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Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals

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SUMMARY

Background: Concern regarding bacterial co-infection complicating SARS-CoV-2 has created a challenge for antimicrobial stewardship. Following introduction of national antibiotic recommendations for suspected bacterial respiratory tract infection complicating COVID-19, a point prevalence survey of prescribing was conducted across acute hospitals in Scotland.

Methods: Patients in designated COVID-19 units were included and demographic, clinical and antimicrobial data were collected from 15 hospitals on a single day between 20th and 30th April 2020. Comparisons were made between SARS-CoV-2 positive and negative patients and patients on non-critical care and critical care units. Factors associated with antibiotic prescribing in SARS-CoV-2 positive patients were examined using Univariable and multivariable regression analyses.

Findings: There were 820 patients were included, 64.8% were SARS-CoV-2 positive and 14.9% were managed in critical care, and 22.1% of SARS-CoV-2 infections were considered probable or definite nosocomial infections. On the survey day, antibiotic prevalence was 45.0% and 73.9% were prescribed for suspected respiratory tract infection. Amoxicillin, doxycycline and co-amoxiclav accounted for over half of all antibiotics in non-critical care wards and meropenem, piperacillin-tazobactam and co-amoxiclav accounted for approximately half prescribed in critical care. Of all SARS-CoV-2 patients, 38.3% were prescribed antibiotics. In a multivariable logistic regression analysis, COPD/chronic lung disease and CRP $\geq$ 100 mg/l were associated with higher odds and probable or confirmed nosocomial COVID-19, diabetes and management on an elderly care ward had lower odds of an antibiotic prescription. Systemic antifungals were prescribed in 9.8% of critical care patients and commenced a median of 18 days after critical care admission.

Interpretation: A relatively low prevalence of antibiotic prescribing in SARS-CoV-2 hospitalised patients and low proportion of broad spectrum antibiotics in non-critical care settings was observed potentially reflecting national antimicrobial stewardship initiatives. Broad spectrum antibiotic and antifungal prescribing in critical care units was observed indicating the importance of infection prevention and control and stewardship initiatives in this setting.

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Research in context

Evidence before this study

There is concern that the COVID-19 pandemic will lead to unnecessary antibiotic use which will further drive antimicrobial resistance. Published evidence indicates high rates of antibiotic prescribing in relation to SARS-CoV-2 infection without supporting evidence of bacterial co-infection. As limiting unnecessary antibiotic use in viral infections is a key focus for antimicrobial stewardship initiatives, the Scottish Antimicrobial Prescribing Group developed recommendations for prudent use of antibiotics in hospital in the context of suspected SARS-CoV-2 in March 2020. A national point prevalence antimicrobial survey was then performed across designated COVID-19 units in acute hospitals to assess antimicrobial prescribing.

Added value of this study

This is the first national survey of antibiotic prescribing in suspected COVID-19 and captured approximately two fifths of hospitalised patients in Scotland with SARS-CoV-2 at the peak of the epidemic. The study demonstrated a relatively low proportions of patients prescribed antibiotics with SARS-CoV-2 (38.3%) than expected and showed that narrow spectrum antibiotics were predominantly used in medical and elderly care wards reflecting national recommendations. Prescribing of broad spectrum antibiotics and antifungals in critical care was indicative of suspected nosocomial bacterial and invasive candida infection. Probable or confirmed nosocomial COVID-19, presence of diabetes and management on an elderly care ward were independently associated with lower odds of an antibiotic prescription suggesting differences in clinical presentation and potentially management strategies. The significance of these findings is further discussed. A relatively low incidence of antibiotic prescribing in hospitalised patients with SARS-CoV-2 and low proportion of broad spectrum antibiotics in non-critical care settings may reflect a mature national stewardship programme in Scotland and a coordinated national response to COVID-19. This experience may support others in stewardship initiatives as the pandemic continues. Broad spectrum antibiotic and antifungal prescribing in the challenging environment of critical care highlights the importance of infection prevention and control and stewardship initiatives in that setting.

Introduction

The nature and rationale for antibiotic prescribing in patients with suspected COVID-19 is not well characterised. Unnecessary antibiotic prescribing is of concern for the individual in view of the risk of antibiotic-related adverse events[1] and to the wider public health due to the impact on antimicrobial resistance.[2] Limiting prescribing when viral respiratory tract infection (RTI) is suspected is an important target for antimicrobial stewardship interventions[3] and particularly in the context of SARS-CoV-2 infection.[4]

When first reported in Wuhan in December 2019, more than 90% of hospitalised patients with COVID-19 received antibiotics with little supporting evidence of associated bacterial infection.[5] The International Severe Acute Respiratory Infection Consortium (ISARIC) study subsequently reported prescribing in 72% of those hospitalised.[6] The World Health Organisation recommends prompt antibiotic therapy (as per local guidance) against likely pathogens causing severe acute respiratory infection or sepsis for those hospitalised with suspected COVID-19.[7] A recent meta-analysis of published reports has estimated community-acquired bacterial co-infection in COVID-19 to be low at approx. 3.5%[8] however prolonged ventilatory and multi-organ support in a proportion of hospitalised patients with severe COVID-19 raises concern for nosocomial bacterial and fungal infection risk.[9]

With clinical overlap between COVID-19 and bacterial lower RTIs and with emerging global COVID-19-related prescribing; COVID-19 Antimicrobial Stewardship advice was issued by the Scottish Antimicrobial Prescribing Group (SAPG) cautioning against routine antibiotic use in suspected COVID-19, and promoting the judicious use of short duration (5 day), narrow spectrum antibiotics when there is clinical suspicion of pneumonia or purulent bronchitis.[10] In order to better understand reasons for, and dynamics of, antibiotic prescribing and identify opportunities for improved prescribing an antimicrobial point prevalence survey (PPS) was conducted to coincide with high clinical activity in Scottish hospitals.

