RESEARCH

Ceftriaxone and cefotaxime use in Victorian hospitals

Marion B Robertson, Tony M Korman, Jonathan G A Dartnell, Lisa L Ioannides-Demos, Sue W Kirsa, Julie A V Lord, Liliana Munafo, Graham B Byrnes and on behalf of the Victorian Drug Usage Evaluation Group

ABSTRACT

Objective: To determine patterns of use of ceftriaxone and cefotaxime (CEFX) in Victorian hospitals and to identify areas for improvement.

Design, patients and setting: A concurrent, observational evaluation of CEFX use in patients commencing a course of these drugs between 8 and 14 September, 1999, in 51 Victorian hospitals.

Main outcome measures: Proportion of patients treated with CEFX; indications; duration of use; concordance with recommendations of national antibiotic guidelines (*Therapeutic guidelines: antibiotic*, 10th edition [AG10]).

Results: 671 patients were treated with CEFX. The overall rate of use was 43 patients per 1000 inpatient separations. Treatment of respiratory tract infection accounted for 352 patients (52%) and surgical prophylaxis for 99 patients (15%). Treatment of skin/soft tissue, urinary tract and gastrointestinal tract infections accounted for about 7% of patients each. The median duration of CEFX courses was 3.0 days. The overall rate of concordance with indications recommended in AG10 was 27%. The rate of concordance for empirical treatment of respiratory tract infection was 24%. Of the 195 patients treated empirically with CEFX for community-acquired respiratory tract infection and assessed as non-concordant, 64% did not have radiological evidence of pneumonia, and a further 30% did not fulfill the criteria for severe pneumonia. All courses given for surgical prophylaxis were non-concordant.

Conclusions: CEFX is widely used in Victorian hospitals, mostly to treat lower respiratory tract infection and in surgical prophylaxis of infection. The rate of concordance with AG10 is low. Potential areas for intervention include empirical treatment of respiratory tract infection and use in surgical prophylaxis.

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IN THE UNITED STATES, use of broad-spectrum cephalosporins has been linked to the emergence of vancomycin-resistant enterococci (VRE) and penicillin-resistant streptococci.[1,2]

VRE was first isolated in Australia in 1994, and since then there has been a steady increase in the number of reports of VRE throughout the country.[3] Broad-spectrum cephalosporins are widely used in Victorian hospitals, and small studies have found that much broad-spectrum cephalosporin use is not concordant with national prescribing guidelines.[4] Following on from a conference on vancomycin-resistant enterococci, where the results of a previous multisite study of vancomycin use were presented,[5] broad-spectrum cephalosporins were identified as a particular target for use evaluation and antibiotic "stewardship". We therefore undertook this study to determine patterns of use of ceftriaxone and cefotaxime (CEFX) in Victorian hospitals, and to identify areas for improvement.

METHODS

All 77 Victorian hospitals that employed a pharmacist listed on the database of the Society of Hospital Pharmacists of Australia (SHPA) were invited to participate. All patients at participating hospitals who started a course of CEFX between 8 September and 14 September, 1999, inclusive, were eligible for enrolment.

Pharmacists at each hospital collected the following data:

- patient demographic details;
- prescribing data for use of CEFX until the end of the course, discharge or death;
- the indication for starting antibiotic therapy, as determined from the medical record;
- contraindications to use of β-lactam and aminoglycoside antibiotics;
- microbiology results of specimens taken up to three days before or concurrent with CEFX therapy;

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- administration of antibiotics in the week before, concurrent with and immediately after CEFX therapy; and
- objective criteria, adapted from the *Therapeutic guidelines: antibiotic*, 10th edition (AG10),[6] for assessing severity of respiratory tract infection (RTI).

Each hospital provided details of the hospital's antibiotic policy and the number of inpatient separations between 8 and 14 September, 1999. Five major metropolitan teaching hospitals also provided information about the number of separations and occupied bed-days for medical and surgical inpatients.

We used algorithms specific for site of infection to assess all courses (except those for specific treatment) for concordance with AG10 recommendations. The final assessment represented the consensus of three assessors (two pharmacists and an infectious diseases physician) working together.

