

Management bundles for candidaemia: the impact of compliance on clinical outcomes

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Objectives: The Mycoses Forum in Japan has developed management bundles for candidaemia to incorporate into bedside practice. The aim of this study was to investigate nationwide compliance with the bundles and their impact on clinical outcomes.

Methods: Non-neutropenic patients treated with antifungals for candidaemia were surveyed. Bundles consist of nine items to complete. Data were sent to the central office between July 2011 and April 2012.

Results: Six hundred and eight patients were analysed. The compliance rate for achieving all elements was 6.9%, and it increased to 21.4% when compliance was analysed by the bundle except for oral switch. There was a significant difference in clinical success between patients with and without compliance [92.9% versus 75.8% ($P=0.011$)]. Compliance with the bundles, however, failed to be an independent factor associated with favourable outcomes. When step-down oral therapy was excluded from the elements of compliance, compliance with the bundles was revealed to be an independent predictor of clinical success (OR 4.42, 95% CI 2.05–9.52) and mortality (OR 0.27, 95% CI 0.13–0.57). Independent individual elements contributing to clinical success were removal of central venous catheters within 24 h, assessment of clinical efficacy on the third to the fifth day and at least 2 weeks of therapy after clearance of candidaemia.

Conclusions: Compliance with the bundles for candidaemia had a beneficial effect on clinical outcomes. Promotion of the bundles approach may have the potential to narrow the gap between clinical evidence and bedside practice.

Keywords: candidiasis, guidelines, intravenous catheters, invasive disease, fungal infections

Introduction

Candidaemia is the fourth most common cause of nosocomial bloodstream infections¹ and invasive candidiasis has a significant impact on patient outcomes.^{2–4} In a review of randomized trials for the treatment of invasive candidiasis, overall mortality was 31.4% and the rate of treatment success was 67.4%.⁵ Despite advances in the recognition of high-risk patients with invasive candidiasis and drug development, the mortality associated with invasive candidiasis has not changed substantially. In the light of the medical need to analyse the scientific evidence and make recommendations, the IDSA⁶ updated the clinical practice

guidelines for the management of candidiasis in 2009. The ESCMID Task Force⁷ developed diagnostic and management/therapeutic guidelines for *Candida* diseases in 2012. In Japan, the Mycoses Forum Task Force published guidelines for the management of deep-seated mycoses in 2007.⁸

Although many guidelines have been published in a wide variety of areas of infectious diseases, the development of guidelines has not necessarily led to changes in clinical behaviour in a timely fashion. For integration into bedside practice, the development of bundles based on key recommendations is considered to be effective. The surviving sepsis campaign bundle is one of the most successful cases.^{9–11} Levy et al.¹⁰ described that the campaign was

associated with sustained, continuous quality improvement and a reduction of mortality rates in participating hospitals.

To introduce the appropriate management of candidaemia into bedside practice, the Mycoses Forum in Japan developed bundles based on key guideline recommendations. Bundled care processes standardize interventions to reduce unintended variations among clinicians by establishing a shared clinical baseline on which further appropriate management can be built. The aim of this study was to investigate nationwide compliance with the bundles and the impact of compliance on clinical outcomes in patients with candidaemia.

Table 1. Bundle elements in patients with candidaemia

Bundles to be accomplished at the start of therapy

1. Removal of existing CVCs within 24 h of diagnosis
2. Initial appropriate selection of antifungals
3. Initial appropriate dosing of antifungals

Bundles to be accomplished after initiation of therapy

4. Ophthalmological examinations
5. Follow-up blood cultures until clearance of candidaemia
6. Assessment of clinical efficacy on the third to fifth day to consider necessity of alternative therapy
7. Appropriate choice of alternative antifungals
8. At least 2 weeks of therapy after documented clearance of *Candida* from bloodstream and resolution of attributable symptoms (prolonged therapy for candidaemia with organ involvement)
9. Step-down oral therapy for patients with favourable clinical course

Methods

The ACTIONS (Appropriate Candidal Treatment Implementation of Non-neutropenic strategies) Project Committee developed bundles based on key guideline recommendations⁶⁻⁸ for the diagnosis and treatment of non-neutropenic patients with invasive candidiasis in 2011. The ACTIONS Project is one of the activities of the Mycoses Forum supported by Pfizer Japan Inc. ACTIONS bundles consist of nine items to complete for candidaemia (Table 1). For the awareness of activities, briefing sessions targeting infection control doctors certified by the Japanese College of Infection Control Doctors were held in 11 geographical regions throughout Japan. Bundle checklists were available on the web site of the Mycoses Forum (http://www.mycoses.jp/actions_project/index.html#BUNDLE) and were printed and widely distributed. Data were entered into the bundle database locally or check sheets were sent to the central office of the Mycoses Forum between July 2011 and April 2012.