Here, results from a PPS of antibiotic and antifungal prescribing in patients with suspected and proven COVID-19 infection in acute hospitals are summarised.

Methods

Study design and inclusion criteria

A Point Prevalence Survey (PPS) of hospitalised adults with suspected or confirmed COVID-19 was designed and conducted in clinical areas where patients with COVID-19 were hospitalised in NHS Scotland. All NHS boards were invited to collect data in at least one acute hospital, in a minimum of one designated adult ward where COVID-19 patients were managed (general medicine or elderly care), and ideally including all designated COVID-19 wards and critical care units. Non-COVID-19 designated wards, community and psychiatric hospitals were excluded. Clinical areas were surveyed on one occasion on a single day between 20th and 30th April 2020. Patients were initially screened for inclusion based on availability of SARS-CoV-2 RT-PCR (reverse transcriptase polymerase chain reaction) test results.

Data collection

Data were collected from written and electronic medical notes and prescription charts. A data collection tool based on one currently used in Glasgow hospitals,[11] the global PPS tool[12] and bespoke PPS[13,14] was used. Data collection was carried out by medical staff, antimicrobial and ward pharmacists and antimicrobial nurses. Where necessary, staff were trained by local clinicians experienced in PPS.

Data definitions

Clinical records were reviewed for SARS-CoV-2 test status. Probable nosocomial COVID-19 and definite nosocomial COVID-19 were defined as a compatible clinical illness with a new positive test 8 to 14 days and more the 14 days following admission, respectively.[15]

Antibiotic prescribing in the two weeks prior to admission and on the day of admission was recorded as detailed in the medical records. Detailed information on antibiotics and systemic antifungals prescribed on the survey day including start date, route and indication as per anatomical source (e.g. respiratory tract, urinary tract etc.) of the suspected infection was recorded.[12] Microbiological investigations were not recorded however prescribing was

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recorded as empirical (prior to microbiological confirmation) or directed (following microbiological confirmation).

Potential factors influencing antibiotic prescribing were collected including: demographics, care home residency and comorbidities (Table 1). Immunocompromised was defined by immunosuppressant therapy including regular corticosteroids, organ or bone marrow transplant, HIV infection, renal replacement therapy, asplenia or recently completed therapy for malignancy.

Descriptive clinical data included presence and nature of sputum production (grouped as 'purulent/bloody' if recorded as green, brown or bloody sputum), CRP (C-reactive protein value) and chest X-ray responses were grouped as normal or abnormal (included COVID-19 compatible, indeterminant, pneumonia or other abnormal).

Other clinical management data included use of oxygen, respiratory support and use of investigational therapeutic agents as part of a clinical trial. Presence of treatment escalation plans and 'do not attempt cardiopulmonary resuscitation' documentation (DNACPR) was recorded where available.

Data management

Following completion of data collection, anonymised data were sent to the core survey team for curation, validation and analysis.

Descriptive analysis

Analyses included patients with a SARS-CoV-2 RT-PCR test result. Prevalence estimates with 95% confidence intervals (95% CI) were calculated and frequency tables of survey population and prescribing characteristics were produced. Patients with missing data were excluded from denominators. Data were examined for the whole patient population and comparisons were made between SARS-CoV-2 RT-PCR positive and negative patients, and those on medical or elderly care wards were compared to those on high dependency and intensive care units (combined as 'critical care'). Pearson's Chi square tests with a continuity correction or Fisher's Exact tests were used to compare percentages between two groups and determine if significantly different. A Mann–Whitney U test compared median ages between groups. Median durations were presented with range (minimum to maximum) and inter-quartile ranges (IQR). Statistical significance was set at $p<0.05$. All analyses were carried out using R (version 3.5.1).

The average daily number of hospitalised patients in NHS Scotland with confirmed COVID-19 infection (positive SARS-CoV-2 RT-PCR test) during the study period was used to estimate the proportion of hospitalised COVID-19 patients in Scotland included in this survey.[15]

Statistical analysis

Univariable and multivariable regression analyses were conducted to identify factors associated with prescribing of at least one antibiotic on the survey day in patients with confirmed COVID-19 infection. A survey weighted binomial model was used (which accounted for clustering of beds within wards) and analyses were conducted in R version 3.5.1 (R package 'survey').

Univariable factors were screened and those with p-values below 0.3 were included in a backward elimination and forward stepwise approach to select the most parsimonious multivariate model. Statistical significance was set at $p<0.05$. A category-level p-value (using the Wald test), odds ratios (OR) and 95% CI were calculated for each factor in the final model.

Ethical approval

Local governance processes for audit/survey of clinical practice were followed. No patient identifiers were collected and there were no interventions or patient contact during the survey.

Results

Survey characteristics

Eight of the 15 Scottish NHS boards participated with data collected from 15 of the 22 acute hospitals (ranging from 400 to 1400 inpatient beds). Of these hospitals, 112 (84.8%) of all 132 designated COVID-19 wards and critical care units were surveyed. In total, 1061 patients were screened and 820 patients tested for SARS-CoV-2 were included. Of the 820, 666 (81.4%) were suspected of having COVID-19 on admission, and 531 (64.8%) tested positive for SARS-CoV-2 up to and including the day of the survey (Table 1). There was a daily average of 1403 (range 1324 to 1520) SARS-CoV-2 positive patients in all hospitals nationally during the survey period suggesting that the SARS-CoV-2 positive population studied here represented approximately two fifths of the total inpatient SARS-CoV-2 positive population at this time.