For the purposes of analysis we considered inpatient separations as the unit of interest. We report the proportion of inpatient separations where patients received at least one course of CEFX and the proportion where patients received at least one course concordant with AG10 recommendations. Definitions of terms are given in Box 1.

Statistical analysis

Analysis was by grouped logistic regression, using the "glm" command in STATA version 7.0.[7] This allowed the assessment of model fit, as well as the significance of individual explanatory variables. Hypothesis testing used the likelihood ratio test (χ^2 value given), or Wald test (odds ratio [OR] and 95% confidence interval [CI] given), as appropriate.

1: Definitions

Course: Administration of at least one dose of ceftriaxone or cefotaxime (CEFX). If the course was administered more than 24 hours after a previous dose (and the drug was re-prescribed), this was considered as a new course.

Empirical treatment: Antibiotic administration commenced before or without identification of CEFX-sensitive bacterial pathogens.

Specific treatment: Antibiotic administration commenced after identification of CEFX-sensitive bacterial pathogens.

Surgical prophylaxis: Antibiotic administration commenced perioperatively to prevent postoperative infection.

Non-surgical prophylaxis: Antibiotic administration to prevent infection in high-risk medical patients or contacts.

Concordant indication: The indication for CEFX was concordant with recommendations in *Therapeutic guidelines: antibiotic*, 10th ed (AG10).

Concordant indication and overall regimen: The indication and dose of CEFX and concurrent antibiotics used were concordant with recommendations in AG10.

Durations of courses: These were calculated by dividing the number of doses administered by the frequency of administration. Single doses of ceftriaxone were given a duration of one day; single doses of cefotaxime were given a duration of 0.3 days.

2: Concordance of empirical treatment with *Therapeutic guidelines: antibiotic*, 10th edition (AG10), by site of infection

Site of infection	Number of patients	Concordant indication	Concordant indication and regimen
Respiratory tract	352	86 (24%)	17 (5%)
Urinary tract	45	27 (60%)	21 (47%)
Skin/soft tissue	43	3 (7%)	1 (2%)
Gastrointestinal tract	40	35 (88%)	9 (23%)
Unknown (eg, septicaemia)	32	1 (3%)	
Biliary tract	17	8 (47%)	1 (6%)
Central nervous system	9	9 (100%)	2 (22%)
Other	6	2 (33%)	
Bone/joint	3	1 (33%)	1 (33%)
Heart	3	0	
Genital tract	1	1 (100%)	
Total	551	173 (31%)	52 (9%)

RESULTS

Hospitals

Fifty-one of 79 eligible hospitals (including two regional private hospitals receiving pharmacy services from public hospitals) participated. These included 42 of 62 public hospitals and nine of 17 private hospitals; 24 of 44 metropolitan hospitals and 27 of 35 regional hospitals. They accounted for an estimated 74% of all public hospital and 24% of all private hospital separations in Victoria, including from hospitals not listed on the SHPA database. Testing for the effect of two variables on participation ("public v private" and "metropolitan v regional") found that metropolitan hospitals were significantly less likely to have participated than regional hospitals (OR, 0.36; 95% CI, 0.13–0.95; $P = 0.04$).

Patients and courses

Six hundred and seventy-one patients (median age, 69 years; range, newborn to 99 years; 340 female) received 674 courses of CEFX (ceftriaxone, 510; cefotaxime, 164); three patients received two courses, and all others received one course. The number of courses prescribed in each hospital ranged from zero to 79, with 10 hospitals (nine public and one private) contributing 420 (62%) courses. The overall use of CEFX was 43 treated patients per 1000 inpatient separations. CEFX use was significantly different between hospitals overall ($\chi^2 = 219$; df = 50; $P < 0.0001$). Neither of the variables "private v public" nor "regional v metropolitan" was significantly associated with CEFX use. CEFX therapy was initiated in 317 patients (47%) when they were in hospital wards; in 211 (31%) therapy was started in emer-

gency departments; in 84 (13%) it was started in operating theatres; and in the remaining 59 it was started in intensive care units, hospital-in-the-home programs and day-procedure units. The median duration of courses was 3.0 days (25th to 75th percentile, 1.0–5.0 days).