Entry criteria were non-neutropenic patients >17 years old treated with antifungals for candidaemia with a positive culture for *Candida* spp. in blood samples. The appropriate selection and dosing regimen of antifungals were decided according to previously published guidelines⁶⁻⁸ (Table 2). If no clinical efficacy was obtained on the third to the fifth day, consideration of alternative therapy was recommended, such as a change to echinocandins or liposomal amphotericin B in patients to whom azoles were administered as initial therapy. Transition to fluconazole is recommended in clinically stable patients with infection due to *Candida albicans*.

Clinical response was judged after the end of all treatment courses, and mortality was evaluated 28 days after the start of antifungal therapy. Treatment was considered to be successful if all attributable signs and symptoms associated with candidaemia had resolved. Treatment was considered to have failed if there was unresponsive infection after at least 5 days of therapy, or if relapse occurred. In patients with treatment failure of initial antifungals or unacceptable adverse events necessitating

Table 2. Appropriate selection and dosing of antifungals in the bundles

Antifungals	Appropriate indication	Standard dosing
Echinocandins	patients with moderately severe to severe illness infection due to <i>C. glabrata</i> and <i>C. krusei</i> patients with candidaemia in whom CVCs cannot be removed consider poor ocular penetration in ocular candidiasis	casposfungin: loading dose of 70 mg, then 50 mg daily micafungin: 100–150 mg daily
Fluconazole	patients who are less critically ill and who have no recent azole exposure infection due to <i>C. parapsilosis</i> and <i>C. albicans</i> transition to fluconazole in clinically stable patients with infection due to <i>C. albicans</i>	loading dose of 800 mg, then 400 mg daily
Voriconazole	alternative therapy step-down oral therapy limitation of intravenous formulation in renal impairment consider therapeutic drug monitoring	6 mg/kg bid for two doses, then 3–4 mg/kg bid
Itraconazole	alternative therapy limitation of intravenous formulation in renal impairment	200 mg bid for 2 days, then 200 mg daily
Liposomal amphotericin B	patients with severe sepsis/septic shock infection due to <i>C. glabrata</i> , <i>C. krusei</i> and <i>C. guilliermondii</i> patients with candidaemia in whom CVCs cannot be removed	2.5–5.0 mg/kg daily
Amphotericin B deoxycholate	recommendation against use due to substantial renal and infusion-related toxicity	—
Flucytosine	combination use with other antifungals	25 mg/kg qid

bid, twice a day; qid, four times a day.

Table 3. Achievement of individual bundle elements in patients with candidaemia

Phase	Elements of the bundles	Population	No. of patients with achievement of the elements (%)
Bundles at the start of therapy	1. removal of existing CVCs within 24 h of diagnosis	patients with CVC placement	414/510 (81.2)
	2. initial appropriate selection of antifungals	all	534/608 (87.8)
	3. initial appropriate dosing of antifungals	all	464/608 (76.3)
Bundles after initiation of therapy	4. ophthalmological examinations	all	326/608 (53.6)
	5. follow-up blood cultures until clearance of candidaemia	all	368/608 (60.5)
	6. assessment of clinical efficacy on the third to fifth day	all	514/608 (84.5)
	7. appropriate choice of alternative antifungals	patients with alternative therapy	269/345 (78.0)
	8. at least 2 weeks of therapy after documented clearance of <i>Candida</i> from bloodstream	all	327/608 (53.8)
	9. step-down oral therapy	all	148/608 (24.3)

a change of initial antifungal therapy, overall treatment was judged to be successful if a favourable clinical response was obtained with alternative therapy.

We defined compliance as evidence that all bundle elements except 'appropriate choice of alternative antifungals' were completely fulfilled. As this item is indicated only for patients in whom antifungals were changed, we excluded this from the analysis of compliance. The element 'removal of central venous catheters (CVCs)' was included for the evaluation of compliance in patients with CVC placement. Missing data regarding the accomplishment of bundle elements were set as 'fail'.