*Characteristics of survey population (*n = *820)*

Over half (51.8%) were male and median age was 71 years (range 17 to 104, IQR 59 to 81). The majority (65.9%) were managed on medical wards, 19.3% on elderly care wards and 14.9% in critical care. There were 11.1% mechanically ventilated, 2.1% were receiving non-invasive ventilation, 0.6% high flow nasal oxygen and 40.8% supplementary oxygen. Six hundred and eighty five patients (83.5%) had a treatment escalation plan recorded, 44.2% of whom were for critical care referral or discussion at an escalation multidisciplinary team (MDT) meeting if required. More than half of surveyed patients (54.4%) had a DNACPR instruction recorded and 13.1% patients were enrolled in a clinical therapeutic trial.

When compared to SARS-CoV-2 negative patients, SARS-CoV-2 positive patients were older (median age 72 versus 69 years, $p=0.005$), more likely admitted from a care home (11.9% versus 4.2%, $p<0.001$), had a DNACPR order recorded (57.7% versus 48.3%, $p=0.01$), and less likely to have COPD/chronic respiratory disease (excluding asthma) (13.6% versus 26.5%, $p<0.001$) or another suspected infection (37.5% versus 58.5%, $p<0.001$). SARS-CoV-2 positive patients were also more likely to have an abnormal chest X-ray (77.3% versus 59.9%, $p<0.001$) and to have a CRP $\geq$ 100 mg/l (45.1% versus 30.7%, $p<0.001$) (Table 1).

Of those who tested SARS-CoV-2 positive and for whom the admission and test dates were recorded; 9.5% were diagnosed prior to admission, 59.8% within 3 days of admission, 8.6% between 3 and 7 days post-admission, 6.7% between 8 and 14 days and 15.4% more than 14 days post-admission. Therefore, approximately one fifth (22.1%) of COVID-19 infections in this population were considered to have a COVID-19 infection of probable or definite hospital-onset.

Antibiotic prescribing prior to and on admission

Prevalence of antibiotic prescribing in the two weeks prior to admission was 29.2% (95%CI: 26.1 to 32.5) and 62.4% (95%CI: 58.9 to 65.7) on the day of admission. Of all patients receiving an antibiotic on the day of admission and for whom a route was recorded; 59.9% received intravenous (IV) therapy (with or without oral antibiotic therapy) and the majority (92.5%) was empirical (Table 2). The most common prescribing indication was RTI

Table 1
Characteristics of the survey population.

Characteristics group	Patient characteristics	All surveyed patients ($n = 820$)			SARS-CoV-2 positive ($n = 531$)			SARS-CoV-2 negative ($n = 289$)			Comparison between SARS-CoV-2 positive and negative patient groups
		Total surveyed patients	Total surveyed patients with characteristic	Percentage	Total surveyed patients	Total surveyed patients with characteristic	Percentage	Total surveyed patients	Total surveyed patients with characteristic	Percentage	
COVID status	SARSCoV2 positive test	820	531	64.8							
	Probable or definite nosocomial COVID-19	820	116	14.1	531	116	21.8				
	COVID-19 suspected on admission	818	666	81.4	529	440	83.2	289	226	78.2	<0.001
Demographics	Age Median (Range)	71 years (range 17 to 104, inter-quartile range (IQR) 59 to 81)			72 years (range 25 to 104 inter-quartile range (IQR) 61 to 82)			69 years (range 17 to 96 inter-quartile range (IQR) 54 to 81)			0.005
	Sex (%m)	820	425	51.8	531	274	51.6	289	151	52.2	0.92
Location	Care home resident	820	75	9.1	531	63	11.9	289	12	4.2	<0.001
	Ward type - Critical care	820	122	14.9	531	110	20.7	289	12	4.2	<0.001
	Ward type - Elderly	820	158	19.3	531	136	25.6	289	22	7.6	
	Ward type - Medical	820	540	65.9	531	285	53.7	289	255	88.2	
Comorbidities	Asthma	820	82	10.0	531	47	8.9	289	35	12.1	0.2
	Cardiovascular disease	819	269	32.8	530	174	32.8	289	95	32.9	1.0
	COPD/Chronic Lung disease	817	148	18.1	530	72	13.6	287	76	26.5	<0.001
	Diabetes	820	193	23.5	531	133	25.0	289	60	20.8	0.2
	Hypertension	818	329	40.2	529	218	41.2	289	111	38.4	0.5
	Immunocompromised	816	107	13.1	528	57	10.8	288	50	17.4	0.8
	Long term renal dialysis	820	18	2.2	531	13	2.4	289	5	1.7	0.7
	Morbid obesity	804	61	7.6	522	36	6.9	282	25	8.9	0.4
	Other chronic condition	818	509	62.2	529	321	60.7	289	188	65.1	0.3
Other	Other suspected infection	817	367	44.9	528	198	37.5	289	169	58.5	<0.001
	Penicillin Allergy	820	121	14.8	531	79	14.9	289	42	14.5	0.9
Diagnostics / clinical signs	Abnormal chest x-ray	807	574	71.1	520	402	77.3	287	172	59.9	<0.001
	CRP ≥100 mg/l	810	324	40.0	523	236	45.1	287	88	30.7	<0.001
	Purulent / bloody sputum	820	77	9.4	531	47	8.9	289	30	10.4	0.6
Management	Clinical therapeutic trial	818	107	13.1	529	100	18.9	289	7	2.4	<0.001
	Supplemental oxygen	819	334	40.8	530	242	45.7	289	92	31.8	<0.001
	Treatment escalation*	685	303	44.2	473	207	43.8	212	96	45.3	<0.001
	DNACPR recorded	816	444	54.4	530	306	57.7	286	138	48.3	0.01

Notes: COPD- Chronic obstructive pulmonary disease and other chronic lung disease; DNACPR – do not attempt cardiopulmonary resuscitation order; CRP – C-reactive protein.
* Treatment escalation – recorded treatment plan including planned multi-disciplinary team discussion.

