A survey of antibiotic prescribing practices in Australian and New Zealand intensive care units

Joel M Dulhunty, Steven A R Webb, David L Paterson, Rinaldo Bellomo, John Myburgh, Jason A Roberts and Jeffrey Lipman

ABSTRACT

Objective: To evaluate antibiotic prescribing practices in empirical and directed treatment of severe sepsis and septic shock in Australian and New Zealand intensive care units.

Design, setting and participants: Case vignette survey of intended antibiotic prescribing for ICU patients with sepsis associated with community-acquired pneumonia (CAP), intra-abdominal infection (IAI), hospital-acquired pneumonia (HAP) or an unidentified infectious cause (UIC). Eighty-four specialists and advanced trainees working in an ICU setting in Australia and New Zealand responded to a questionnaire survey conducted between February and May 2009.

Main outcome measures: Empirical and directed antibiotic therapy, including mode of administration, frequency of administration, dose and duration of therapy.

Results: A total of 656 antibiotics were empirically "prescribed", including 25 unique antibiotics. Combination therapy was prescribed in 82% of cases, with dual cover for CAP and triple therapy for IAI most common. Directed single-agent cover for *Pseudomonas aeruginosa* in HAP and flucloxacillin monotherapy for methicillin-sensitive *Staphylococcus aureus* bacteraemia were prescribed in 65% and 51% of cases, respectively. Supportive gentamicin therapy was commonly recommended (32% of all cases), predominantly in the form of once-daily dosing. Daily gentamicin dosage varied from 3 to 7 mg/kg (excluding one outlier), and was largely compliant with recommendations (76% of doses being $\geqslant$ 5 mg/kg). Main areas of non-compliance with guidelines were provision of broader cover for resistant organisms and β-lactam underdosing. Continuous and extended infusions were uncommon (5%).

Conclusions: Antibiotic prescribing was largely appropriate, but consideration of site-specific resistance profiles and avoidance of low dosing is advocated to provide appropriate upfront cover, prevent underdosing and reduce the risk of developing resistant organisms.

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The management of infection is a common challenge in the intensive care unit. In a recent large international point-prevalence study, half of all ICU patients were considered infected on the day of the study.[1] Sepsis occurs in 20%–38% of ICU patients,[2,3] and rates of nosocomial infection and antibiotic resistance are higher than in non-ICU or community settings.[4] Evidence from observational studies suggests that improved patient outcomes are achieved through prescribing early and appropriate antibiotic therapy.[5,6] Although antibiotic guidelines such as the Infectious Diseases Society of America practice guidelines (available at http://www.idsociety.org) and the Australian *Therapeutic guidelines: antibiotic*[7] have been developed, studies on antibiotic prescribing practices in Australia and New Zealand are limited,[8-11] and prescribing variability and guideline compliance in this setting are largely unknown.

Knowledge of antibiotic choice, single versus combination therapy, dose selection and proposed duration of treatment would be instructive for determining adequacy of ICU prescribing practices. The aim of our study was to obtain contemporary information on antibiotic prescribing used for the empirical treatment of severe sepsis and septic shock in Australian and New Zealand ICUs.

Methods

Target population and dissemination procedures

Specialists and advanced trainees working in an ICU setting in Australia and New Zealand were invited to complete an online questionnaire on antibiotic prescribing practices. The survey was conducted between February and May 2009. Participation was promoted via email distribution to the Australian and New Zealand Intensive Care Society Clinical Trials Group and via a Joint Faculty of Intensive Care Medicine e-newsletter. Local dissemination was also carried out by the study investigators.

Questionnaire

The questionnaire comprised four case vignettes of patients requiring admission to the ICU with severe sepsis or septic shock (Appendix): Case 1 — community-acquired pneumonia (CAP); Case 2 — intra-abdominal infection (IAI); Case 3 — hospital-acquired pneumonia (HAP); and Case 4 — unidentified infectious cause (UIC) on a background of immunosuppression. For each case, participants were asked to "prescribe" up to three empirical intravenous antibiotics

and to specify the mode of administration, frequency of administration, dose (in g/dose or mg/kg) and duration of therapy.

Mode of administration was categorised as intermittent (≤ 1 hour), extended (> 1 hour and ≤ 4 hours), or continuous infusion. The focus was on usual antibiotic therapy, and respondents were asked to exclude antituberculosis, antifungal and antiviral therapy from consideration. The estimated weight for each patient was 80 kg, and source control of the infection was assumed. In Case 3 (HAP), participants were asked whether identification of *Pseudomonas aeruginosa* from a bronchoalveolar lavage specimen would affect their choice of antibiotic therapy. In Case 4 (UIC), participants were asked to indicate whether methicillin-sensitive *Staphylococcus aureus* (MSSA) identified via blood culture would alter their antibiotic management.

Guideline compliance

Antibiotic prescribing choices for each case scenario were compared with recommendations in the Australian *Therapeutic guidelines*.[7] Compliance was evaluated in terms of drug choice and, for medications that complied with the recommendations, in terms of dosage. For Case 1, compliance was evaluated against guidelines for CAP in adults (risk class V and patients requiring ICU management), and for Case 2, against guidelines for peritonitis due to a perforated viscus. For Case 3, compliance was separately evaluated against guidelines for (a) HAP (low risk of multidrug-resistant [MDR] organisms); and (b) HAP (high risk of MDR organisms). For Case 4, compliance was separately evaluated against guidelines for (a) severe sepsis: empirical therapy (no obvious source of infection) — adults; and (b) severe sepsis: empirical therapy (no obvious source of infection) — febrile neutropenic patients.