Clinical efficacy and mortality were evaluated according to the compliance. To identify the contribution of each element to improvement of clinical outcomes, the ORs of clinical success and mortality were adjusted for the following factors affecting clinical outcomes: surgery, chemotherapy for cancer, malnutrition, total parenteral nutrition, age >70 years, chronic renal failure/haemodialysis, severe illness, steroid/immunosuppressant use, mechanical ventilation, use of a CVC, malignancy, ICU stay, diabetes mellitus and isolation of non-*albicans Candida*. Bundle elements such as 'third to fifth day follow-up' and '2 weeks of antifungal therapy' can only be achieved in patients who survive. To exclude deaths and dropouts before completion of bundle elements to be achieved after the start of therapy, we performed sub-population analysis in patients who survived >28 days after the start of antifungal therapy.

This study was approved by the institutional review board of Hyogo College of Medicine. The institutional review board waived the need for patients' informed consent. Ethics approval was the responsibility of each participating centre. If necessary, investigators obtained formal approval of the protocol by the regional ethics committee. The crude OR in univariate analysis was estimated for each variable by the χ^2 test and potential confounders were examined by cross tabulation. The variables selected by univariate analysis ($P < 0.1$) were subsequently entered into a stepwise logistic regression model to estimate the magnitude of association (adjusted OR and 95% CI). The level of significance was set at $P < 0.05$. SPSS ver. 16 (SPSS Inc., Chicago, IL, USA) was used to perform these analyses.

Results

Six hundred and forty-one subjects were registered. The analysis included 608 patients for whom information on clinical efficacy was obtained. Mortality was evaluated in 479 patients. *C. albicans* was commonly identified (46.4%). The other species identified included *Candida parapsilosis* (18.4%), *Candida glabrata* (16.0%),

Candida tropicalis (7.6%), *Candida krusei* (4.6%), *Candida guilliermondii* (3.5%) and others (3.3%). The achievement of individual elements is shown in Table 3. In 81.2% of patients, CVCs were removed within 24 h of the diagnosis of candidaemia. Components for which the achievement rate was relatively low were ophthalmological examination (53.6%), follow-up blood cultures (60.5%), at least 2 weeks of therapy after the end of candidaemia (53.8%) and step-down oral therapy (24.3%). Because of the low achievement rate of oral switch, the compliance rate for achieving all elements was as low as 6.9% (42 of 608 patients), and increased to 21.4% (130 of 608 patients) when compliance was assessed by the completion of the bundles, except for step-down oral therapy.

The clinical success rate was 77.0% (468 of 608 patients) and the mortality rate was 26.5% (127 of 479 patients). There was a significant difference in clinical outcomes between patients with and without compliance [success rate 92.9% versus 75.8% ($P = 0.011$)]. The mortality rate in patients with compliance tended to be lower than that in patients without compliance [8.3% versus 27.5% ($P = 0.054$)]. There was a clear correlation between the number of elements accomplished and the clinical outcomes in patients with CVC placement [clinical success: 0–2 elements, 21.6% ($n = 37$); 3 elements, 43.2% ($n = 44$); 4 elements, 74.3% ($n = 74$); 5 elements, 76.8% ($n = 95$); 6 elements, 89.2% ($n = 102$); 7 elements, 95.8% ($n = 120$); and 8 elements, 92.1% ($n = 38$)]/respective mortality rates: 58.0% ($n = 31$); 52.9% ($n = 34$); 21.4% ($n = 56$); 32.9% ($n = 76$); 27.5% ($n = 91$); 6.9% ($n = 101$); and 9.1% ($n = 22$)].

After adjusting for host and fungal factors, compliance with the bundles was not an independent factor associated with clinical success (adjusted OR 3.93, 95% CI 0.90–17.17) or improved survival (adjusted OR 0.15, 95% CI 0.07–1.50). The small number of compliant patients might have caused the negative result. If the element of oral switch was excluded from the assessment of bundle compliance, improved clinical success (adjusted OR 4.42, 95% CI 2.05–9.52) and mortality (adjusted OR 0.27, 95% CI 0.13–0.57) were confirmed in compliant patients (Table 4). Independent bundle elements that contributed to clinical success were the removal of CVCs within 24 h after confirmation of candidaemia, assessment of clinical efficacy on the third to the fifth day to consider the necessity of alternative antifungals, and at least

Table 4. Impact of compliance with the bundles on clinical outcomes in patients with candidaemia

Definition of compliance	Clinical success				Mortality			
	patients with compliance no. of patients (%)	patients without compliance (%)	crude OR (95% CI)	adjusted OR (95% CI)	patients with compliance no. of patients (%)	patients without compliance (%)	crude OR (95% CI)	adjusted OR (95% CI)
Achievement of all evaluable bundle elements	39/42 (92.9)	429/566 (75.8)	4.15 (1.26–13.7)	3.93 (0.90–17.17)	2/24 (8.3)	125/455 (27.5)	0.24 (0.06–1.04)	0.15 (0.07–1.50)
Achievement of all evaluable bundle elements except oral switch	121/130 (93.1)	347/478 (72.6)	5.08 (2.50–10.29)	4.42 (2.05–9.52)	10/97 (10.3)	117/383 (30.5)	0.26 (0.13–0.52)	0.27 (0.13–0.57)