Table 2
Antibiotic and antifungal prescribing on day of admission and day of survey, by ward type and by SARS-CoV-2 result.

	All surveyed patients ($n=820$)			Medical and elderly wards									Critical care wards							
				All surveyed patients ($n=698$)			SARSCoV-2 positive ($n=421$)			SARSCoV-2 negative ($n=277$)			All surveyed patients ($n=122$)			SARSCoV-2 positive ($n=110$)			SARSCoV-2 negative ($n=12$)	
	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%	Total surveyed patients	Total surveyed patients with characteristic	%
Antibiotic(s) on admission	789	492	62.4	672	409	60.9	402	257	63.9	270	152	56.3	122	83	68.0	105	79	75.2	12	4	33.3
Empirical antibiotic(s) on admission	403	389	96.5	327	315	96.3	230	219	95.2	97	96	99.0	76	74	97.4	73	71	97.3	3	3	100.0
IV antibiotic(s) on admission	461	276	59.9	384	212	55.2	243	126	51.9	141	86	61.0	77	64	83.1	73	60	82.2	4	4	100.0
Antibiotic(s) on day of survey	818	368	45.0	697	314	45.1	421	153	36.3	276	161	58.3	121	54	44.6	109	50	45.9	12	4	33.3
Empirical antibiotic(s) on day of survey	367	320	87.2	313	281	89.8	153	133	86.9	160	148	92.5	54	39	72.2	50	35	70.0	4	4	100.0
IV antibiotic(s) on day of survey	364	178	48.9	312	129	41.3	152	60	39.5	160	69	43.1	52	49	94.2	48	45	93.8	4	4	100.0
Systemic antifungal on day of survey	818	13	1.6	672	1	0.1	402	1	0.2	270	0	0.0	122	12	9.8	105	12	11.4	12	0	0.0
Empirical systemic antifungal on day of survey	13	5	38.5	1	0	0.0	1	0	0.0	0	0	–	12	5	41.7	12	5	41.7	0	0	–

Table 3
Total number and percentage of antibiotics prescribed for all indications, by ward type and by SARS-CoV-2 result.

Antibiotics Prescribed on day of survey*	Total number of antibiotics	Percentage of total antibiotics prescribed (%)	Medical and elderly Wards		Critical care	
			SARSCoV-2 positive	SARSCoV-2 negative	SARSCoV-2 positive	SARSCoV-2 negative
Amoxicillin	107	21.9	37	65	5	0
Azithromycin	5	1.0	1	2	2	0
Aztreonam	6	1.2	0	3	3	0
Ceftriaxone	1	0.2	1	0	0	0
Ciprofloxacin	13	2.7	5	6	2	0
Clarithromycin	19	3.9	5	10	3	1
Co-amoxiclav	62	12.7	25	27	9	1
Co-trimoxazole	12	2.5	7	5	0	0
Doxycycline	81	16.6	45	35	1	0
Flucloxacillin	16	3.3	4	9	3	0
Gentamicin	23	4.7	10	13	0	0
Levofloxacin	9	1.8	6	2	1	0
Meropenem	19	3.9	5	1	12	1
Metronidazole	25	5.1	6	18	0	1
Other	18	3.7	6	8	2	2
Piperacillin-tazobactam	33	6.7	11	10	11	1
Temocillin	12	2.5	4	6	2	0
Trimethoprim	8	1.6	6	2	0	0
Vancomycin	20	4.1	11	3	6	0
Total	**489**	100.0	**195**	**225**	**62**	**7**

* Patients may have received more than one antibiotic. The name of one antimicrobial was not recorded for one patient (COVID-19 positive and in critical care) receiving an antibiotic on the day of the survey for a respiratory indication.

(59.8%) followed by urinary tract infection (8.7%), skin and soft tissue (3.7%), systemic (3.0%), gastrointestinal (1.6%), and other sites (2.4%) with no indication was recorded for 102 patients receiving an antibiotic on admission (20.7%).

Antibiotic prescribing on the survey day

Prevalence of antibiotic prescribing on the survey day was 45.0% (95%CI: 41.6 to 48.4) and a total of 490 antibiotics were prescribed to 368 patients (Table 3). Antibiotics were most frequently prescribed for suspected RTI (73.9%) followed by urinary tract infection (10.1%), skin and soft tissue infection (4.1%), systemic infection (3.5%), gastrointestinal (2.7%) and infections of other/unspecified sites (5.2%).

The three most frequently prescribed antibiotics were amoxicillin (107, 21.9%), doxycycline (16.6%) and co-amoxiclav (12.7%) accounting for over half of all antibiotics on the survey day. In critical care, meropenem, piperacillin-tazobactam and co-amoxiclav were most frequently prescribed accounting for 18.8%, 17.4% and 14.5%, respectively and approximately half of all antibiotics prescribed in critical care.