Indications for use

Most patients (551 [82%]) were given CEFX for empirical treatment of infection; 99 (15%) were given CEFX for surgical prophylaxis of infection; 18 (3%) for specific treatment; and three for non-surgical prophylaxis. Empirical treatment of RTI accounted for 352 courses (52%). CEFX was used for surgical prophylaxis for abdominal (38 courses), cardiac (18), head, neck and thoracic (13), obstetric and gynaecological (11), urological (7) and other (12) procedures.

Adherence to hospital antibiotic policy

Thirteen hospitals had antibiotic policies that restricted the prescribing of CEFX to:

- infectious diseases approval (eg, approval number for each course or approval for courses outside a specified list) (7 hospitals);
- specific units (eg, intensive care unit, oncology unit) (2 hospitals);
- specific prescribers (eg, visiting medical officers) (3 hospitals);
- specific indications (eg, severe community-acquired pneumonia) (4 hospitals); or
- specific circumstances (eg, course of up to 24 hours) (4 hospitals).

In the 13 hospitals that restricted CEFX prescribing, the overall proportion of courses that met the criteria for hospital approval was 68% (range, 0–100%).

Concordance with AG10

The indication for use of CEFX was concordant with AG10 for 174 (27%) of 653 patients, including 53 (8%) patients who received courses that were concordant for both the indication and overall regimen. Four patients were prescribed CEFX for indications not covered in AG10.

3: Summary of *Therapeutic guidelines: antibiotic*, 10th edition,[6] recommendations for the treatment of respiratory tract infection

CEFX is recommended for the empirical treatment of:

- acute epiglottitis;
- severe community-acquired pneumonia;
- mild to moderate hospital-acquired pneumonia in patients hypersensitive to penicillin or with significant renal failure; and
- severe early-onset hospital-acquired pneumonia

Severe pneumonia: In adults, is defined by the presence of one or more of the following, not attributable to another cause: respiratory rate, >30/min; diastolic blood pressure, <60 mmHg; systolic blood pressure, <90 mmHg; evidence on chest x-ray of bilateral involvement or involvement of multiple lobes; increase in the size of chest x-ray opacity by 50% or more within 48 hours of admission; white blood cell count $<4 \times 10^9$/L or $>30 \times 10^9$/L; Po_2 <60 mmHg or oxygen saturation <90% in room air, requirement for mechanical ventilation or FIO_2 >35% to maintain oxygen saturation >90%; PCO_2 >50 mmHg in room air; confusion; shock; recent deterioration in renal function.

4: Concordance of treatment with *Therapeutic guidelines: antibiotic*, 10th edition (AG10), for the 352 patients with respiratory tract infections

Details of concordance	Number of patients
Community-acquired infections	273 (78%)
Concordant indication	78 (29%)
Concordant indication and overall regimen	13 (5%)
Non-concordant	195 (71%)
No chest x-ray evidence of pneumonia	*124 (64% of 195)*
Not severe pneumonia	*59 (30% of 195)*
Aspiration pneumonia	*7 (4% of 195)*
Other	*5 (3% of 195)*
Hospital-acquired infections	79 (22%)
Concordant indication	8 (10%)
Concordant indication and overall regimen	4 (5%)
Non-concordant	71 (90%)
No pneumonia on chest x-ray	*26 (37% of 71)*
Severe late-onset hospital-acquired pneumonia (including 3 aspiration pneumonia)	*24 (34% of 71)*
No contraindication to penicillins or gentamicin	*18 (25% of 71)*
Other	*3 (4% of 71)*

There was large variation in the proportion of patients receiving concordant treatment for the different indications (Box 2). The indication was non-concordant for all 99 patients given CEFX for surgical prophylaxis.

Concordance for patients treated for respiratory tract infection

Box 3 summarises the AG10 recommendations for use of CEFX in RTI, and our findings in relation to these recommendations are shown in Box 4. The indication was concordant for 78 (29%) of 273 patients treated for community-acquired RTI and 8 (10%) of 79 patients treated for hospital-acquired RTI. Most were assessed as non-concordant because there was no chest x-ray evidence of pneumonia (45% of patients treated for community-acquired infections and 33% of patients treated for hospital-acquired infections). A further 22% of patients treated for community-acquired RTI had non-concordant indications because none of the indicators for severe pneumonia were present.

