Supplementary. Multifaceted intervention for improving discharge antimicrobial prescription in the emergency department

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Supplementary Table 1. A list of indications and appropriate antimicrobial prescriptions for infectious diseases encountered in the emergency department

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| --- | --- | --- | --- |
| Diagnosis | Summary of antibiotic treatment indications | Drug, dosage | References |
| Sinusitis | Prescribe antimicrobial agents to adults with acute bacterial sinusitis (diagnosed strictly per criteria) with 1) Onset with persistent symptoms or signs compatible with acute rhinosinusitis lasting >10 days without any evidence of clinical improvement, 2) Onset with severe symptoms or signs of high fever (>39°C [102°F]) and purulent nasal discharge or facial pain lasting at least 3–4 consecutive days at the beginning of illness, 3) Onset with worsening symptoms or signs characterized by a new onset of fever, headache or increase in nasal discharge following a typical viral upper respiratory tract infection (URI) lasting 5–6 days despite initial improvement of symptoms | Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily  Amoxicillin 500 mg orally three times daily  Doxycycline 100 mg orally twice daily  For patients with a history of penicillin allergy:  Doxycycline 100 mg orally twice daily  Levofloxacin 500 mg orally once daily  Moxifloxacin 400 mg orally once daily | Chow et al.1 |
| Pharyngitis | Prescribe antimicrobial agents only to patients with proven acute group A streptococcal pharyngitis or patients with high likelihood of streptococcal infection (e.g. 4 Centor criteria) | Penicillin V 250 mg orally four times daily or 500 mg orally twice daily (N/A in Japan)  Amoxicillin 1000 mg orally once daily or 500 mg orally twice daily  For patients with a history of penicillin allergy:  Cephalexin 500 mg orally twice daily  Clindamycin 300 mg orally three times daily  Azithromycin 500 mg orally once daily  Clarithromycin 250 mg orally twice daily | Choby et al.2  ESCMID Sore Throat Guideline Group et al.3 |
| Suppurative otitis media | Antimicrobial therapy is not recommended immediately except in cases of immunocompromised patients, patients with persistent symptoms or those with suppurative otitis media. | Amoxicillin 500 mg orally three times daily  Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily  For patients with a history of penicillin allergy:  Cefdinir 300 mg orally twice daily  Cefpodoxime 200 mg orally twice daily  Ceftriaxone 1 g once daily  Cefuroxime 500 mg orally twice daily | Neff, M. J. et al.4  NICE guideline [NG91]5 |
| Pneumonia | Antimicrobial therapy is recommended. | 1) Previously healthy patients with no antimicrobial use within the previous 3 months:  Azithromycin 500 mg orally once daily or one 2 g dose orally  Clarithromycin 500 mg orally twice daily  Doxycycline 100 mg orally twice daily  2) Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected):  Levofloxacin 750 mg orally once daily or moxifloxacin 400 mg orally once daily  Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily or ceftriaxone 1-2 g once daily and either azithromycin 500 mg orally once daily or one dose of azithromycin 2 g orally or clarithromycin 500 mg orally twice daily | Mandell et al. 6 |
| COPD exacerbation | Antimicrobial agents should be given to patients with acute exacerbations who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence. | Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily  Azithromycin 500 mg orally once daily or one 2 g dose orally  Clarithromycin 500 mg orally twice daily  Doxycycline 100 mg orally twice daily | Vogelmeier et al.7 |