Of all patients receiving antibiotics on the survey day, 48.9% were receiving therapy via IV route (41.3% receiving antibiotics on medical and elderly wards, 94.2% in critical care) and prescribing was empirical in 87.2% (89.8% on medical and elderly wards, and 72.2% on critical care wards).

Median time from admission to prescribing was 2 days (range 1 to 344, IQR 1 to 10). This was 2 days (range 1 to 344, IQR 1 to 7) on medical and elderly wards and 14 days (range 1 to 28, IQR 1.75 to 18.25 in critical care). More than half of all antibiotics that patients were still receiving on the survey day (52.7%) were prescribed on the day of admission or day two (56.4% for patients on medical and elderly wards and 38.9% in critical care).

Antibiotic prescribing in SARS-CoV-2 positive patients

Antibiotics were prescribed in 203 patients who were confirmed SARS-CoV-2 positive (prevalence: 38.3%, 95% CI: 34.3 to 42.5), approximately one quarter of whom were in critical care ($n = 50$, 24.6%). In confirmed SARS-COV-2 positive critical care patients, 45.9% were receiving antibiotics compared with 36.3% of those on medical and elderly wards (Table 2).

Clinical variables examined by Univariable logistic regression analysis for an association with antibiotic prescribing on the survey day in patients who were SARS-CoV-2 RT-PCR positive are shown in Table 4. In a multivariable logistic regression analysis, COPD/chronic lung disease and a CRP$\geq$100 mg/l were associated with higher odds of receiving at least one antibiotic, and patients with probable or confirmed nosocomial COVID-19, diabetes and patients receiving care on an elderly ward had lower odds of receiving at least one antibiotic on the survey day (Table 5).

Antifungal prescribing

Systemic antifungals were prescribed in 13 patients (prevalence: 1.6%, 95% CI: 0.9 to 2.7) on the survey day (Table 3). All were SARS-CoV-2 positive, 12 were in critical care and 11 were mechanically ventilated. Caspofungin was prescribed in seven, fluconazole in five and voriconazole in one. Antifungals were directed in seven, empirical in five and one medical ward patient was receiving long term fluconazole prophylaxis. Two patients were immunocompromised and two were diabetic. Twelve of 122 (9.8%) in critical care on the survey day received an antifungal agent, commenced a median of 19 days (range 5 to 23, IQR 16.5 to 20) after hospital admission and a median 18 days (range 5 to 23, IQR 16.5 to 20) after critical care admission. Concomitant broad spectrum antibiotics were prescribed in all who received an antifungal agent.

Discussion

To our knowledge, this is the first national PPS of antibiotic and antifungal prescribing in hospitalised adults with suspected and confirmed COVID-19 infection. The prevalence of antibiotic prescribing on the survey day was 45.0% which, while not directly comparable, is higher than reported prevalence estimates from two Scottish PPS of antibiotic prescribing in acute adult inpatients (35.7% in 2016 and 33.2% in 2011).[16] This was not unexpected as the present PPS was restricted to patients cared for in hospital units designated for suspected and confirmed COVID-19 cases in the midst of the pandemic. In the 2016 national PPS, higher prevalence estimates were also seen in specialties with more acutely

Table 4
Results of univariable logistic regression analysis for association with antibiotic prescribing in SARS-CoV-2 RT-PCR positive patients on day of survey.

Risk factor theme	Risk factor	Category	Odds ratio*	Odds ratio 95% Lower CI	Odds ratio 95% Upper CI	Category p-value	Risk factor p-value
COVID-19 status	**Probable/definite nosocomial COVID-19 (>day8)**	**No***	1.00				
		Yes	0.40	0.26	0.60	<0.001	<0.001
	Positive SARSCoV2 test result prior to admission	**No***	1.00				
		Yes	1.48	0.75	2.93	0.26	0.26
	Positive SARSCoV2 test from admission to day 7	**No***	1.00				
		Yes	1.64	1.09	2.47	0.02	0.02
Demographics	**Age**	**Cont.**	0.98	0.97	0.99	0.002	0.002
	Sex	**Female***	1.00				
		Male	0.93	0.63	1.40	0.74	0.74
Location	**Care home resident**	**No***	1.00				
		Yes	1.21	0.77	1.88	0.41	0.41
	Ward type	**Critical care***	1.00				
		Elderly	0.37	0.22	0.61	<0.001	
		Medical	0.78	0.54	1.13	0.19	0.001
Length of stay from admission to survey	**Length of stay**	**Cont.**	0.99	0.97	1.00	0.06	0.06
Comorbidities	**Asthma**	**No***	1.00				
		Yes	1.56	0.86	2.82	0.14	0.14
	Cardiovascular disease	**No***	1.00				
		Yes	1.02	0.67	1.56	0.92	0.92
	COPD/Chronic lung disease	**No***	1.00				
		Yes	1.55	0.95	2.54	0.09	0.09
	Diabetes	**No***	1.00				
		Yes	0.54	0.36	0.81	0.004	0.004
	Hypertension	**No***	1.00				
		Yes	0.92	0.58	1.48	0.74	0.74
	Immunocompromised	**No***	1.00				
		Yes	1.36	0.79	2.35	0.27	0.27
	Long term renal dialysis	**No***	1.00				
		Yes	1.65	0.56	4.89	0.37	0.37
	Morbid obesity	**No***	1.00				
		Yes	0.84	0.42	1.69	0.63	0.63
	Other chronic illness	**No***	1.00				
		Yes	0.83	0.60	1.15	0.26	0.26
End of life	**DNACPR**	**No***	1.00				
		Yes	0.67	0.46	0.95	0.03	0.03
Diagnostics/ clinical signs	**Chest x-ray**	**Normal***	1.00				
		Abnormal	1.56	0.93	2.61	0.09	0.09
	CRP	**0–99 mg/l**	1.00				
		≥100 mg/l	1.81	1.24	2.65	0.003	0.003
	Sputum	**Normal***	1.00				
		Purulent or bloody	1.34	0.73	2.46	0.35	0.35