Drug compliance was rated as (1) non-compliant (medications used were not specified in the guidelines); (2) compliant (medication choice matched guidelines); or (3) compliant, but with additional non-compliant antibiotics. Dosage was rated as compliant if the prescribed daily dose (PDD) equalled the recommended daily dose or fell within the recommended range; and above or below recommendations if outside this range. Directed therapy for MSSA bacteraemia was evaluated against guidelines for severe sepsis: *S. aureus* in terms of drug choice, dosing compliance and duration of therapy (minimum of 14 days).

Statistical analysis

Statistical analysis included descriptive and comparative analysis using the Pearson χ^2 test or Fisher's exact test, as appropriate. Dose (in grams) was multiplied by frequency of administration to obtain the PDD. Doses reported in mg/kg were multiplied by a conversion factor (0.080 kg·g/mg based on an assumed weight of 80 kg) to obtain grams per dose. Median and range are reported for PDD and duration of therapy. Differences in PDD and therapy duration were explored by the Mann–Whitney *U* test for two groups or the Kruskal–Wallis test for more than two groups. A two-tailed *P* value < 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS software, version 15.0 (SPSS Inc, Chicago, Ill, USA).

Ethics approval

Ethics approval for our study was obtained from the Royal Brisbane and Women's Hospital Institutional Review Board for Low and Negligible Risk Research.

Table 1. Demographic characteristics and place of clinical work of respondents (*N* = 84)*

Characteristic	Number (%) of respondents†
Mean years since medical school graduation (SD)	17.4 (7.0)
Qualification/level of appointment	
Intensive care specialist	57 (67.9%)
Advanced trainee	8 (9.5%)
Other specialist‡	6 (7.1%)
Hospital type	
University hospital	56 (66.7%)
Non-university hospital	15 (17.9%)
Public hospital	67 (79.8%)
Private hospital	4 (4.8%)
ICU type	
Mixed medical/surgical	71 (84.5%)
Closed	67 (79.8%)
Open	4 (4.8%)
ICU level	
Adult level 3	55 (65.5%)
Adult level 2	16 (19.0%)
Location	
Victoria	15 (17.9%)
New South Wales	13 (15.5%)
Queensland	12 (14.3%)
New Zealand	12 (14.3%)
South Australia	7 (8.3%)
Western Australia	8 (9.5%)
Tasmania	2 (2.4%)
Northern Territory	2 (2.4%)

ICU = intensive care unit. * There were 13 missing responses. † Figures are number (%) of respondents unless otherwise specified. ‡ Includes anaesthetists (3) and physicians (3), two with subspecialty qualifications in infectious diseases and/or respiratory medicine.

Results

Study participants and overall antibiotic prescribing practice

The questionnaire was completed by 84 respondents (Table 1). A total of 656 antibiotics were empirically prescribed across the four case vignettes, and 25 unique antibiotics were used. The number of antibiotics prescribed per case is shown in Figure 1. Empirical antibiotic usage for each case is summarised in Tables 2–5, and guideline compliance in Table 6. All 84 respondents completed Case 1, 79 completed Case 2, 74 completed Case 3 and 72 completed Case 4, resulting in a total of 309 responses across all four cases.

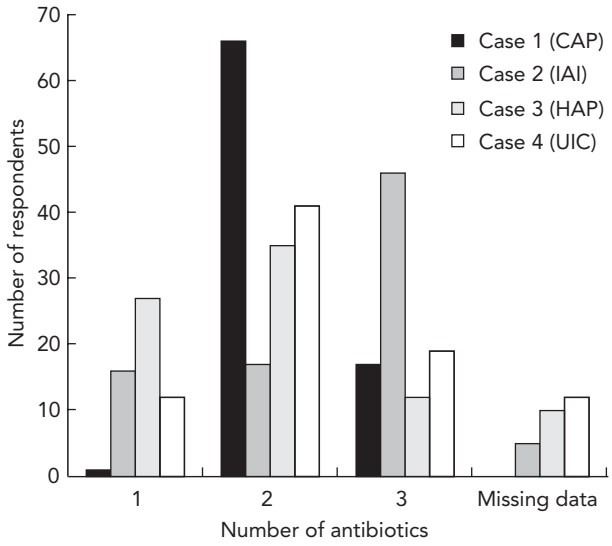
Case 1: community-acquired pneumonia

Two antibiotics were prescribed by 79% of respondents (66/84) for CAP, with 20% (17/84) prescribing three antibiotics. There was only one instance of single-agent therapy (ceftriaxone). A β-lactam and macrolide were prescribed in 89% of cases (75/84). The most common combinations included ceftriaxone + azithromycin (31/66 and 7/17), ticarcillin/clavulanate + azithromycin (6/66 and 3/17) and cefuroxime + erythromycin (6/66). Drug choice compliance was 52% overall (44/84), with a further 8% (7/84) being compliant but with additional non-compliant medications. For the 39% of choices (33/84) that were non-compliant, the most commonly selected antibiotics were ticarcillin/clavulanate (11), vancomycin (10), cefuroxime (6) and piperacillin/tazobactam (5). Dosing exceeded recommendations in 70% of compliant cases (31/44), and was below recommendations in 23% (10/44).