2 weeks of therapy after clearance of *Candida* from the bloodstream (Table 5). As regards mortality, the removal of CVCs within 24 h, at least 2 weeks of therapy and step-down oral therapy were independent elements that were statistically associated with improved survival (Table 5). To correct for selection bias by patients who died before the latter two bundle elements were reached, we separately analysed the effect of bundle compliance in patients who survived >28 days.

Even in patients surviving >28 days, compliance of the bundles except oral switch improved clinical efficacy [compliance 97.7% versus non-compliance 86.6% ($P=0.004$)] and was an independent predictor of clinical success (adjusted OR 5.245, 95% CI 1.194–23.043). In addition, the beneficial effect was confirmed in individual elements to be achieved after initiation of therapy. Assessment on the third to the fifth day [94.3% versus 50.0% ($P<0.001$)], at least 2 weeks of therapy [96.0% versus 78.1% ($P<0.001$)], ophthalmological examination [93.9% versus 82.9% ($P=0.001$)] and follow-up blood culture [94.0% versus 80.8% ($P<0.001$)] significantly increased the clinical success rate in patients surviving >28 days. Independent bundle elements associated with clinical success were assessment on the third to the fifth day (adjusted OR 9.347, 95% CI 3.158–27.668) and at least 2 weeks of therapy after clearance of *Candida* from the bloodstream (adjusted OR 2.754, 95% CI 1.027–7.387).

Discussion

To the best of our knowledge, this is the first study to confirm the beneficial impact of ‘bundles’ on clinical outcomes in patients with candidaemia. In a similar study, Antworth et al.¹² developed a candidaemia care bundle incorporating key elements from the guidelines for the management of candidemia.⁶ However, no significant differences in clinical outcomes were identified in their study. In ACTIONs bundles, independent individual elements that contributed to clinical success in patients with candidaemia were the removal of CVCs within 24 h of diagnosis, assessment of clinical efficacy on the third to the fifth day and at least 2 weeks of therapy after the clearance of candidaemia.

In candidaemia without documented organ involvement, treatment aims were to clear the infection and at the same time to avoid deep-organ involvement caused by metastatic infectious foci. This can be achieved by treatment for 2 weeks after the end of candidemia.⁷ Although Oude Lashof et al.¹³ failed to demonstrate a correlation between the duration of antifungal treatment and the development of late complications in patients with candidaemia, this recommendation is based on the results of several prospective, randomized trials in which this rule has been successfully applied, and it is generally associated with few complications and relapses.^{14–16} The higher success rate and improved survival rate achieved by the removal of CVCs are consistent with other published studies^{17,18} and a recent meta-analysis.⁵ The ACTIONs Project Committee recommended that alternative antifungal therapy should be considered in patients with no clinical improvement or based on identified *Candida* species on the third to the fifth day after starting initial therapy. Hsu et al.¹⁹ reported that a higher overall response rate was obtained in patients with early initiation (within 72 h of positive culture) of an echinocandin; they recommended that the clinical response be assessed on the third day in patients with initial

Table 5. Impact of individual bundle elements on clinical outcomes in patients with candidaemia: univariate and multivariate analyses