| UTI\* | Antimicrobial therapy is recommended. | **Acute uncomplicated cystitis:**  Trimethoprim-sulfamethoxazole 160/800 mg orally twice daily  Nitrofurantoin monohydrate/macrocrystals 100 mg orally twice daily (N/A in Japan)  Pivmecillinam 400 mg orally twice daily (N/A in Japan)  **Acute pyelonephritis:**  Initial 1-time dose of a long-acting parenteral antimicrobial and trimethoprim-sulfamethoxazole 160/800 mg orally twice daily | Gupta et al.8 |
| Acute gastroenteritis  (treatment for travelers’ diarrhea) \*\* | Antimicrobial therapy is not recommended, except in cases of Travelers’ diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. | Levofloxacin 500 mg orally once daily  Ciprofloxacin 750 mg orally once daily  Ofloxacin 400 mg orally once daily  Azithromycin 1 g orally once or 500 mg orally once daily | Riddle et al.9 |
| Intra-abdominal infection | Antimicrobial therapy is recommended. | Antibiotics active against enteric gram-negative aerobic, facultative bacilli, and enteric gram-positive streptococci and coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colonic infections. | Solomkin et al.10 |
| Cutaneous and mucosal infections | Antimicrobial therapy is recommended. | **Impetigo:**  Cephalexin 250 mg orally four times daily  Erythromycin 250 mg orally four times daily  Clindamycin 300-400 mg orally four times daily  Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily  **SSTI:** patients with no SIRS, altered mental status or hemodynamic instability  Clindamycin 300-450 mg orally four times daily  Cephalexin 500 mg orally four times daily  Doxycycline/Minocycline 100 mg orally twice daily  Trimethoprim-sulfamethoxazole 160/800-320/1600 mg orally twice daily | Stevens et al.11 |
| Traumatic injury | 1) Open fractures; antimicrobial therapy is recommended.  2) Some bite wounds; routine antimicrobial therapy is not recommended for every uninfected animal bite injury. The following conditions should be considered: patients who (a) are immunocompromised; (b) have advanced liver disease; (c) have pre-existing or resultant edema in the affected area; (d) have moderate to severe injuries, especially to the hand or face; or (e) have injuries that may have penetrated the periosteum or joint capsule. | **Bites wounds;**  Amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily  The following regimens can be considered for adults with penicillin allergy:  Clindamycin 300 mg orally four times daily and either ciprofloxacin 500 mg orally twice daily or levofloxacin 500 mg orally daily or trimethoprim-sulfamethoxazole 160/800 mg orally twice daily  **Open fracture:**  For type 1 fractures, systemic antibiotic coverage directed at gram-positive organisms  For type 3 fractures, additional gram-negative coverage should be added. | Stevens et al.11  Hoff et al.12 |
| STD | Antimicrobial therapy is recommended. | **Diseases characterized by urethritis (esp. *N. gonorrhoeae* and *C. trachomatis)*:**  Ceftriaxone 1 g, 1 dose and azithromycin 1 g, 1 dose orally  Azithromycin 1 g, 1 dose orally or doxycycline 100 mg orally twice daily  **Pelvic inflammatory diseases:**  Ceftriaxone 1 g, 1 dose and doxycycline 100 mg orally twice daily  with or without metronidazole 500 mg orally twice daily | Workowski et al.13 |
| Febrile neutropenia | Antimicrobial therapy is recommended. | Ciprofloxacin 400-500 mg twice daily and either amoxicillin-clavulanate 500/125 mg orally three times daily or 875/125 mg orally twice daily | Freifeld et al.14 |