Case 2: intra-abdominal infection

Triple-agent therapy was proposed by 58% of respondents (46/79) for IAI. The most common triple cover comprised a β-lactam (amoxycillin or ampicillin in 37/42), gentamicin and metronidazole (42/46). Dual-agent therapy (17/79) most commonly comprised a β-lactam + gentamicin (7/17), a β-lactam + vancomycin (7/17) or a β-lactam + metronidazole (3/17). Single-agent therapy (16/79) most commonly comprised ticarcillin/clavulanate (9/16) or piperacillin/tazobactam (7/16). Compliance in drug choice was 68% (54/79), with 33% of choices dosage-compliant (18/54) and 59% (32/54) below dosing recommendations. Dosages were below the recommended level in all 32 cases for the β-lactam antibiotic, in four cases for gentamicin (PDD = 0.24–0.30 g), and in two cases for metronidazole (PDD = 0.50 g). Compliant therapy with additional non-compliant antibiotics occurred in 27% of cases (21/79), most commonly involving meropenem (5/21) or vancomycin (5/21).

Figure 1. Number of empirical antibiotics used in each case vignette



Case 3: hospital-acquired pneumonia

Forty-seven per cent of respondents (35/74) proposed dual therapy for HAP and 36% (27/74) single-agent therapy. The most common dual agents were ticarcillin/clavulanate + gentamicin (10/35), ticarcillin/clavulanate + vancomycin (9/35), piperacillin/tazobactam + vancomycin (6/35) and meropenem + vancomycin (6/35). Vancomycin was prescribed in 30 of 47 cases of combination therapy. The most common single agents were ticarcillin/clavulanate (8/27), piperacillin/tazobactam (6/27) and cefuroxime (5/27). Drug choice compliance was higher for cases involving high risk of MDR organisms (58% [43/74]) than for those involving low risk of MDR organisms (12% [9/74]). Dosing was compliant with high-risk MDR guidelines in 63% of cases (27/43); 26% (11/43) were below dosing recommendations.

The identification of *P. aeruginosa* prompted a change in antibiotic choice in 50% of respondents (37/74). Of the respondents who indicated they would not change the therapy, all had proposed empirical anti-pseudomonal cover, with 27% (10/37) prescribing gentamicin plus a suitable β-lactam. Respondents who indicated they would change the therapy had commenced empirical therapy with anti-pseudomonal cover in 76% of cases (28/37), with only 14% (5/37) empirically prescribing two drugs with suitable activity. Of the respondents who proposed a change in therapy, 43% (16/37) subsequently prescribed dual-agent cover against *P. aeruginosa*. In total, 35% of respondents (26/74) prescribed double anti-pseudomonal cover. Single-agent cover with a carbapenem was chosen by 9% of participants (7/74).

Case 4: unidentified infectious cause

Fifty-seven per cent of respondents (41/72) proposed dual-agent therapy for an UIC: meropenem + vancomycin (10/41), piperacillin/tazobactam + vancomycin (6/41), piperacillin/tazobactam + gentamicin (5/41) and ticarcillin/clavulanate + gentamicin (4/41). Triple-agent therapy most commonly involved a β-lactam + gentamicin + vancomycin (8/19); the β-lactam component comprised ticarcillin/clavulanate (3), piperacillin/tazobactam (2), meropenem (2) and cefepime (1). Meropenem was the agent of choice (7/12) for proposed monotherapy.

Drug choice was compliant with guidelines for severe sepsis with febrile neutropenia in 29% of cases (21/72), and compliant but with additional non-compliant antibiotics in 21% (15/72). Of the 36 non-compliant responses, 56% (20/36) involved carbapenem use. When compared with guidelines for severe sepsis due to an UIC, only one response (1%) was compliant, and 46% (33/72) were compliant but with additional non-compliant antibiotics. Of the choices compliant with guidelines for febrile neutropenia, 57% (12/21) were dose-compliant and 29% (6/21) were below dosing recommendations.

Seventy-eight per cent of respondents (56/72) indicated they would change the antibiotic therapy if MSSA bacteraemia was identified. A change to flucloxacillin monotherapy occurred most frequently (37/56 [51% of all respondents]), with an additional five respondents changing to dicloxacillin monotherapy. Two respondents said they would de-escalate to flucloxacillin + gentamicin (from ticarcillin/clavulanate + gentamicin + vancomycin and vancomycin + meropenem) and one suggested continuing flucloxacillin + gentamicin for 14 and 7 days, respectively, compared with a 5-day duration for each antibiotic, as commenced.