Key bundle elements	Clinical success				Mortality			
	patients who achieved the element no. of patients (%)	patients who did not achieve the element no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)	patients who achieved the element no. of patients (%)	patients who did not achieve the element no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)
Removal of CVCs within 24 h	336/414 (81.2)	60/96 (62.5)	2.59 (1.60–4.18)	2.97 (1.51–5.85)	72/329 (21.9)	35/82 (42.7)	0.38 (0.23–0.63)	0.41 (0.23–0.74)
Appropriate initial selection of antifungals	425/534 (79.6)	43/74 (58.1)	2.81 (1.69–4.67)	—	112/424 (26.4)	15/55 (27.3)	0.96 (0.51–1.80)	—
Appropriate dosing	375/464 (80.8)	93/144 (64.6)	2.31 (1.53–3.49)	—	98/372 (26.3)	29/107 (27.1)	0.96 (0.59–1.56)	—
Assessment of clinical efficacy on the third to fifth day	431/514 (83.9)	37/94 (39.4)	8.00 (4.97–12.87)	5.53 (2.54–12.04)	92/406 (22.7)	35/73 (47.9)	0.32 (0.19–0.53)	—
At least 2 weeks of therapy after clearance of <i>Candida</i> from bloodstream	302/327 (92.4)	166/281 (59.1)	8.37 (5.22–13.42)	4.65 (2.35–9.19)	32/256 (12.5)	95/223 (42.6)	0.19 (0.12–0.30)	0.23 (0.13–0.40)
Ophthalmological examinations	281/326 (86.2)	187/282 (66.3)	3.17 (2.13–4.73)	—	47/259 (18.1)	80/220 (36.4)	0.39 (0.26–0.59)	—
Follow-up blood cultures	318/368 (86.4)	150/240 (62.5)	3.87 (2.57–5.67)	—	60/292 (20.5)	67/187 (35.8)	0.46 (0.31–0.70)	—
Step-down oral therapy	133/148 (89.9)	335/460 (72.8)	3.31 (1.87–5.86)	—	13/108 (12.0)	114/371 (30.7)	0.31 (0.17–0.57)	0.34 (0.15–0.76)

fluconazole therapy, and an echinocandin is preferred as an alternative therapy in patients with a poor response.

In patients with a poor clinical response to initial antifungals, overall treatment was judged to be successful if a favourable clinical response was obtained with alternative therapy. With early alternative therapy, initial inappropriate selection of antifungals might not have affected clinical outcomes in our study. Poor prognosis as a result of initial inappropriate therapy was demonstrated in patients with septic shock²⁰ and was closely related to the severity of infection. However, patient severity ranged from mild to fatal in our study. Kollef *et al.*¹⁸ demonstrated that concurrent performance of early appropriate therapy and adequate source control were required to improve survival among patients with septic shock caused by candidaemia. The presence of both delayed antifungal administration and inadequate source control had a risk of mortality similar to the presence of either one of these variables alone.

ESCMID guidelines⁷ suggest simplification of treatment by stepping down to an oral azole if the patient is stable and tolerates the oral route, and if the species is susceptible. Step-down oral therapy could have benefits, such as reduced use of intravenous catheters, earlier patient discharge and cost savings.^{21,22} We demonstrated a significantly higher clinical success rate and lower mortality rate in patients with adherence to step-down oral therapy. As step-down therapy was indicated in patients with a favourable course, the results should be interpreted with caution. Owing to the small number of compliant patients, compliance with the bundles failed to be an independent factor associated with favourable clinical outcomes. Upon exclusion of the element of oral switch, compliance was revealed to have a beneficial effect on clinical outcomes.

The bundle approach is also a useful way to assess the present status of guideline adherence.¹⁰ However, even when compliance was defined as achievement of all bundle elements except step-down oral therapy, the rate remained 21.4%. We regarded this value as the baseline, and intend to compare it with the compliance rate in a future follow-up study to ensure the effect of the project. In the case of severe sepsis bundles, Levy *et al.*¹⁰ reported that the compliance rate of the resuscitation bundle was 10.9% in the first quarter and increased over time. The other components for which the achievement rate was relatively low were ophthalmological examination, follow-up blood cultures and at least 2 weeks of therapy after clearance of *Candida* from the bloodstream. Considering the high ocular involvement in patients with candidaemia,²³ a more vigorous promotion of ophthalmological examination should be considered. The recommendation of follow-up cultures is difficult to accept by general physicians in patients whose symptoms have already resolved when candidaemia is diagnosed. In such patients, 2 weeks of therapy is performed without confirmation of the end of candidaemia.

Certain limitations must be considered in interpreting these findings. Firstly, as the main participants were certified infection control doctors and participation was entirely voluntary, the compliance rates for bundles are not necessarily representative of those by general clinicians, and the universality of our findings is therefore speculative. Secondly, as participants judged the appropriateness of antifungal selection according to the recommendations described in the checklist, the committee did not have detailed information on how they judged this item. Thirdly, the small number of patients who achieved step-down oral therapy

might have caused a negative result in compliant patients. To confirm the usefulness of compliance with the bundles, an increase in the achievement of this item is required. Finally, a cluster randomized trial including hospitals with and without the bundles would provide better scientific evidence. In conclusion, the introduction of a multifaceted performance improvement initiative with bundles was useful in the treatment of candidaemia. Although the efficacy of bundles should be evaluated in more rigorous studies, promotion of the bundle approach may have the potential to narrow the gap between clinical evidence and bedside practice.

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