Abbreviations:

COPD, chronic obstructive pulmonary disease; UTI, urinary tract infection; SSTI, skin and soft tissue infection; STD, sexually transmitted disease

\* Quinolones are not indicated for treatment of UTI due to quinolone resistance in *E. coli* exceeding > 10% at the study institution.

\*\* If symptoms are not resolved after 24 h, complete a 3-day course of antimicrobial therapy

Supplementary Table 2. The definition of antimicrobial appropriateness

|  |  |
| --- | --- |
| Term | Definition |
| Appropriate | Not meeting the following classification of misuse |
| Misuse | Antimicrobial prescription at discharge which failed to meet the criteria outlined in the pocket guide |
| Unnecessary | The use for non-infectious conditions, nonbacterial infections or self-limiting bacterial infections and included antimicrobial use in cases of uncertain diagnosis |
| Inappropriate | The use of an antimicrobial agent not conforming to current treatment protocols or against a pathogen resistant to the agent |
| Suboptimal | The use of an antimicrobial that could have been improved in one of the following categories: drug delivery route, dosage interval or dosage. |

Note. We referred to the previously mentioned criteria.15-17

Supplementary Table 3. Baseline characteristics of patients with APD in the emergency department (N=2,835)

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| --- | --- | --- | --- |
| Characteristics | Pre-intervention period  (N=1,555) | Intervention  period  (N=1,280) | P  value |
| Demographics |  |  |  |
| Age, year, median (range) | 45 (13-98) | 51 (14-95) | <0.001 |
| ≤ 40 | 653 (42.0) | 454 (35.5) | Ref. |
| 40-65 | 491 (31.6) | 387 (30.2) | 0.17 |
| ≥ 65 | 411 (26.4) | 439 (34.3) | <0.001 |
| Female gender | 852 (54.9) | 731 (57.1) | 0.22 |
| Residential status prior to ED visit |  |  |  |
| Home | 1550 (99.7) | 1,262 (98.6) | Ref. |
| Nursing home | 5 (0.3) | 18 (1.4) | 0.001 |
| Post-travel visit | 5 (0.3) | 0 (0) | N/A |
| Antimicrobial allergy | 28 (1.8) | 70 (5.8) | <0.001 |
| Comorbidity/past medical history |  |  |  |
| Congestive heart failure | 23 (1.5) | 30 (2.3) | 0.09 |
| History of myocardial infarction | 42 (2.7) | 25 (2.0) | 0.19 |
| History of asthma | 129 (8.3) | 109 (8.5) | 0.83 |
| Chronic lung disease | 20 (1.3) | 49 (3.8) | <0.001 |
| Active solid organ malignancy | 106 (6.8) | 53 (4.1) | 0.002 |
| Diabetes mellitus | 115 (7.4) | 100 (7.8) | 0.68 |
| Hypertension | 234 (15.0) | 245 (19.1) | 0.004 |
| Peptic ulcer disease | 39 (2.5) | 8 (0.6) | <0.001 |
| Cerebrovascular disease | 56 (3.6) | 50 (3.9) | 0.67 |
| Chronic liver disease | 18 (1.2) | 34 (2.7) | 0.003 |
| Chronic kidney disease | 14 (0.9) | 8 (0.6) | 0.41 |
| Connective tissue disease | 47 (3.0) | 49 (3.8) | 0.24 |
| Dementia | 28 (1.8) | 19 (1.5) | 0.51 |
| Psychiatric illness | 67 (4.3) | 67 (5.2) | 0.25 |
| Systemic steroid use (≥ 5 mg) in the last 28 days | 37 (2.4) | 26 (2.0) | 0.53 |
| Chemotherapy in the last 28 days | 33 (2.1) | 29 (2.3) | 0.80 |
| HIV | 3 (0.2) | 1 (0.1) | 0.42 |
| Time of visit to the ED |  |  |  |
| Daytime (8:00-16:59) | 795 (51.1) | 624 (48.8) | Ref. |
| Night (17:00-23:59) | 540 (34.8) | 437 (34.1) | 0.72 |
| Late-night (0:00-7:59) | 220 (14.1) | 219 (17.1) | 0.03 |
| Day of ED visit |  |  |  |
| Weekday (Monday through Friday) | 808 (52.0) | 651 (50.9) | Ref. |
| Weekend (Saturday and Sunday) or holiday | 747 (48.0) | 629 (49.1) | 0.56 |
| Seasonality |  |  |  |
| April-September (spring and summer) | 811 (52.1) | 544 (42.5) | Ref. |
| October-March (autumn and winter) | 744 (47.9) | 736 (57.5) | 0.004 |

NOTE.

Data are presented as a number (%) unless otherwise specified.

Abbreviations: ED, emergency department; COPD, chronic obstructive pulmonary disease

Supplementary Table 4. Characteristics of physicians prescribing discharge antimicrobials in the emergency department (N=2,835)

|  |  |  |
| --- | --- | --- |
| Characteristics | Pre-intervention period  (N=1,555) | Intervention period  (N=1,280) |
| Department |  |  |
| Emergency Department | 927 (59.6) | 832 (65.0) |
| Department of Medicine a | 167 (10.7) | 128 (10.0) |
| Department of Surgery b | 421 (27.1) | 320 (25.0) |
| Occupational status of prescribing physicians |  |  |
| Resident | 958 (61.6) | 832 (65.0) |
| Physician in a medical subspecialty c | 269 (17.3) | 128 (10.0) |
| Physician in a surgical subspecialty c | 328 (21.1) | 320 (25.0) |
| Prescribing physician’s post graduate year |  |  |
| ≤ 3 | 418 (26.9) | 459 (35.9) |
| 4-7 | 774 (47.8) | 561 (43.8) |
| ≥ 8 | 363 (23.3) | 260 (20.3) |
| Sex |  |  |
| Male | 991 (63.7) | 840 (65.6) |
| Female | 564 (36.3) | 440 (34.4) |

NOTE.