Of 32 respondents who indicated they would commence empirical vancomycin therapy, seven said they would continue vancomycin therapy after identification of MSSA. Of

Table 2. Antibiotic use in Case 1 (community-acquired pneumonia)*

Antibiotic	Frequency *N* (%)	Median PDD (g/day) (range)	Median duration (days) (range)
β-lactam (non-carbapenem)			
Ceftriaxone	46 (25.0%)	2.0 (1.0–4.0)	7 (5–10)
Ticarcillin/ clavulanate	11 (6.0%)	12.4 (3.1–12.4)	7 (5–14)
Cefuroxime	6 (3.3%)	2.3 (2.3–4.5)	10 (7–10)
Benzylpenicillin	5 (2.7%)	7.2 (4.8–12.0)	7 (5–14)
Piperacillin/ tazobactam	5 (2.7%)	13.5 (13.5–18.0)	7 (5–10)
Amoxycillin/ clavulanate	3 (1.6%)	3.6 (3.0–3.6)	10 (7–10)
Cefotaxime	3 (1.6%)	3.0 (2.0–4.5)	7 (7–10)
Amoxycillin	2 (1.1%)	7.0 (6.0–8.0)	7†
Flucloxacillin	2 (1.1%)	6.0 (4.0–8.0)	8.5 (7–10)
β-lactam (carbapenem)			
Meropenem	2 (1.1%)	3.0†	10†
Macrolide			
Azithromycin	58 (31.5%)	0.50 (0.40–2.0)	7 (3–14)
Erythromycin	19 (10.3%)	4.0 (1.5–6.0)	7 (5–14)
Roxithromycin	1 (0.5%)	0.30†	7†
Glycopeptide			
Vancomycin	10 (5.4%)	2.0 (1.0–3.0)	3 (1–7)
Aminoglycoside			
Gentamicin	7 (3.8%)	0.40 (0.40–0.48)	5 (1–7)
Quinolone			
Ciprofloxacin	2 (1.1%)	0.80†	5†
Moxifloxacin	2 (1.1%)	0.40†	8.5 (7–10)

PDD = prescribed daily dose. * Total number of antibiotics: 184. † Range = 0.

Table 3. Antibiotic use in Case 2 (intra-abdominal infection)*

Antibiotic	Frequency *N* (%)	Median PDD (g/day) (range)	Median duration (days) (range)
β-lactam (non-carbapenem)			
Amoxycillin	23 (12.2%)	4.0 (3.0–16.0)	10 (5–14)
Ampicillin	19 (10.1%)	4.0 (3.0–12.0)	7 (5–14)
Piperacillin/ tazobactam	15 (8.0%)	13.5 (12.0–18.0)	10 (5–14)
Ticarcillin/ clavulanate	13 (6.9%)	12.4 (9.3–12.4)	10 (7–14)
Ceftriaxone	5 (2.7%)	1.0 (1.0–2.0)	7 (7–10)
Amoxycillin/ clavulanate	2 (1.1%)	3.6†	8.5 (7–10)
Aztreonam	1 (0.5%)	6.0†	10†
Cefuroxime	1 (0.5%)	4.5†	7†
β-lactam (carbapenem)			
Meropenem	5 (2.7%)	3.0 (1.5–3.0)	10 (7–10)
Aminoglycoside			
Gentamicin	49 (26.1%)	0.40 (0.24–0.96)	7 (1–14)
Nitroimidazole			
Metronidazole	45 (23.9%)	1.0 (0.50–10.0)	7 (5–14)
Glycopeptide			
Vancomycin	10 (5.3%)	2.0 (1.0–2.0)	6 (1–14)

PDD = prescribed daily dose. * Total number of antibiotics: 188. There were five missing responses. † Range = 0.

the 40 respondents who did not propose empirical vancomycin therapy, four said they would switch to vancomycin monotherapy and one to vancomycin + meropenem therapy if MSSA bacteraemia was identified. Drug choice was compliant with directed therapy guidelines for MSSA in 58% of cases (42/72), and compliant but with additional non-compliant antibiotics in 10% (7/72). The dose was compliant in 38% of cases (16/42), below recommendations in 38% (16/42), and above recommendations in 24% (10/42). In 52% of cases (22/42), the duration of therapy was compliant with guidelines, with the remaining 48% of responses (20/42) suggesting a duration of < 14 days.

Table 4. Antibiotic use in Case 3 (hospital-acquired pneumonia)*

Antibiotic	Frequency *N* (%)	Median PDD (g/day) (range)	Median duration (days) (range)
β-lactam (non-carbapenem)			
Ticarcillin/ clavulanate	29 (21.8%)	12.4 (5.0–12.4)	7 (5–10)
Piperacillin/ tazobactam	17 (12.8%)	13.5 (12.4–18.0)	7 (5–10)
Cefepime	5 (3.8%)	3.0 (2.0–4.0)	7 (5–10)
Cefuroxime	5 (3.8%)	2.3 (2.3–4.5)	5 (5–7)
Amoxycillin	3 (2.3%)	3.0 (3.0–6.0)	10†
Ceftriaxone	3 (2.3%)	2.0 (1.0–2.0)	5 (5–7)
Amoxycillin/ clavulanate	2 (1.5%)	3.6†	10†
Ceftazidime	1 (0.8%)	3.0†	7†
β-lactam (carbapenem)			
Meropenem	9 (6.8%)	3.0 (1.5–4.0)	10 (7–14)
Imipenem	1 (0.8%)	2.0†	7†
Glycopeptide			
Vancomycin	30 (22.6%)	2.0 (1.0–3.2)	7 (1–14)
Aminoglycoside			
Gentamicin	17 (12.8%)	0.40 (0.24–0.48)	5 (1–10)
Quinolone			
Ciprofloxacin	6 (4.5%)	0.80 (0.40–1.2)	7 (2–10)
Moxifloxacin	1 (0.8%)	0.40†	7†
Macrolide			
Azithromycin	1 (0.8%)	0.50†	10†
Erythromycin	1 (0.8%)	3.0†	5†
Nitroimidazole			
Metronidazole	2 (1.5%)	1.5†	10†

PDD = prescribed daily dose. * Total number of antibiotics: 133. There were 10 missing responses. † Range = 0.