* **Comparing group with antibiotic versus no antibiotic for SARS-CoV-2 positive only patients.** COPD- Chronic obstructive pulmonary disease and other chronic lung disease; DNACPR – do not attempt cardiopulmonary resuscitation order; CRP – C-reactive protein. Modelling excludes records with unknown antimicrobial status, COPD/ Chronic lung disease, morbid obesity, Treatment for HBP, Cardiovascular disease, Immuno-compromised as per HPS/SG advice, other chronic illness and DNAR. This left 694 rows for inclusion in the analysis of factors associated with antimicrobial prescribing for a respiratory indication, and 511 rows for inclusion in analysis of factors associated with antimicrobial prescribing in patients who had confirmed COVID-19.

Table 5
Multivariable analysis of factors associated with antimicrobial prescribing in patients who had confirmed COVID-19.

Variable	OR	Lower 95% CI	Upper 95% CI	Wald test p-value
Probable or definite nosocomial COVID	0.54	0.35	0.83	0.006
COPD/Chronic lung disease	1.81	1.02	3.23	0.05
Diabetes	0.57	0.37	0.89	0.02
CRP ≥ 100 mg/l	1.52	1.00	2.33	0.06
Ward type Critical care	1.00			
Ward type Elderly	0.58	0.36	0.94	
Ward type Medical	0.98	0.66	1.44	0.05

Note: COPD- Chronic obstructive pulmonary disease and other chronic lung disease. Modelling excludes records with unknown antimicrobial status, COPD/ Chronic lung disease, Morbid obesity, Treatment for HBP, Cardiovascular disease, Immuno-compromised as per HPS/SG advice, Other chronic illness and DNACPR. This left 694 rows for inclusion in the analysis of factors associated with antimicrobial prescribing for a respiratory indication, and 511 rows for inclusion in analysis of factors associated with antimicrobial prescribing in patients who had confirmed COVID-19.

unwell patients, e.g. ICU medical (48.1%) and respiratory medicine (56.6%).[16]

Of all surveyed patients, two thirds had virologically confirmed SARS-CoV-2 infection and approximately one fifth of confirmed infections treated on designated COVID-19 units were considered to have an infection of probable or definite hospital-onset (22.1%). Nationally, the percentage of all (hospital- and community-diagnosed) cumulative (up to 7th June 2020) COVID-19 infections that had a probable or confirmed hospital-onset was 7.3%.[17] In a hospital based PPS hospital onset infection is likely to be more prevalent as patients are already hospitalised for other medical or social reasons and therefore stay is prolonged.

The prevalence of antibiotic prescribing on the survey day in patients with confirmed SARS-CoV-2 infection was 38.3% and a number of variables were independently associated with antibiotic prescribing. The presence of COPD/ other chronic lung disease (excluding asthma) and a raised CRP≥100 mg/l were both independently associated with higher odds of antibiotic therapy. This may represent ongoing clinical uncertainty regarding the presence of co-existent bacterial (and particularly respiratory tract) infection and a lack of validated therapeutic options for COVID-19 infection at the time. While an elevated CRP is typical in COVID-19 infection, it is more usually associated with significant bacterial infection and often used by prescribers to differentiate bacterial from viral RTI. It is possible that as targeted antiviral and anti-inflammatory treatments become routine,[18,19] there will be less reliance on CRP by prescribers to direct antibiotic therapy. Procalcitonin (PCT), another biomarker for bacterial infections, is not used routinely in NHS Scotland and therefore was not evaluated in this study. Others have recently reported its potential usefulness in limiting unnecessary antibiotic use in confirmed COVID-19.[20]

Patients with probable or definite nosocomial COVID-19 had lower odds of receiving an antibiotic. It is possible these patients were diagnosed as part of a nosocomial outbreak and therefore bacterial infection was not suspected or alternatively symptoms were not severe compared to community onset infection which had necessitated admission. Alternatively those with nosocomial infection were treated earlier in their hospital admission and had discontinued or completed a course of antibiotics by the time of the survey.

Probable/definitive nosocomial COVID-19 status was not strongly correlated with patient length of stay (correlation coefficient=−0.58) and better fitted the data indicating that is not just about duration. Patients managed on elderly care wards had lower odds of antibiotic therapy potentially reflecting greater concern regarding ecological consequences of antibiotics in the older population. The presence of diabetes in SARS-CoV-2 positive patients was also independently associated with lower odds of antibiotic therapy. Further study is required to determine if there are differences in the clinical presentation of COVID-19 infection in the diabetic compared to non-diabetic population. It is plausible that there is a lower threshold for admission of diabetic patients with mild COVID-19 symptoms in view of higher complication risk or alternatively diabetic patients may present with metabolic rather than overtly infective complications.[21]