Data are presented as a number (%) unless otherwise specified.

a Medical department includes the department of general medicine and the pulmonary, gastroenterology, nephrology, and infectious diseases departments.

b Surgical department includes the departments of general surgery, otorhinolaryngology, urology,

obstetrics/gynecology, oral surgery, orthopedics, plastic surgery, neurosurgery, and dermatology.

c Physicians in subspecialties include subspecialty fellows and attending physicians.

Supplementary Table 5. Interrupted time-series analysis of changes in APD trends

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Regression intercept | Pre-intervention trend | Change  after the start of intervention | P | Change in  trend during intervention period | P |
| Number of antimicrobial prescriptions | 43.70  (37.73 to 49.73) | -0.19  (-0.98 to 0.59) | -8.57  (-15.92 to 1.22) | 0.03 | +1.08  (0.10 to 2.07) | 0.03 |
| Proportion of  appropriate prescriptions | 40.70  (33.26 to 48.23) | +1.18  (0.23 to 2.11) | +18.07  (9.68 to 26.50) | <0.01 | +0.24  (-1.19 to 1.24) | 0.97 |
| Proportion of overall misuse prescriptions | 59.26  (51.77 to 66.74) | -1.18  (-2.12 to -0.23) | -18.01  (-26.43 to -9.69) | <0.01 | -0.03  (-1.24 to 1.19) | 0.97 |
| Unnecessary prescriptions | 31.19  (25.44 to 36.94) | -0.38  (-1.22 to 0.46) | -16.41  (-23.90 to -8.92) | <0.001 | +0.13  (-0.96 to 1.22) | 0.81 |
| Inappropriate prescriptions | 24.84  (22.58 to 27.10) | -0.76  (-1.19 to 0.34) | -3.08  (-6.87 to 0.70) | 0.10 | +0.03  (0.58 to 0.64) | 0.92 |
| Suboptimal prescriptions | 3.23  (1.64 to 4.82) | -0.03  (-0.25 to 0.19) | +1.49  (-1.26 to 4.23) | 0.27 | -0.19  (-0.54 to 0.16) | 0.28 |

Data are presented as mean monthly prescriptions per 1,000 visits with 95% confidence intervals unless otherwise specified.

Supplementary Table 6. Details of prescribing patterns in 250 physicians in the emergency department

|  |  |
| --- | --- |
| Number of physicians | (N =250) |
| Number of discharge antimicrobial prescriptions per physician, median (range) | 4 (1-32) |
| Number of physicians with at least one episode of misuse of discharge antimicrobial prescription | 139 (55.6) |
| Number of physicians prescribing antimicrobials appropriately on the next prescribing occasion | 97/139 (69.8) |
| Number of physicians with more than two episodes of misuse of discharge antimicrobial prescription | 59 (23.6) |
| Number of physicians with at least one episode of unnecessary discharge antimicrobial prescription | 72 (28.8) |
| Number of physicians prescribing antimicrobials appropriately on the next prescribing occasion | 36/72 (50.0) |
| Number of physicians with more than two episodes of unnecessary discharge antimicrobial prescription | 22 (8.8) |
| Number of physicians with at least one episode of inappropriate discharge antimicrobial prescription | 84 (33.6) |
| Number of physicians prescribing antimicrobials appropriately on the next prescribing occasion | 47/84 (56.0) |
| Number of physicians with more than two episodes of inappropriate discharge antimicrobial prescription | 24 (16.0) |
| Number of physicians with at least one episode of suboptimal discharge antimicrobial prescription | 28 (11.2) |
| Number of physicians prescribing antimicrobials appropriately on the next prescribing occasion | 14/28 (50.0) |
| Number of physicians with more than two episodes of suboptimal discharge antimicrobial prescription | 10 (4.0) |