Aminoglycoside use

Thirty-two per cent of all responses (98/309) included adjuvant gentamicin therapy. There were no instances of aminoglycoside monotherapy being prescribed. Gentamicin was uniformly prescribed as a once-daily dose, with the exception of one instance of empirical 8-hourly dosing. In

Table 5. Antibiotic use in Case 4 (unidentified infectious cause)*

Antibiotic	Frequency *N* (%)	Median PDD (g/day) (range)	Median duration (days) (range)
β-lactam (non-carbapenem)			
Piperacillin/ tazobactam	20 (13.2%)	13.5 (12.4–18.0)	7 (5–14)
Ticarcillin/ clavulanate	17 (11.3%)	12.4 (5.0–16.4)	10 (7–14)
Flucloxacillin	6 (4.0%)	6.0 (4.0–8.0)	7 (5–7)
Cefepime	4 (2.6%)	2.3 (2.3–4.5)	5 (5–7)
Aztreonam	2 (1.3%)	4.5 (3.0–6.0)	6 (5–7)
Ceftriaxone	2 (1.3%)	1.5 (1.0–2.0)	6 (5–7)
Amoxycillin	1 (0.7%)	3.0†	7†
Amoxycillin/ clavulanate	1 (0.7%)	3.6†	5†
Benzylpenicillin	1 (0.7%)	8.0†	7†
Ceftazidime	1 (0.7%)	3.0†	7†
Cefuroxime	1 (0.7%)	4.5†	7†
β-lactam (carbapenem)			
Meropenem	20 (13.2%)	3.0 (1.0–3.0)	7 (2–14)
Imipenem	1 (0.7%)	2.0†	7†
Glycopeptide			
Vancomycin	32 (21.2%)	2.0 (1.0–3.0)	7 (2–14)
Aminoglycoside			
Gentamicin	25 (16.6%)	0.40 (0.24–0.56)	5 (1–10)
Tobramycin	1 (0.7%)	0.56†	5†
Quinolone			
Ciprofloxacin	6 (4.0%)	1.0 (0.40–1.5)	7 (5–14)
Sulfonamide/trimethoprim			
Sulfamethoxazole/ trimethoprim	5 (3.3%)	1.6 (1.2–9.6)	14 (10–21)
Nitroimidazole			
Metronidazole	3 (2.0%)	1.5 (1.0–1.5)	7 (5–7)
Macrolide			
Azithromycin	1 (0.7%)	0.50†	10†
Erythromycin	1 (0.7%)	2.0†	14†

PDD = prescribed daily dose. * Total number of antibiotics: 151. There were 12 missing responses. † Range = 0.

Table 6. Compliance of prescribing with *Therapeutic guidelines: antibiotic*[7]

Case	Guideline category‡	Drug choice*			Dosing†		
		NC	C	C + NC	BR	C	AR
Case 1: CAP	CAP in adults (risk class V and patient requiring ICU management)	33 (39%)	44 (52%)	7 (8%)	10 (23%)	3 (7%)	31 (70%)
Case 2: IAI	Peritonitis due to perforated viscus	4 (5%)	54 (68%)	21 (27%)	32 (59%)	18 (33%)	4 (7%)
Case 3: HAP	HAP: low risk of multidrug-resistant organisms	41 (55%)	9 (12%)	24 (32%)	0	8 (89%)	1 (11%)
Case 3: HAP	HAP: high risk of multidrug-resistant organisms	24 (32%)	43 (58%)	7 (9%)	11 (26%)	27 (63%)	5 (12%)
Case 4: UIC	Severe sepsis: empirical therapy (no obvious source of infection): adults	38 (53%)	1 (1%)	33 (46%)	0	1 (100%)	0
Case 4: UIC	Severe sepsis: empirical therapy (no obvious source of infection): febrile neutropenic patients	36 (50%)	21 (29%)	15 (21%)	6 (29%)	12 (57%)	3 (14%)
Case 4: MSSA	Severe sepsis: *Staphylococcus aureus*§ bacteraemia	22 (31%)	42 (59%)	7 (10%)	16 (38%)	16 (38%)	10 (24%)

AR = above recommendations. BR = below recommendations. C = compliant. C + NC = compliant, but with additional non-compliant antibiotics. CAP = community-acquired pneumonia. HAP = hospital-acquired pneumonia. IAI = intra-abdominal infection. MSSA = methicillin-sensitive *Staphylococcus aureus*. NC = non-compliant. UIC = unidentified infectious cause. * Drug choice compliance reported as *N* (%). Total numbers for drug choice are numbers of responses for each case (ie, 84, 79, 74 and 72, respectively). † Dosing compliance reported as *N* (%) for patients with compliant drug choice. ‡ Guideline category used as basis for comparison. § Details missing in one case of directed therapy.

directed therapy for *P. aeruginosa*, there was one instance of 8-hourly dosing (5 mg/kg). In directed therapy for MSSA, there was one instance of 8-hourly dosing (5 mg/kg) and one of 12-hourly dosing (3 mg/kg). Apart from one outlier (0.32 g 8-hourly [equivalent to 12 mg/kg]), empirical gentamicin dosing ranged from 3 to 7 mg/kg, with 57% of respondents (56/98) prescribing 5 mg/kg and 7% (7/98) prescribing 7 mg/kg. Twenty-three per cent of suggested dosages (23/98) were < 5 mg/kg and 19% (19/98) were > 5 mg/kg. PDD and duration of therapy did not differ significantly between cases ($P = 0.64$ and $P = 0.11$, respectively).