The composition of the survey population was similar in age, sex, comorbidities and disease severity to the larger, published UK COVID-19 ISARIC hospital cohort.[22] We did not attempt to estimate false negative SARS-CoV-2 RT-PCR test results although 9.8% of those receiving critical care for COVID-19 were SARS-CoV-2 RT-PCR negative, and chest X-rays were suggestive of or indeterminant for COVID-19 in 14.3% and 23.5% of all surveyed SARS-CoV-2 negative patients, respectively. False-negative results are associated with poorly obtained nose/throat specimens and up to 33% of nasal swabs are negative when taken at least 10 days after the onset of symptoms.[23]

Antibiotic prescribing on the day of admission was 62.4% and most frequently for suspected RTI. On the survey day, 45.0% were receiving antibiotics and this was no different in patients managed in critical care units or on hospital wards. Antibiotic prescribing prevalence in patients with confirmed SARS-CoV-2 infection was 38.3% significantly lower than on admission and on medical and elderly wards, the proportion of patients receiving antibiotics and who tested SARS-CoV-2 positive was lower than those who tested negative, suggesting review and rationalisation of antibiotic prescribing in the context of the virology result.

There were clear differences in antibiotic choice between those managed on medical and elderly wards compared with critical care. Narrow spectrum antibiotics amoxicillin and doxycycline, promoted within Scottish guidance for suspected mild and moderate severity lower RTI, were prescribed most frequently followed by co-amoxiclav which is recommended for severe lower RTI.[10] Quinolones and cephalosporins were prescribed infrequently reflecting their restriction in view of their association with *C. difficile*.[24] Critical care patients were more frequently prescribed piperacillin-tazobactam and meropenem and these were commenced later in the course of the admission suggesting use in suspected nosocomial infection. Although specific microbiological data were not collected, about one in four of those receiving antibiotics in critical care received microbiologically directed broad spectrum therapy. Prolonged respiratory support including the need for prone ventilation as well as nutritional and other organ support is typical in severe COVID-19 and when combined with the need for complex personal protection equipment an extremely challenging environment for prevention of nosocomial infection is created.[9] This is reflected in a recent report from five UK intensive care units showing a predominance of Enterobacterales species, *Staphylococcus aureus* and Pseudomonal species typical of hospital- or ventilator-associated pneumonia occurring at a median of 14 days following admission.[25]

We also observed that about one in ten in critical care were prescribed systemic antifungal agents and in half of these therapy was microbiology-directed. Antifungals were prescribed in combination with broad spectrum antibiotics and later in the critical care unit admission suggesting suspected nosocomial infection. All patients except one were receiving either first or second line anti-candida therapy (fluconazole or caspofungin) as per SAPG published good practice recommendations[26] and only one patient was receiving voriconazole. Although invasive *Aspergillus* has been described in the context of severe SARS-CoV-2 infection[27] there is no clear cut association to date as has been observed with severe influenza.[28]

This survey was subject to limitations common in other hospital PPSs including over representation and bias towards patients with longer durations of stay (and hence higher risk of COVID-19 infection, other HAI and the need for antibiotic therapy). Furthermore, the survey was conducted approximately two weeks after peak number of SARS-CoV-2 diagnoses in Scotland and four weeks after updated prescribing advice from SAPG[10] which might be expected to improve adherence to guidance. Results might not be true for other time periods which is important in a rapidly-changing pandemic situation. It is also possible that some clinical variables important to risk factor analyses may not have been collected.

While there are limitations, this study provides a unique snapshot of antibiotic management in suspected and proven COVID-19 infection across hospitals in Scotland at a time of peak pandemic activity. We have shown a relatively low prevalence of antibiotic prescribing on general and critical care units perhaps reflecting early national guidance on COVID-19 antibiotic prescribing and the maturity of antimicrobial stewardship in Scotland. We have also shown clear differences in antibiotic and antifungal prescribing between those in general wards and those in critical care indicat-

ing the importance of nosocomial infection in the critical care setting and the need for ongoing infection prevention and control and antimicrobial stewardship initiatives. It was reassuring that broad spectrum antibiotics were rarely used outside of critical care units. This is important experience to share to support prudent antibiotic use during the evolving SARS-CoV-2 pandemic and for preparedness as resurgence of infection is anticipated in coming months.

Declaration of Competing Interest

None of the authors have interests to declare.

CRediT authorship contribution statement

Ronald A. Seaton: Conceptualization, Visualization, Data curation, Writing - original draft, Writing - review & editing. **Cheryl L. Gibbons:** Visualization, Formal analysis, Writing - original draft, Writing - review & editing. **Lesley Cooper:** Visualization, Formal analysis, Writing - original draft, Writing - review & editing. **William Malcolm:** Conceptualization, Visualization, Data curation, Writing - original draft, Writing - review & editing. **Rachel McKinney:** Data curation, Writing - review & editing. **Stephanie Dundas:** Data curation, Writing - review & editing. **David Griffith:** Data curation, Writing - review & editing. **Danielle Jeffreys:** Data curation, Writing - review & editing. **Kayleigh Hamilton:** Writing - review & editing. **Brian Choo-Kang:** Data curation, Writing - review & editing. **Suzanne Brittain:** Data curation, Writing - review & editing. **Debbie Guthrie:** Data curation, Writing - review & editing. **Jacqueline Sneddon:** Conceptualization, Visualization, Data curation, Writing - original draft, Writing - review & editing.