Supplementary Table 7. Diagnosis for discharge antimicrobial prescriptions in the ED (N=2,835)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Physician’s diagnosis | Pre-intervention period  (N=1,555) | Per 1,000 visits | Intervention  period  (N=1,280) | Per 1,000 visits |
| Sinusitis | 34 (2.2) | 0.9 | 18 (1.4) | 0.5 |
| Pharyngitis | 103 (6.6) | 2.8 | 96 (7.5) | 2.8 |
| Acute tonsillitis | 19 (1.2) | 0.5 | 34 (2.7) | 1.0 |
| Other upper respiratory tract infections | 10 (0.6) | 0.2 | 1 (0.1) | 0.03 |
| Acute otitis media | 42 (2.7) | 1.2 | 24 (1.9) | 0.7 |
| Acute otitis externa | 8 (0.5) | 0.2 | 2(0.2) | 0.06 |
| Odontogenic infection | 18 (1.2) | 0.5 | 31 (2.4) | 0.9 |
| Neck infection | 1 (0.1) | 0.03 | 1 (0.1) | 0.03 |
| Bronchitis | 23 (1.5) | 0.7 | 11 (0.9) | 0.3 |
| Asthma attack | 2 (0.1) | 0.06 | 1 (0.1) | 0.03 |
| Pneumonia | 277 (17.8) | 7.6 | 216 (16.9) | 6.4 |
| COPD exacerbation | 7 (0.5) | 0.2 | 20 (1.6) | 0.6 |
| Urinary tract infection | 213 (13.7) | 5.9 | 210 (16.4) | 6.2 |
| Sexually transmitted disease | 22 (1.4) | 0.6 | 17 (1.3) | 0.5 |
| Other genitourinary infections | 9 (0.6) | 0.2 | 8 (0.6) | 0.2 |
| Skin and soft tissue infection | 233 (15.0) | 6.4 | 267 (20.9) | 7.9 |
| Prophylaxis for wound infection after traumatic injury | 162 (10.4) | 4.5 | 61 (4.8) | 1.8 |
| Animal bite | 90 (5.8) | 2.5 | 89 (7.0) | 2.6 |
| Intra-abdominal infection | 118 (7.6) | 3.2 | 99 (7.8) | 3.0 |
| Gastroenteritis | 38 (2.4) | 1.0 | 13 (1.0) | 0.4 |
| “Just in case use” despite low likelihood of bacterial infection | 92 (5.9) | 2.5 | 40 (3.1) | 1.2 |
| Febrile neutropenia | 6 (0.4) | 0.2 | 4 (0.3) | 0.12 |
| Others \* | 28 (1.8) | 0.8 | 17 (1.3) | 0.5 |

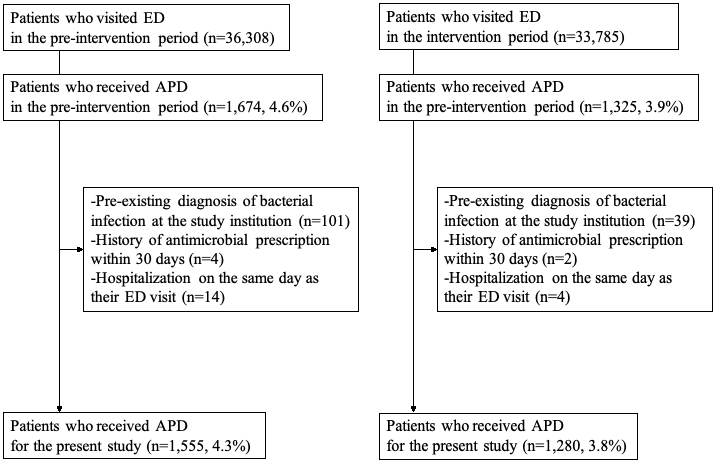
NOTE.

Data are presented as a number (%) unless otherwise specified.

Abbreviations: COPD, chronic obstructive pulmonary disease

\* Others include miscellaneous bacterial infections (N=9 in the pre-intervention period, N=11 in the intervention period), sialadenitis (N=7, N=3), lymphangitis (N=6, N=0), bursitis (N=4, N=3), and septic arthritis (N=2, N=0).

Supplementary Figure 1. Description of the study population.

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