Mode of administration

The favoured modes of administration for all four cases are shown in Table 7. Vancomycin (a glycopeptide) was the agent most commonly prescribed as a continuous or extended infusion (20% [16/82]). Continuous or extended administration of β-lactams was used in only 3% of prescriptions for that antibiotic class (9/321): benzylpenicillin (3), amoxicillin (3), ceftriaxone (1), piperacillin/tazobactam (1) and ticarcillin/clavulanate (1). Macrolides (erythromycin [4] and azithromycin [2]) were prescribed as extended infusions in 8% of cases in that antibiotic class (6/76).

Discussion

This article identifies empirical and targeted antibiotic prescribing practices of Australian and New Zealand ICU clinicians and demonstrates largely appropriate prescription that complies with Australian guidelines. We estimate that our sample represented over 9% of intensive care specialists in the region, but only about 2% of advanced trainees. We found highest levels of compliance in the case of IAI and lowest compliance in the case of an UIC with a background of immunosuppression. Combination empirical therapy was common, occurring in four-fifths of cases. The frequent use of gentamicin and vancomycin matches usage patterns in a previous prospective study conducted in Australian and New Zealand ICUs.[8]

Recommendations for empirical antibiotic treatment of CAP in patients requiring ICU management include cover against common and significant pathogens.[7,11,12] We found that 89% of respondents prescribed dual therapy with a β-lactam and a macrolide, which is consistent with Australian and international guidelines.[7,13] The greatest deviation from guidelines occurred in selecting antibiotics to be used when there is concern about organism resistance.[14] However, a multicentre Australian study found that only 5.4% of episodes of CAP involved an organism resistant to dual therapy with benzylpenicillin and doxycycline or a macrolide.[11]

While the proposed management of IAI was most compliant with recommended guidelines in terms of drug choice, β-lactam dosing was below the recommended level in 40% of cases. Given that low dosing can reduce rates of clinical cure and increase rates of organism resistance,[15,16] this finding may be significant. Another area in which intended practice differed from guidelines was the use of additional non-recommended agents with broader cover, including meropenem and vancomycin. Given the high cost of interventions in the ICU,[17] our study highlights the importance

Table 7. Mode of administration, by antibiotic class

Antibiotic class	Intermittent, *N* (R%)	Extended, *N* (R%)	Continuous, *N* (R%)
β-lactam (non-carbapenem)	274 (97%)	1 (< 1%)	8 (3%)
β-lactam (carbapenem)	38 (100%)	0	0
Aminoglycoside	99 (100%)	0	0
Macrolide	76 (93%)	6 (7%)	0
Glycopeptide	66 (81%)	9 (11%)	7 (9%)
Nitroimidazole	50 (100%)	0	0
Quinolone*	15 (94%)	1 (6%)	0
Sulfonamide/ trimethoprim	3 (60%)	1 (20%)	1 (20%)
Total	621 (95%)	18 (3%)	16 (2%)

* Mode of administration was missing for one antibiotic.
R% = row per cent.

of reducing selective pressure to encourage the growth of multiresistant organisms, which may lead to morbidity, prolonged length of stay and increased costs.[18]

The proposed treatment for HAP was in accordance with guidelines for high risk of MDR organisms, despite the patient in the case vignette coming from a low-risk setting. Risk factors for resistant organisms in HAP include prior antimicrobial therapy, neurological disturbance or aspiration on ICU admission, and ICU stay greater than 8 days,[19] none of which were a feature in this case vignette. As in the previous cases, the practice of providing cover against MDR organisms places selection pressure towards increasing rates of resistance and should be carefully considered in line with individual and site-specific risks for resistance.

In the treatment of HAP, half the respondents prescribed initial anti-pseudomonal cover, with the remaining respondents indicating they would switch to anti-pseudomonal cover if *P. aeruginosa* was identified. Given that *P. aeruginosa* has multiple intrinsic mechanisms for developing resistance,[20] and that delay in initiating appropriate anti-pseudomonal cover increases mortality,[21] many experts in infectious disease suggest dual-agent cover against *Pseudomonas*, certainly until antibiotic sensitivities are available to allow de-escalation.[22,23] A meta-analysis has shown that β-lactam monotherapy is as efficacious as combination therapy with an aminoglycoside in immunocompetent patients,[24] and two-thirds of the respondents in our study followed this practice of β-lactam monotherapy. However, combination therapy may reduce mortality in patients with *P. aeruginosa* bacteraemia.[25]

The proposed treatment for severe sepsis with a UIC and immunosuppression followed guidelines for the management of febrile neutropenia, despite the patient in the case vignette not strictly meeting the criterion for neutropenia (ie, neutrophils $< 1 \times 10^9$/L). Vancomycin was chosen in 21% of cases and meropenem in 13% of cases, suggesting respondents were basing treatment on the presumption of a high risk of infection with methicillin-resistant *S. aureus* and extended-spectrum β-lactamase-producing bacteria. While this practice supports the principle of getting antibiotic cover right the first time,[26,27] drug choice decisions must take into account site-specific organism resistance profiles. A meta-analysis has suggested that single-agent gram-negative cover is as good as dual-agent cover in cases of febrile neutropenia,[28] which supports the use of cefepime and meropenem monotherapy by a minority of respondents in our study (11% of cases).