Of the 74 patients treated for severe community-acquired pneumonia, the indication and overall regimen were concordant for 12 (16%). The main reason for non-concordance was the omission

5: Comparison of the major metropolitan teaching hospitals

	Hospital				
	1	2	3	4	5
Number of patients	77	45	39	39	22
Number of courses	79	45	39	39	22
Number of separations	1212	927	1289	820	1006
Patients per 1000 separations	64	49	30	48	22
Median length of hospital stay (days)	7.0	7.0	9.0	12.0	6.0
Patients according to where CEFX therapy was initiated					
Emergency department	29 (38%)	12 (27%)	9 (23%)	13 (33%)	12 (55%)
Ward	26 (34%)	10 (22%)	26 (67%)	25 (64%)	8 (36%)
Operating theatre	17 (22%)	16 (36%)	0	0	0
Other	5 (6%)	7 (16%)	4 (10%)	1 (3%)	2 (9%)
Median duration of courses (days)	3.0	3.0	3.0	4.0	1.5
Number of bed-days	4182	3599	6224	2572	3871
Defined daily doses per 1000 bed-days	35	26	22	39	12
Number of patients according to indications for use					
Treatment	59 (77%)	32 (71%)	39 (100%)	35 (90%)	22 (100%)
Prophylaxis	18 (23%)	13 (29%)	0	4 (10%)	0
Prescribing restrictions	No	Yes*	Yes*	Yes*	Yes†
Courses given hospital approval	n/a	44 (98%)	30 (77%)	24 (62%)	18 (82%)
Patients receiving courses concordant with AG10‡ for indication	20 (26%)	15 (33%)	11 (28%)	7 (18%)	10 (45%)
Patients receiving empirical courses concordant with AG10‡ for indication	20 (38% of 56)	15 (47% of 32)	11 (30% of 37)	7 (22% of 32)	10 (48% of 21)

*Specified units or indications, or infectious diseases approval required. †Infectious diseases approval and number required. ‡ *Therapeutic guidelines: antibiotic*, 10th edition.

of intravenous (IV) erythromycin from the regimen (60 patients, including 24 who were treated with oral roxithromycin instead of IV erythromycin).

For 37 (11%) of the 352 patients with RTI, there was no documentation as to whether a chest x-ray had been done, or the results of the x-ray or indicators of the severity of pneumonia were not recorded. If these cases are counted as appropriate indications for CEFX, concordance increases from 29% to 37% for community-acquired infections and remains the same for hospital-acquired infection.

Specific therapy

Eighteen patients were given CEFX for specific therapy. In five (28%), this therapy was for treatment of infections with organisms resistant to penicillin or ampicillin and was assessed as appropriate.

Hospital-in-the-home

Twenty-six patients were treated with ceftriaxone (24) or cefotaxime (2) as part of treatment in a "hospital in the home" program. The main indications for use were skin and soft tissue infection (11 patients [42%]), with a mean treatment duration of 6.4 days, and RTI (eight patients [31%]), with a mean treatment duration of 7.0 days. Use of CEFX was appropriate for seven patients (3/3 for specific and 4/23 for empirical treatment). Three patients returned to the main hospital campus, where antibiotic treatment was changed.

Comparison of all hospitals

CEFX use: This varied significantly between Victorian hospitals overall ($\chi^2 = 219$; df = 50; $P < 0.0001$). The 13 hospitals with restrictive policies did not have significantly lower proportions of CEFX use than those without (OR, 0.90; 95% CI, 0.77–1.05). In addition, the variables "private v public" and "regional v metropolitan" were not significant explanatory factors. None of the collected parameters were adequate to explain the interhospital variation in use, emphasising the contribution of casemix and other hospital-specific factors.

Concordance: The proportion of patients treated in concordance with AG10 recommendations differed significantly between hospitals ($\chi^2 = 72$; df = 47; $P = 0.011$). Concordance was significantly lower in private hospitals (OR, 0.49; 95% CI, 0.28–0.87). Use for surgical prophylaxis was high in private hospitals, accounting for 29% of the patients treated compared with 12% in public hospitals. Concordance in the 13 hospitals with restrictive policies was 29%, and was not significantly higher

than in hospitals without restrictive policies (OR, 1.24; 95% CI, 0.88–1.76).