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References

1. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med.* 2017;**177**:1308–15.
2. UK Department of Health. Tackling Antimicrobial Resistance 2019 to 2024: the UK's 5-Year National Action Plan. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf (accessed 7th July 2020)
3. Scottish Antimicrobial Prescribing Group. Scottish Reduction in Antimicrobial Prescribing (ScRAP) https://www.nes.scot.nhs.uk/education-and-training/by-theme-initiative/healthcare-associated-infections/training-resources/scottish-reduction-in-antimicrobial-prescribing-(scrap).aspx (accessed 7th July 2020)
4. Seaton R. A COVID-19 and its Impact on Antimicrobial Stewardship https://revive.gardp.org/covid-19-and-its-impact-on-antimicrobial-stewardship/ (accessed 7th July 2020)
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–62.
6. International Severe Acute Respiratory and Emerging Infections (ISARIC) Report 27 April 2020 https://ISARIC_Data_Platform_COVID-19_Report_27APR20.pdf (accessed 7th July 2020)
7. World Health Organisation. Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 Disease is Suspected. Interim Guidance. 13th March 2020. https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf
8. Langford B.J., So M., Raybardhan S., Leung V., Westwood D., MacFadden D R. et al. Bacterial Co-Infection and Secondary Infection in Patients with COVID-19: a Living Rapid Review and Meta-analysis Clin Micro Infect, 10.1016/j.cmi.2020.07.016
9. Cornelius J, Clancy M, Hong NCoronavirus Disease Superinfections, and antimicrobial development: what can we expect? *Clin Infect Dis* 2019 ciaa524. doi:10.1093/cid/ciaa524.
10. Scottish Antimicrobial Prescribing Group. SAPG Response to COVID-19 https://www.sapg.scot/about-us/latest-updates/sapg-response-to-covid-19/ (accessed 7th July 2020)
11. Seaton RA, Nathwani D, Burton P, McLaughlin C, MacKenzie AR, Dundas S, Ziglam H, Gourlay Y, Beard K, Douglas E. Point prevalence survey of antibiotic use in Scottish hospitals utilising the glasgow antimicrobial audit tool (GAAT. *Int J Antimicrob Agents* 2007;**29**:693–9.
12. Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (2019 Global PPS) https://www.global-pps.com/wp-content/uploads/2019/02/Global-PPS-2019-protocol.pdf (accessed 7th July 2020)
13. Robson SE, Cockburn A, Sneddon J, et al. Optimizing carbapenem use through a national quality improvement programme. *J Antimicrob Chemother* 2018;**73**:2223–30.
14. Semple Y, Bennie M, Sneddon J, Cockburn A, Seaton RA. Thomson AH development and evaluation of a national gentamicin and vancomycin quality improvement programme. *J Antimicrob Chemother* 2020. dkaa096 https://doi.org/10.1093/jac/dkaa096 .
15. Scottish Government. Coronovirus (COVID-19) Trends in Daily Data https://www.gov.scot/publications/coronavirus-covid-19-trends-in-daily-data/ (accessed 7th July 2020)
16. Health Protection Scotland. National Point Prevalence Survey of Healthcare Associated Infection and Antimicrobial Prescribing 2016 https://www.hps.scot.nhs.uk/web-resources-container/national-point-prevalence-survey-of-healthcare-associated-infection-and-antimicrobial-prescribing-2016/
17. Public Health Scotland. Hospital onset COVID-19 Cases in Scotland https://beta.isdscotland.org/find-publications-and-data/population-health/covid-19/ (accessed 7th July 2020)
18. Horby P., Lim W S., Emberson J. et al. Effect of Dexamethasone in Hospitalised Patients with COVID-19: Preliminary Report pre-print doi: https://doi.org/10.1101/2020.06.22.20137273
19. Beigel JH, Tomshek K M, Dodd L E, et al. Remdesivir for the treatment of COVID-19 – preliminary report. *N Eng J Med* 2020. doi:10.1056/NEJMoa2007764.
20. Williams E.J., Mair L., de Silva I.T. et al. Routine measurement of serum Procalcitonin allows antibiotics to be safely withheld in patients admitted to hospital with SARS-CoV-2 infection doi: https//doi.org/ 10.1101/2020.06.29.20136572
21. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: an unholy interaction of two pandemics. *Diabetes Metab Syndr* 2020. doi:10.1016/j.dsx.2020.04.049.
22. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ* 2020;**369**. doi:10.1136/bmj.m1985.
23. Wikramaratna P., Paton R.S., Ghafari M., Lourenco J. Estimating False-Negative Detection Rate of SARS-CoV-2 by RT-PCR https://www.medrxiv.org/content/10.1101/2020.04.05.20053355v1.full.pdf
24. Ritchie ND, Irvine SC, Helps A, Robb F, Jones BL, Seaton RA. Restrictive antibiotic stewardship associated with reduced hospital mortality in gram-negative infection. *Quart J Med* 2017;**110**:155–61.
25. Dhesi Z., Enne V.I., Brealey D. et al. Organisms causing secondary pneumonia in COVID-19 patients in 5 UK ICUs as detected with the FilmArray test https://www.medrxiv.org/content/10.1101/2020.06.22.20131573v1.full.pdf
26. Scottish Antimicrobial Prescribing Group. Good practice recommendations for the treatment of Candidaemia and use of antifungal agents (March 2019) https://www.sapg.scot/media/4612/candidaemia-and-antifungal-agents.pdf (accessed 7th July 2020)
27. Blaize M, Mayaux J, Nabet C, Lampros A, Marcelin A, Thellier M. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. *Emerg. Infect. Dis.* 2020;**26**:1636–7 https://dx.doi.org/. doi:10.3201/eid2607.201603.
28. Wauters J, Baar I, Meersseman P, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. *Intensive Care Med* 2012;**38**:1761–8.