The large majority of aminoglycosides in our survey were administered as a single daily dose of $\geqslant 5$ mg/kg. This is in keeping with international studies showing that it is now common practice to administer single daily doses or extended interval dosing of aminoglycosides.[29,30] Divided doses produce more renal toxicity,[31] and the practice of giving divided doses was limited to four instances in our survey. Only 7% of respondents who prescribed gentamicin in our study indicated that they would use the base dose of 7 mg/kg recommended by Nicolau and colleagues.[29]

One of the limitations of using a case vignette approach in our study was its reliance on self-reported behaviour.[32] The intended prescribing practices were not validated against actual practice. However, this technique enabled consistent comparison across common, significant and potentially contentious infectious challenges in the ICU setting. Furthermore, our study was not designed to explore issues relating to switching from intravenous to oral antibiotic medication, an approach that has been identified as efficacious, cost-effective and associated with lower morbidity in the treatment of CAP.[33] Except in the case of guidelines for the treatment of MSSA bacteraemia, compliance with duration of therapy could not be evaluated, as this is dependent on the type of organism, the patient's response to therapy, and duration of both intravenous and oral therapy. The extent to which empirical prescribing patterns are modified according to the organism and the clinical response could not be determined, except for directed therapy for *P. aeruginosa* and MSSA. Compliance was evaluated against therapeutic guidelines that were developed for an Australian setting and may not be in widespread use across Australia and New Zealand, despite similar susceptibility profiles in both regions. Moreover, these guidelines were published in 2006, and current practices may differ from the guidelines based on new evidence published in the critical care literature.

Conclusions

Our survey revealed that empirical antibiotic prescribing patterns in an Australian and New Zealand ICU setting are in general appropriate and in keeping with published guidelines, although there was a tendency to provide broader cover for multidrug-resistant organisms and to under-dose with β-lactam antibiotics. Empirical therapy based on site-specific resistant organism profiles and the avoidance of low-dose prescribing is advocated to provide appropriate initial cover, prevent under-dosing and reduce the risk of resistance. Our data provide a baseline of antibiotic prescribing from which changes in practice could be tracked by repeating the survey in the future.

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Author details

Joel M Dulhunty, Research Fellow[1,2]
Steven A R Webb, Senior Staff Specialist[3,4]
David L Paterson, Professor of Medicine[5,6]
Rinaldo Bellomo, Director of Research[7]
John Myburgh, Director and Professor,[8] and Senior Physician[9]
Jason A Roberts, Senior Clinical Pharmacist[1,2]
Jeffrey Lipman, Director,[1] and Professor[2]

1 Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD.
2 Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, QLD.
3 Intensive Care Unit, Royal Perth Hospital, Perth, WA.
4 School of Medicine and Pharmacology and School of Population Health, University of Western Australia, Perth, WA.
5 Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, QLD.
6 University of Queensland Centre for Clinical Research, Brisbane, QLD.
7 Department of Intensive Care Medicine, Austin Hospital, Melbourne, VIC.
8 Division of Critical Care and Trauma, George Institute for International Health, Sydney, NSW.
9 Department of Intensive Care Medicine, St George Hospital, Sydney, NSW.

Correspondence: Joel_Dulhunty@health.qld.gov.au

References

1 Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302: 2323-9.
2 Dulhunty JM, Lipman J, Finfer S. Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. *Intensive Care Med* 2008; 34: 1654-61.
3 Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; 34: 344-53.
4 Singh N, Yu VL. Rational empiric antibiotic prescription in the ICU. *Chest* 2000; 117: 1496-9.
5 Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* 2003; 31: 2742-51.
6 Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115: 462-74.
7 Therapeutic Guidelines Limited. Therapeutic guidelines: antibiotic. Version 13, 2006. In: eTG complete: electronic version (updated November 2009). http://www.tg.org.au (accessed May 2010).
8 Bellomo R, Bersten AD, Boots RJ, et al. The use of antimicrobials in ten Australian and New Zealand intensive care units. Australian and New Zealand Intensive Care Multicentre Studies Group Investigators. *Anaesth Intensive Care* 1998; 26: 648-53.
9 Ferguson J, Doherty P, Cooper C, et al. Hospital antibiotic utilisation in three states. *Aust Infect Control* 2003; 8: 7-12.
10 Boots RJ, Lipman J, Bellomo R, et al. The spectrum of practice in the diagnosis and management of pneumonia in patients requiring mechanical ventilation. Australian and New Zealand practice in intensive care (ANZPIC II). *Anaesth Intensive Care* 2005; 33: 87-100.
11 Charles PG, Whitby M, Fuller AJ, et al. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. *Clin Infect Dis* 2008; 46: 1513-21.
12 Wilson PA, Ferguson J. Severe community-acquired pneumonia: an Australian perspective. *Intern Med J* 2005; 35: 699-705.
13 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 Suppl 2: S27-72.
14 Waterer GW. Combination antibiotic therapy with macrolides in community-acquired pneumonia: more smoke but is there any fire? *Chest* 2003; 123: 1328-9.
15 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; 26: 1-10.
16 Schrag SJ, Pena C, Fernandez J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *JAMA* 2001; 286: 49-56.
17 Dorman T, Pauldine R. Economic stress and misaligned incentives in critical care medicine in the United States. *Crit Care Med* 2007; 35 (2 Suppl): S36-43.
18 Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med* 2009; 37: 1463-9.
19 Leroy O, Jaffre S, D'Escrivan T, et al. Hospital-acquired pneumonia: risk factors for antimicrobial-resistant causative pathogens in critically ill patients. *Chest* 2003; 123: 2034-42.
20 Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006; 43 Suppl 2: S49-56.
21 Lodise TP Jr, Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infec-