Three Victorian hospitals did not have any patients treated with CEFX and these hospitals were omitted from our dataset. The effect of the variable "metropolitan v regional" was not significant (OR, 1.3; 95% CI, 0.95–2.07), nor was there evidence of interaction. Examining residuals for the model suggested that one hospital should be omitted from the data, having none of 13 patients treated in concordance with recommendations. With this hospital removed, the single factor "private v public" adequately explained the variation in proportion of concordance across the 47 remaining hospitals (goodness-of-fit test, $\chi^2 = 48.0$; df = 43; $P = 0.28$). The OR for "private v public" was little changed by this omission (OR, 0.46; 95% CI, 0.26–0.82).

Comparison of the five major teaching hospitals

CEFX use: A comparison of the five major metropolitan teaching hospitals is shown in Box 5. Within these, CEFX use was significantly higher in the hospital without a restrictive policy (Hospital 1) (OR, 1.82; 95% CI, 1.37–2.42). However, this should be interpreted with caution, for several reasons. Firstly, the four hospitals with restrictive policies were significantly inhomogeneous ($\chi^2 = 14.7$; df = 3; $P = 0.002$), so pooling them for the purpose of comparison may not be valid. Secondly, the data could be explained by division into two groups: "high" CEFX users (Hospitals 1, 2, and 4) and "low" CEFX users ($\chi^2 = 4.85$; df = 1; $P = 0.18$). Adding "restrictive policy" to this model did not result in a significant improvement ($\chi^2 = 3.28$; df = 1; $P = 0.07$). Further, Hospital 1 did not have significantly higher use of CEFX than the other "high"-use hospitals (OR, 1.34; 95% CI, 0.98–1.85). Thirdly, as only one of these hospitals did not have a restrictive policy (Hospital 1), higher use might have been the result of other factors specific to the hospital.

Concordance: Among the five major teaching hospitals, "hospital" was not a significant factor in predicting concordance ($\chi^2 = 5.92$; df = 4; $P = 0.21$). In particular, the hospital without a restrictive prescribing policy (Hospital 1) was not significantly different from those with restrictive policies (OR, 0.83; 95% CI, 0.45–1.55). Use for surgical prophylaxis was high in Hospitals 1 and 2 and low in Hospitals 3, 4 and 5.

DISCUSSION

We found extensive inappropriate use of CEFX in Victorian hospitals of all sizes. Our sample was large, representing 74% of all public hospital, but only 24% of all private hospital, inpatient separations in Victoria during the study period.

The rate of use varied significantly between hospitals, but this was not explained by whether hospitals were public, private, metropolitan, regional, or whether or not they had restrictive antibiotic policies. We compared use with recommendations in national antibiotic prescribing guidelines (AG10) and found that the indications for more than 70% of patients were not in concordance with the recommendations.

Potential limitations of our study are (i) the participating hospitals may not have been representative of all Victorian hospitals; (ii) a limited set of data and objective criteria was used to assess the indication for use and may not have accurately represented the reason for use and the condition of the patient in all cases; (iii) the study focused on the use of CEFX for all indications, but did not evaluate the use of other antibiotics for those indications; and (iv) use of CEFX was compared with prescribing guidelines, which cannot provide appropriate advice for all patients.

Empirical treatment of RTI accounted for about half of all patients given CEFX. An important finding for educators is that most courses in these patients (76%) were non-concordant with AG10 guidelines because basic criteria were not met, such as chest x-ray evidence of pneumonia. It is relevant to note that in the most recent (11th) edition of the *Therapeutic guidelines: antibiotic*,[8] the recommendation for use of CEFX in the treatment of severe community-acquired pneumonia has been further restricted to patients who are hypersensitive to penicillin. Fewer courses would be considered concordant if compared with the more recent edition.

The second most frequent indication for CEFX was for surgical prophylaxis (15% of courses), despite not being recommended for surgical prophylaxis in AG10, and receiving limited mention, if any, in other authoritative guidelines.[9,10] However, surgical prophylaxis is a registered indication in product information for CEFX, and these drugs can be promoted by their manufacturers for this use. Such inconsistencies are clearly problematic.

We presented our results to a multihospital, multidisciplinary forum as well as to the participating hospitals.[11] Hospitals are responding to the findings individually, in ways such as removing CEFX from operating theatres and implementing interactive checklists on computer-based approval systems. The concerns are unanimous: continuing inappropriate use of CEFX will result in increasing antimicrobial resistance.

