a crucial component of the humoral immune system upon which vaccine strategies depend to generate an anamnestic response. Multiple myeloma results from an abnormal proliferation of B cells [17]; thus, myeloma therapy often targets these cells that happen to be the cornerstone of vaccine strategies. As expected, vaccine efficacy has been reported to be low among MM patients [9]. Furthermore, although CDC/Infectious Diseases Society of America recommends vaccination of HSCT recipients 6 months after their transplantation [6, 10], for patients such as those undergoing tandem transplantations for treatment of the underlying cancer, the treatment plan might not permit timely vaccine administration because of the need for multiple and frequent cycles of chemotherapy. Therefore, treating physicians on occasions resort to chemoprophylaxis, albeit not favored, as a prevention strategy during the influenza season [11]. Chemoprophylaxis-dependent strategies for influenza prevention depend on early recognition and timely implementation of vital interventions to be effective. However, vigilance for influenza during the summer months might be lower than during the typical influenza season.

Another infection control challenge that cancer patients face is optimal environmental engineering for outpatient care. Stem cell transplantation historically has been performed in closed bone marrow transplant units with restricted access. These units also typically have HEPA filtration and laminar airflow [12]; however, with increasing use of less immunosuppressive conditioning and the shift from bone marrow to HSCT, the need for such units, especially for autologous stem cell recipients, has reduced. Stem cell transplantation is frequently

being performed in the outpatient setting [13]. As a result of high pedestrian traffic in outpatient areas, social distancing is difficult to achieve, and, consequently, a high potential exists for droplet transmission. In this center, the inpatient unit houses 30 single-patient rooms and a maximum of 32 staff per shift in a 23 812-square-foot area, in contrast with the outpatient center that serves 120–150 patients daily and is staffed by 30–38 staff per shift in a 21 992-square-foot area. Thus, patient density, coupled with ongoing immunosuppression, creates ideal conditions for an outbreak such as this to occur. Evidence suggesting the potential for airborne transmission of viruses, such as influenza [1], raises questions as to whether ambulatory transplant centers are prone to airborne transmission in this manner. The lack of documented cases among patients outside the transplant center suggests that immunosuppression and outpatient clinic characteristics might have played a key role in this outbreak.

Of note, although a majority of the patients involved in the outbreak had normal white blood cell counts and absolute neutrophil counts >1000 cells/mm³, these patients were in all likelihood somewhat immunosuppressed because of recent receipt of corticosteroids, stem cell transplantations, ongoing myeloma treatment, and the high prevalence of low lymphocyte counts. T-cell recovery can take as long as 12 months among patients who receive HSCT [14] or considerably longer among patients receiving multiple transplantations. Persistent immunosuppression might also explain why typical influenza symptoms (eg, fever) were not common among these patients [15]. Relying solely on clinical symptoms or ILI case definitions that have been proposed by CDC [16], in this patient population would have impaired case detection because this strategy identified only 23% of cases. In contrast, CRP-guided screening was able to identify 68% of cases. A limitation of this investigation was that most of the patients tested were those receiving treatment at the ambulatory stem cell center where CRP is performed daily; consequently, cases outside of this setting might have been missed. Second, the unique nature of the patient population also might mean certain measures undertaken to contain the outbreak would not be feasible or generalizable to other patient populations.

CONCLUSIONS

In summary, influenza prevention among ambulatory cancer patient populations is challenging, and chemoprophylaxis-dependent strategies require availability and access to certain resources, including staff, information technology, laboratory, and pharmaceutical resources to be effective. Clinicians should also recognize immunosuppressive states among cancer patients and be cognizant of the limitations of symptom-dependent surveillance mechanisms for influenza case detection. Surveillance with laboratory markers (eg, CRP) and follow-up viral testing

among such patients seems to be a better strategy for case detection. Infection control vigilance should remain high outside of normal influenza seasons, even in centers that adopt mandatory vaccination policies for employees. Strategies to improve vaccine efficacy among immunocompromised patients also warrant exploration because chemoprophylaxis-dependent strategies are costly and prone to pitfalls. In addition, in practicing good infection control measures, the unique nature of ambulatory stem cell transplantation should be considered; specific guidelines for such patient populations are needed.

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