tions: impact of delayed appropriate antibiotic selection. *Antimicrob Agents Chemother* 2007; 51: 3510-5.

22 Niederman MS. De-escalation therapy in ventilator-associated pneumonia. *Curr Opin Crit Care* 2006; 12: 452-7.

23 Eachempati SR, Hydo LJ, Shou J, Barie PS. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? *J Trauma* 2009; 66: 1343-8.

24 Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004; 328: 668.

25 Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004; 4: 519-27.

26 Lipman J, Boots R. A new paradigm for treating infections: "go hard and go home". *Crit Care Resusc* 2009; 11: 276-81.

27 Fish DN, Ohlinger MJ. Antimicrobial resistance: factors and outcomes. *Crit Care Clin* 2006; 22: 291-311.

28 Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003; 326: 1111.

29 Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother* 1995; 39: 650-5.

30 Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother* 1996; 37: 645-63.

31 Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis* 2009; 48: 713-21.

32 Sintchenko V, Iredell JR, Gilbert GL, Coiera E. What do physicians think about evidence-based antibiotic use in critical care? A survey of Australian intensivists and infectious disease practitioners. *Intern Med J* 2001; 31: 462-9.

33 Cunha BA. Empiric therapy of community-acquired pneumonia: guidelines for the perplexed? *Chest* 2004; 125: 1913-9. ❑

Appendix. Case vignettes

Case 1

A previously well 55-year-old man has been admitted to the ICU from the emergency department (ED) with community-acquired pneumonia. He presented to the ED with a 2-day history of progressive worsening of cough, pleuritic chest pain and breathlessness. In the ED he remained in shock, despite volume resuscitation with 3000 mL of fluid. He was intubated and ventilated after worsening tachypnoea despite non-invasive ventilation. After intubation there was a further drop in blood pressure, and noradrenaline treatment was commenced. A chest x-ray showed extensive dense consolidation in the right upper and lower lobes and left upper lobe of the lungs.

Case 2

A 45-year-old man has been admitted to the ICU with septic shock secondary to peritonitis after activation of the hospital's medical emergency team. Six days previously, he had undergone an elective left hemicolectomy for carcinoma. At the time of transfer to the ICU he was in shock, and had severe metabolic acidosis and an elevated respiratory rate, but was still passing urine and had a normal creatinine level. A computed tomography scan showed extensive air and fluid within the peritoneal cavity, with a large loculated collection in the left subphrenic space. He is being intubated before transfer to the operating theatre for a laparotomy. He received antibiotic prophylaxis at the time of his elective surgery but has not received any subsequent antibiotics.

Case 3

A 76-year-old man with multiple comorbidities has been admitted to the ICU with hospital-acquired pneumonia after elective upper abdominal surgery. He has a history of mild Parkinson's disease, type II diabetes mellitus, hypertension and previous coronary artery bypass grafting, with moderately depressed left ventricular function but normal renal function. He was admitted to hospital 8 days previously for a laparoscopic cholecystectomy. The procedure was complicated by bleeding that required conversion to an open procedure, which was completed without additional complication. He had made a slow but satisfactory postoperative recovery until 2 days ago, when he developed increasing breathlessness, confusion and fever. A chest x-ray showed patchy but extensive consolidation in both right and left lungs. He had deteriorating oxygenation and a rising arterial partial pressure of CO_2, and required intubation on the ward before being transferred to the ICU.

Case 4

A 68-year-old woman with septic shock on a background of immunosuppression has been admitted to the ICU. She has a 25-year history of rheumatoid arthritis, which is currently treated with prednisolone 10 mg/day and weekly methotrexate. She has type II diabetes mellitus requiring treatment with insulin. She presented to hospital after becoming progressively unwell over the previous 2 days, with fevers, rigors, diarrhoea and breathlessness. She was in shock at the time of presentation and remained so despite aggressive volume resuscitation and noradrenaline treatment. Her abdomen was soft and non-tender, and a chest x-ray was clear. Her white cell count was 2.4×10^9/L, with a left shift and toxic granulation. Her temperature was 38.9C, and she had a C-reactive protein level of 364 mg/L. None of her joints were acutely swollen or inflamed.