We believe a coordinated, sustained and iterative approach is needed to effectively monitor and improve hospital use of antibiotics. Drug audits like this one, which involve transcribing information from medical records, are laborious and time-consuming. The information systems in Victorian hospitals are inadequate, both in terms of tracking how patients are managed and in supporting clinicians in clinical decision making. Data on drug use are not linked to patients, indications or prescribers, let alone clinical outcomes. Clinical information is generally not available at the point of decision making. To achieve quality use of antibiotics, both data linkage and provision of clinical information are needed.

COMPETING INTERESTS

We have no competing interests, and the funding body (the Victorian Department of Human Services) was not involved in the design of the study, the collection, analysis or interpretation of data, the writing of the article, or the decision to submit the final manuscript for publication.

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book reviews

Medicine and botany: strange bedfellows?

A doctor in the garden: Australian flora and the world of medicine. John Pearn, Brisbane: Amphion Press, 2001 (497 pp, $79.95). ISBN 1 86499 503 3.

A DOCTOR IN THE GARDEN, by well-known Australian medical historian Professor John Pearn, is clearly a life's work. It is a collection of historical anecdotes about medical people, or those with a connection to medicine, who have been remembered in the botanical name of a plant. The work is quarto size and beautifully published in hard cover. It is richly illustrated with photographs, some of which are in colour, and drawings of both the honoured doctor (or healer) and the reference plant. The anecdotes are arranged alphabetically by family name. There is a detailed index and a comprehensive bibliography.

The book mainly covers doctors who have lived or worked in Australia, although some classical and early modern identities are included. It is dedicated to Surgeon Robert Brown (1773-1858), who accompanied Mathew Flinders and Joseph Banks on the *Investigator* in 1801 and named many of the nation's distinctive plants.

The text comprises a profusion of historical vignettes. They are, in the author's words, a "fusion of biography, medicine, botany and history". Many familiar names spring from the pages, such as Bancroft, Cleland, Leichhardt and Macadam. There are also some surprise inclusions, such as Elsey, Braidwood Wilson and a wounded Prince Albert. Historians of medicine may be a little disappointed that the enduring relationship between doctors and botany has not been treated more comprehensively.

Reference works detailing the source of plant names abound, but *A doctor in the garden* is a unique reference to a subspecialty that few realise exists. It will long remain of use to medical historians. But if you just like to browse, as I do, then you will find it a delight. Rummage among the vignettes and then, as I think the author would like, look at plant names with a little more thought.

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ER registrar in book form

Emergency medicine. Diagnosis and management. 2nd ed. Anthony F T Brown. Melbourne: Butterworth Heinemann, 2001 (xx+379 pp, $64.96). ISBN 0 75068 956 0.

EMERGENCY MEDICINE is a 24-hour specialty managing a large variety of acute conditions. Although the range of knowledge necessary to practise at a consultant level is extensive, there is a core of information that should be available to all who manage acutely unwell patients. This information is even more valuable to those who only require it infrequently — particularly in peripheral, rural and remote locations where specialist advice is limited or absent.

Associate Professor Brown is a well-respected academic, clinician and teacher. He was a recipient of the first teaching prize from the Australasian College for Emergency Medicine and is an active participant in a hospital-based critical care retrieval service. He is a man very much in tune with the needs of his target audience: junior medical staff, general practitioners, senior medical students, critical care nursing staff, paramedics and others who may not have immediate access to specialist-level advice.

Emergency medicine has been written as a handbook. The format is logical, methodical and provides a framework for the management of a wide spectrum of illnesses and injury. The structure is concise and consistent, with an emphasis on rapid diagnosis, immediate management and subsequent referral. Each section guides the reader step by step through the necessary elements of acute care.

This latest edition of a popular text includes updated adult and paediatric resuscitation guidelines and new sections including environmental emergencies, acute coronary syndromes, hyponatraemia, hypercalcaemia, purpura, triage, retrieval and transfer. The introduction of a risk-management section reflects the evolving medicolegal environment that we work in and reminds us of the importance of practising quality medicine.

The conciseness, portability and affordability of this text make it an excellent "registrar in book form".

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